

Quality assurance of pharmaceuticals: a compendium of guidelines and related materials

Tenth Edition • Volume 1
Good practices and related regulatory guidance



**World Health
Organization**

Quality assurance of pharmaceuticals: a compendium of guidelines and related materials

Tenth Edition • Volume 1
Good practices and related regulatory guidance



**World Health
Organization**

Quality assurance of pharmaceuticals: a compendium of guidelines and related materials, tenth edition. Volume 1. Good practices and related regulatory guidance

(Quality assurance of pharmaceuticals: a compendium of guidelines and related materials, tenth edition. Volume 1. Good practices and related regulatory guidance – Volume 2. Good manufacturing practices and inspection)

This is the tenth edition of the first volume of the first edition entitled “*Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Volume 1*” published in 1997. The remaining editions are available electronically (CD-ROM/USB).

ISBN 978-92-4-009942-5 (electronic version)

ISBN 978-92-4-009943-2 (print version)

ISBN 978-92-4-009944-9 (ePub version)

© World Health Organization 2024

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo>).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: “This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition”.

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization (<http://www.wipo.int/amc/en/mediation/rules/>).

Suggested citation. Quality assurance of pharmaceuticals: a compendium of guidelines and related materials, tenth edition. Volume 1. Good practices and related regulatory guidance. Geneva: World Health Organization; 2024 (Quality assurance of pharmaceuticals: a compendium of guidelines and related materials). Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at <https://iris.who.int/>.

Sales, rights and licensing. To purchase WHO publications, see <https://www.who.int/publications/book-orders>. To submit requests for commercial use and queries on rights and licensing, see <https://www.who.int/copyright>.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

Design and layout by Interligar - Branding & Design

List of all previous QA compendiums

Edition	Title	Volumes	Format
9 th edition	Quality assurance of pharmaceuticals [electronic resource]: WHO guidelines, good practices, related regulatory guidance and GXP training materials - 2019 edition.	NA	Electronic (CD-ROM/USB)
8 th edition	Quality assurance of pharmaceuticals [electronic resource]: WHO guidelines, good practices, related regulatory guidance and GXP training materials - 2018 edition. ISBN 978-92-4-155031-4.	NA	Electronic (CD-ROM/USB)
7 th edition	Quality assurance of pharmaceuticals [electronic resource]: WHO guidelines, good practices, related regulatory guidance and GXP training materials - 2017 edition.	NA	Electronic (CD-ROM/USB)
6 th edition	Quality assurance of pharmaceuticals [electronic resource]: WHO guidelines, good practices, related regulatory guidance and GXP training materials - 2016 edition.	NA	Electronic (CD-ROM/USB)
5 th edition	Quality assurance of pharmaceuticals [electronic resource]: WHO guidelines, good practices, related regulatory guidance and GXP training materials - 2015 edition.	NA	Electronic (CD-ROM/USB)
4 th edition	Quality assurance of pharmaceuticals [electronic resource]: WHO guidelines, good practices, related regulatory guidance and GXP training materials - 2014 edition.	NA	Electronic (CD-ROM/USB)
3 rd edition	Quality assurance of pharmaceuticals [electronic resource]: WHO guidelines, good practices, related regulatory guidance and GXP training materials - 2013 edition.	NA	Electronic (CD-ROM/USB)
2 nd edition (update)	Volume 2 (update) 2011 electronic version/CD-ROM: Quality assurance of pharmaceuticals [electronic resource]: a compendium of guidelines and related materials - updated 2011 ed.	NA	Electronic (CD-ROM/USB)
2 nd edition	Volume 2, second edition (2007) Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 2, Good manufacturing practices and inspection (who.int).	2	PDF/print
1 st edition (update)	Volume 2 (2004) including updates, it is unclear which edition this is: Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 2 (including updates), Good manufacturing practices and inspection (who.int).	2	PDF/print
1 st edition	Volume 2 (1999) Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 2, Good manufacturing practices and inspection (who.int).	2	PDF/print
1 st edition	Volume 1 (1997) Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 1 (who.int).	1	PDF/print

Contents

Foreword	ix
Acknowledgements	x
Abbreviations	xi
Executive summary	xvi
Introduction	1
1. Pharmaceutical development	9
1.1 Pharmaceutical development of multisource (generic) finished pharmaceutical products – points to consider Annex 3, WHO Technical Report Series, 970, 2012	9
1.2 Development of paediatric medicines: points to consider in formulation Annex 5, WHO Technical Report Series, 970, 2012	36
2. Marketing authorization: quality	65
2.1 Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part Annex 6, WHO Technical Report Series, 986, 2014	65
2.2 Guidelines for the registration of fixed-dose combination medicinal products Annex 5, WHO Technical Report Series, 929, 2005	133
2.3 Stability testing of active pharmaceutical ingredients and finished pharmaceutical products Annex 10, WHO Technical Report Series, 1010, 2018	181
2.4 Guidelines on packaging for pharmaceutical products Annex 9, WHO Technical Report Series, 902, 2002	222
2.5 Recommendations for quality requirements when plant-derived artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients Annex 6, WHO Technical Report Series, 992, 2015	260
2.6 Recommendations on risk of transmitting animal spongiform encephalopathy agents via medicinal products Annex 1, WHO Technical Report Series, 908, 2003	268
3. Marketing authorization: bioequivalence	269
3.1 Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability Annex 8, WHO Technical Report Series, 1052, 2024	269
3.2 Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products Annex 8, WHO Technical Report Series, 992, 2015	316
3.3 WHO guideline on Biopharmaceutics Classification System-based biowaivers Annex 7, WHO Technical Report Series, 1052, 2024	321
3.4 WHO Biowaiver List: proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms Annex 6, WHO Technical Report Series, 1052, 2024	345

3.5	Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver Annex 4, WHO Technical Report Series, 1019, 2019 (under revision)	356
4.	Regulatory standards: general guidance	371
4.1	Good regulatory practices in the regulation of medical products Annex 11, WHO Technical Report Series, 1033, 2021	371
4.2	Good review practices: guidelines for national and regional regulatory authorities Annex 9, WHO Technical Report Series, 992, 2015	405
4.3	WHO guideline on the implementation of quality management systems for national regulatory authorities Annex 13, WHO Technical Report Series, 1025, 2020	424
4.4	Quality management system requirements for national inspectorates Annex 5, WHO Technical Report Series, 1025, 2020 (revised)	476
4.5	WHO guidelines on quality risk management Annex 2, WHO Technical Report Series, 981, 2013	490
4.6	Guideline on data integrity Annex 4, WHO Technical Report Series, 1033, 2021	522
4.7	WHO general guidance on variations to multisource pharmaceutical products Annex 10, WHO Technical Report Series, 996, 2016	545
4.8	WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation Annex 3, WHO Technical Report Series, 917, 2003	556
4.9	Guidelines on the implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce Annex 9, WHO Technical Report Series, 1033, 2021	580
5.	Contract research organizations	611
5.1	Guidance for organizations performing in vivo bioequivalence studies Annex 9, WHO Technical Report Series, 996, 2016	611
5.2	Guidelines for the preparation of a contract research organization master file Annex 7, WHO Technical Report Series, 957, 2010	651
5.3	Guidelines for good clinical practice for trials on pharmaceutical products Annex 3, WHO Technical Report Series, 850, 1995	657
6.	Prequalification	699
6.1	Guidelines on submission of documentation for a multisource (generic) finished product. General format: preparation of product dossiers in common technical document format Annex 15, WHO Technical Report Series, 961, 2011	699
6.2	Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products Annex 4, WHO Technical Report Series, 953, 2009	711
6.3	Guidelines on active pharmaceutical ingredient master file procedure Annex 4, WHO Technical Report Series, 948, 2008	724
6.4	Procedure for prequalification of pharmaceutical products Annex 10, WHO Technical Report Series, 961, 2011	734

6.5	Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality parts Annex 4, WHO Technical Report Series, 970, 2012	751
6.6	Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities Annex 5, WHO Technical Report Series, 986, 2014	821
6.7	WHO guidelines on variations to a prequalified product Annex 3, WHO Technical Report Series, 981, 2013	825
6.8	Guidelines on the requalification of prequalified dossiers Annex 6, WHO Technical Report Series, 957, 2010	887
6.9	Prequalification of quality control laboratories: procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies Annex 3, WHO Technical Report Series, 1003, 2017	893
7.	Regulatory standards: collaborative procedures and reliance	905
7.1	Good reliance practices in the regulation of medical products: high level principles and considerations Annex 10, WHO Technical Report Series, 1033, 2021	905
7.2	Good practices of national regulatory authorities in implementing the collaborative registration procedures for medical products Annex 6, WHO Technical Report Series, 1019, 2019	935
7.3	Collaborative procedure between the World Health Organization (WHO) Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines Annex 8, WHO Technical Report Series, 996, 2016	987
7.4	Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities Annex 11, WHO Technical Report Series, 1010, 2018	1028
7.5	Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions Annex 9, WHO Technical Report Series, 1010, 2018	1082
8.	Storage, distribution and supply	1117
8.1	Guidelines on import procedures for medical products Annex 5, WHO Technical Report Series, 1019, 2019	1117
8.2	Points to consider for setting the remaining shelf-life of medical products upon delivery Annex 8, WHO Technical Report Series, 1044, 2022	1129
8.3	Model quality assurance system for procurement agencies Annex 3, WHO Technical Report Series, 986, 2014	1142
8.4	Good trade and distribution practices for pharmaceutical starting materials Annex 6, WHO Technical Report Series, 996, 2016	1293
8.5	Good storage and distribution practices for medical products Annex 7, WHO Technical Report Series, 1025, 2020 (revised)	1309

8.6	Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products Annex 9, WHO Technical Report Series, 961, 2011	1339
8.7	Technical supplements to Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products Annex 5, WHO Technical Report Series, 992, 2015	1392
9.	Good pharmacy practices	1421
9.1	Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services Annex 8, WHO Technical Report Series, 961, 2011	1421
9.2	FIP–WHO technical guidelines: Points to consider in the provision by health-care professionals of children-specific preparations that are not available as authorized products Annex 2, WHO Technical Report Series, 996, 2016	1436
10.	Post-market surveillance	1459
10.1	Guidelines on the conduct of surveys of the quality of medicines Annex 7, WHO Technical Report Series, 996, 2016	1459
10.2	WHO guidelines for sampling of pharmaceutical products and related materials Annex 4, WHO Technical Report Series, 929, 2005	1493
10.3	Considerations for requesting analysis of medicines samples Annex 3, WHO Technical Report Series, 1010, 2018	1526
10.4	WHO guidance on testing of “suspect” falsified medicines Annex 5, WHO Technical Report Series, 1010, 2018	1534
11.	Quality control	1575
11.1	WHO good practices for pharmaceutical quality control laboratories Annex 4, WHO Technical Report Series, 1052, 2024	1575
11.2	WHO good practices for pharmaceutical microbiology laboratories Annex 2, WHO Technical Report Series, 961, 2011	1659
11.3	WHO guidelines for preparing a laboratory information file Annex 13, WHO Technical Report Series, 961, 2011	1685
11.4	Good pharmacopoeial practices Annex 1, WHO Technical Report Series, 996, 2016	1691
11.5	Good pharmacopoeial practices: Chapter on monographs for compounded preparations Annex 6, WHO Technical Report Series, 1010, 2018	1709
11.6	Good pharmacopoeial practices: Chapter on monographs on herbal medicines Annex 7, WHO Technical Report Series, 1010, 2018	1714
11.7	Good chromatography practices Annex 4, WHO Technical Report Series, 1025, 2020 (new)	1721
11.8	Model certificate of analysis Annex 4, WHO Technical Report Series, 1010, 2018	1733
11.9	WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines Annex 1, WHO Technical Report Series, 1003, 2017	1738
	Further reading	1753
	Revision history	1755

Foreword

I am delighted to present the new edition of the Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. This publication represents a significant achievement in our ongoing effort to ensure that everyone can reach the highest possible level of health.

Over the last three decades, we have seen the transformation of the pharmaceutical industry and the increasing intricacy of the product life cycle. The challenges we face today are very different from those we faced when the first edition of this Compendium was published in 1997. However, our mission remains the same: to promote health, keep the world safe and serve the vulnerable. The new edition reflects the collective knowledge and expertise of countless professionals who have worked diligently to develop, revise, and implement WHO guidelines for pharmaceuticals. This includes experts from World Health Organization (WHO), Member States, our Expert Advisory Panels and Expert Committees on Specifications for Pharmaceutical Preparations and other organizations and has undergone extensive consultation with stakeholders worldwide.

This Compendium covers development through manufacturing and quality control to post-marketing surveillance. It provides a comprehensive framework for quality assurance that is both strong and flexible, capable of meeting the requirements of a rapidly changing global health landscape. The 10th edition is a collection of knowledge and tools for empowerment, enabling all stakeholders in the pharmaceutical industry to make informed decisions that prioritize patient safety and well-being.

In conclusion, I would like to express my sincere appreciation to everyone who has contributed their time, effort, expertise, and financial resources to the development of this Compendium. I encourage its widespread use by all stakeholders to ensure that pharmaceuticals produced and available in all Member States are of assured quality, safe and efficacious for a healthier world.



Yukiko. n

Dr Yukiko Nakatani,
Assistant Director-General
Access to Medicine and Health Products
World Health Organization

Acknowledgements

This publication, which is based on the reports of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, was produced by the Norms and Standards for Pharmaceuticals team of the World Health Organization (WHO), Geneva, Switzerland.

Acknowledgments are due to all those who contributed to the original reports, as well as to Mr M.R. Abdelfattah, Technical Officer, WHO Prequalification – Inspection Services, Dr S. Estevão Cordeiro, Technical Officer, WHO Norms and Standards for Pharmaceuticals, Dr L. Gwaza, Team Lead, WHO Norms and Standards for Pharmaceuticals, Dr A. Inoubli Regional Advisor for Medical Products Quality and Regulation, WHO Regional Office for South-East Asia, Mrs. B. Kibret, Assistant to Team, WHO Norms and Standards for Pharmaceuticals, Mr F. Masekela, Head of Evaluations and Registration, Medicines Control Authority of Zimbabwe, Mr W. Z. Worku, Technical Officer, WHO Prequalification - Medicines, who contributed to the preparation of this publication.

WHO would like to thank the Bill and Melinda Gates Foundation for the financial support towards the development and production costs for this publication.

Abbreviations

3S	smart safety surveillance
ACT	Access to COVID-19 Tools
ALCOA	attributable, legible, contemporaneous, original and accurate
AMR	antimicrobial resistance
AMRH	African Medicines Regulatory Harmonization Initiative
AMRO	WHO Regional Office for the Americas
APEC	Asia-Pacific Economic Cooperation
API	active pharmaceutical ingredient
APIMF	active pharmaceutical ingredient master file
AQL	acceptance quality level
ASEAN	Association of Southeast Asian Nations
ATMP	Advanced Therapy Medicinal Product
AUC	area under the curve
AUDA-NEPAD	African Union Development Agency-New Partnership for Africa's Development
AWaRe	access, watch and reserve
BCS	Biopharmaceutics Classification System
BE	bioequivalence
BMDL	benchmark dose level
BPW	bulk purified water
BWFI	bulk water for injection
CAPA	corrective and preventive action
CpK	process capability
CPP	certificate of a pharmaceutical product
CRP Lite	collaborative registration procedure-Lite
CRS	chemical reference substance
DABT	Diplomate of the American Board of Toxicology
DAD	diode array detector

DIRA	data integrity risk assessment
EAP	WHO Expert Advisory Panel on <i>The International Pharmacopoeia</i> and Pharmaceutical
ECBS	Expert Committee on Biological Standardization
EC-EML	Expert Committee on the Selection and Use of Essential Medicines
ECSP	Expert Committee on Specifications for Pharmaceutical Preparations
eCTD	electronic Common Technical Document
EDI	electro-deionization
EDQM	European Directorate for the Quality of Medicines and Healthcare
EMA	European Medicines Agency
EML	WHO Model List of Essential Medicines
EMLc	WHO Model List of Essential Medicines for Children
EOI	expression of interest
EQAAS	WHO External Quality Assurance Assessment Scheme
ERT	European Registered Toxicologist
EU	European Union
EV71	enterovirus 71
FAT	factory acceptance test
FEFO	first expiry-first out
FENSA	WHO Framework of Engagement with Non-State Actors
FPP	finished pharmaceutical product
GBT	Global Benchmarking Tool
GC	gas chromatography
GCFR	global competency framework
GCP	good clinical practices
GDP	good distribution practices
GLP	good laboratory practices
GMP	good manufacturing practices
GPW13	WHO's 13th General Programme of Work
GRelP	good reliance practices

GRP	good regulatory practices
GTDP	good trade and distribution practices
GVP	good pharmacovigilance practices
GxP	good practices
HBEL	health-based exposure limit
HPLC	high-performance liquid chromatography
HPS	Health Products Policy and Standards (WHO department)
HVAC	heating, ventilation and air-conditioning
IAEA	International Atomic Energy Agency
IAU	Innovation, Access and Use (WHO team)
ICDRA	International Conferences of Drug Regulatory Authorities
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICRS	International Chemical Reference Substances
ICP	Inductively coupled plasma
IEC	International Electrotechnical Commission
IMP	investigational medical products
IMWP	International Meeting of World Pharmacopoeias
INN	International Nonproprietary Names
IQ	installation qualification
ISO	International Organization for Standardisation
LC	liquid chromatography
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
mAb	monoclonal antibody
MDR-TB	multidrug-resistant tuberculosis
MHRA	Medicines & Healthcare Products Regulatory Agency
MKT	mean kinetic temperature
mRNA	messenger ribonucleic acid
MS	mass spectrometry

MSC	maximum safe carryover
MSM	Member State Mechanism
MSSR	maximum safe surface residue
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NRA	national regulatory authority
NSP	Norms and Standards for Pharmaceuticals (WHO team)
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
OES	optical emission spectrometry
OMCLs	official medicine control laboratories
OQ	operational qualification
PAHO	Pan American Health Organization
PDE	permissible daily exposure
PDE	permitted daily exposure
PDG	Pharmacopoeial Discussion Group
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PQCL	pharmaceutical quality control laboratory
PQT	WHO Prequalification Team
PQT/INS	WHO Prequalification Team for Inspection Services
PQT/MED	WHO Prequalification Team for Medicines Assessment
PVDC	polyvinylidene chloride
PVDF	polyvinylidene difluoride
Q&A	question and answer
QA	quality assurance
QCL	quality control laboratory
QMS	quality management system
QRM	quality risk management
QSE	quality, safety and efficacy

R&D	research and development
RHT	Regulation of Medicines and Other Health Technologies (unit)
RO	reverse osmosis
rpm	rotations per minute
RSS	Regulatory System Strengthening (WHO team)
SAT	site acceptance test
SDGs	Sustainable Development Goals
SF	substandard and falsified
SoINN	School of International Nonproprietary Names
SOP	standard operating procedure
SPC	statistical process control
SmPC	summary of product characteristics
SRA	stringent regulatory authority
TB	tuberculosis
TLC	thin-layer chromatography
TOC	total organic carbon
UN	United Nations
UNEP	United Nations Environment Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
URS	user requirement specifications
USFDA	United States Food and Drug Administration
UV	ultraviolet
VRL	visible residue limit
WFI	water for injection
WHO	World Health Organization
WLA	WHO-listed authority
WPU	water for pharmaceutical use

Executive summary

The World Health Organization (WHO) developed the Quality Assurance of Pharmaceuticals Compendium, Volume 1, to ensure the quality, safety, and effectiveness of medicines using the product life cycle approach. This summary provides an overview of the key features and updates in the latest edition.

The quality of pharmaceuticals has been a concern of WHO since its inception. As such, the setting of global standards is articulated in Article 2 of the WHO Constitution, which states, “develop, establish and promote international standards with respect to good, biological, pharmaceutical and similar products” as one of its core functions. Despite global efforts to ensure the availability of quality medicines, substandard and falsified products still pose challenges in healthcare delivery in many countries. To address this issue, the WHO's Expert Committee on Specifications for Pharmaceutical Preparations continues to make numerous recommendations to establish standards and guidelines and promote effective regulatory and control systems.

The Compendium is a valuable tool for countries to establish robust regulatory systems and uphold international standards in pharmaceutical quality assurance. It consolidates essential recommendations and guidelines related to pharmaceuticals in a structured manner, facilitating easy access to vital information. It addresses various requirements in the life cycle of pharmaceutical products, such as development, regulatory approval, storage, distribution, supply, and post-marketing surveillance of pharmaceuticals. It aims to ensure the quality, safety, and efficacy of these products, which are crucial for preventing and treating diseases and improving global health.

The Compendium has been updated and expanded with new texts to reflect the current and relevant recommendations. It now contains 61 guidelines that cover topics related to pharmaceutical development, regulatory approval, prequalification of medicines by WHO, procurement, storage and distribution, collaborative procedures, quality control, post-market surveillance, and regulatory standards for reproductive health devices. Nine of these guidelines have been updated to include the latest developments and address new challenges in the pharmaceutical industry, while seven new guidelines have been added to cover areas that were not previously explored. These new areas include a protocol for conducting equilibrium solubility experiments for the classification of active pharmaceutical ingredients for biowaiver, good regulatory and good reliance practices in the regulation of medical products, implementing quality management systems for national regulatory authorities, good practices in implementing collaborative registration procedures, points to consider for setting the remaining shelf-life of medical products upon delivery, good chromatography practices and a series of regulatory standards for reproductive health devices.

The Compendium is organized into sections: pharmaceutical development, marketing authorizations, general regulatory standards, prequalification, collaborative procedures and reliance, procurement, storage and distribution, good pharmacy

practices, post-market surveillance, quality control, and regulatory standards for reproductive health devices. Each section offers detailed advice and comprehensive coverage of pharmaceutical quality assurance.

The guidelines within the Compendium align with internationally recognized texts and establish acceptable international standards. However, they allow for necessary adaptations to address unique conditions in individual countries if deviations are validated for equivalence.

The tenth edition of the Quality Assurance of Pharmaceuticals Compendium builds upon the success of the previous edition, incorporating revised guidelines to reflect the latest developments and introducing new guidelines to address emerging needs. It is an indispensable resource for regulatory authorities, pharmaceutical manufacturers, and other stakeholders involved in ensuring the quality, safety, and efficacy of pharmaceutical products.

Introduction

In an era where the global healthcare landscape is continuously evolving, ensuring the quality of medicines that have a positive benefit-risk ratio in local populations is essential for protecting and promoting public health. The persistent threats posed by substandard and falsified medicines, coupled with complex supply chains, make it crucial that assuring that medicines are safe, effective, and of good quality in all countries is not just a regulatory necessity but a moral imperative. Thus, the “Quality Assurance of Pharmaceuticals: a Compendium of Guidelines and Related Materials” serves as an indispensable resource to guide stakeholders in maintaining acceptable standards throughout the supply chain. The publication consolidates WHO’s essential recommendations and guidelines related to the quality assurance of pharmaceuticals into a single, structured publication. Additionally, it supports countries in establishing robust regulatory systems and maintaining international standards to combat the proliferation of substandard and falsified medicines.

From its inception, WHO committed to addressing the quality assurance of medicines. Article 2 of the Constitution mandates that WHO develops and promotes international standards for food, biologicals, pharmaceuticals, and related products. Global standards are essential to ensure the development, manufacture, storage, distribution, and use of quality, safe and effective medicines worldwide.

Over time, the World Health Assembly has adopted multiple resolutions urging WHO to develop international standards, recommendations, and instruments for assuring the quality of medicines produced and traded both nationally and internationally. In response, the WHO Expert Committee on Specifications for Pharmaceutical Preparations has made several recommendations on quality assurance and control. However, these recommendations were published separately in various technical reports, making it challenging for users to perceive them as a cohesive system, accessing and implementing the relevant WHO guidelines.

To address these challenges, the Compendium serves as a centralized, continuously updated resource for regulators, healthcare professionals, industry experts, and other stakeholders. Designed as a 'one-stop-shop,' this publication eliminates the need to consult multiple texts by consolidating all existing and newly updated WHO guidelines, recommendations, and annexes into a single, comprehensive document. Further enhancing its utility, the Compendium arranges these texts in a logical manner that reflects their application in real-world settings, thereby simplifying access and interpretation. As a result, users will find it easier to implement WHO's guidelines quickly and effectively. This publication serves as an indispensable, logically organized, and regularly updated resource that simplifies and harmonizes the approach to pharmaceutical quality assurance and control.

The Compendium consists of two volumes. Volume 1, initially published in 1997, focuses on regulatory systems, product development, registration, quality control,

distribution, and related regulatory standards. Volume 2, first published in 1999, centers around good manufacturing practices (GMP) and the inspection of pharmaceutical manufacturers and distribution channels. GMP is a critical part of quality assurance and serves as the technical standard for the WHO Certification Scheme on the Quality of Pharmaceutical Products in International Commerce.

Overview of the Compendium

Volume 1 of the "Quality Assurance of Pharmaceuticals: A Compendium of Guidelines and Related Materials" provides comprehensive guidelines, guidance, and regulatory standards to support key regulatory functions, other than inspections (covered in Volume 2), that are essential for multisource (generic) medicines. Further, it provides the requirements for the prequalification of medicines programme. Additionally, it addresses requirements for storage, distribution and supply essential for procurement agencies. The Compendium also provides general regulatory guidance, emphasizing good regulatory and review practices, quality management systems, and data integrity. These guidelines are essential for establishing robust regulatory frameworks, ensuring high standards in pharmaceutical quality, and combating the circulation of substandard and falsified medicines.

Structure of the Compendium

The Compendium is divided into sections, covering pharmaceutical development, marketing authorizations, general regulatory standards, prequalification, collaborative procedures and reliance, procurement, storage and distribution, good pharmacy practices, post-market surveillance, and quality control. Regulatory standards for reproductive health devices are provided as further reading.

Pharmaceutical development

This section encompasses critical guidance to support the development of both generic and paediatric medicines. The development of generic finished pharmaceutical products focuses on ensuring these products meet acceptable quality standards and are therapeutically equivalent to the comparator/innovator products, providing patients with affordable, safe, and effective medicines. Key aspects include formulation development, selection of excipients, process validation, and stability testing. For pediatric medicines, the guidance addresses unique challenges such as appropriate dosage forms, excipients, and formulation techniques to ensure safety, efficacy, and acceptability for children. This includes considerations for palatability, dosage accuracy, and ease of administration. This guidance is critical for developing formulations that meet the specific needs of pediatric patients, who often require different dosage forms and strengths compared to adults. Ultimately, these guidances support global health by improving the development

of affordable essential medicines, including paediatric formulations, and enhancing healthcare outcomes, particularly in resource-limited settings, thus contributing to broader public health goals.

Marketing authorizations

The marketing authorization section covers quality or chemistry, manufacturing, and controls (CMC) requirements, and bioequivalence requirements for multisource products. This includes detailed documentation requirements for generic finished pharmaceutical products to verify their quality and standards. This section also addresses the registration of fixed-dose combination medicines, stability testing for active pharmaceutical ingredients and finished pharmaceutical products, and appropriate packaging to maintain product integrity. Additionally, it offers recommendations for quality requirements when using plant-derived artemisinin in antimalarial drugs and guidelines to mitigate the risk of transmitting animal spongiform encephalopathy agents through medicinal products. The primary objective is to ensure that all medicines meet international quality standards, thereby safeguarding public health and maintaining trust in pharmaceutical products.

Further, to ensure therapeutic equivalence, this section includes guidelines to establish the interchangeability of generic pharmaceutical products with the comparator product. It includes requirements for selecting appropriate comparator products for equivalence assessment and offers the Biopharmaceutical Classification System (BCS)-based approach to waive in vivo bioequivalence studies (biowaivers). This section also presents the WHO Biowaiver List, which outlines conditions under which in vivo bioequivalence studies can be waived for immediate-release, solid oral dosage forms listed in the WHO Model List of Essential Medicines. Furthermore, it includes protocols for conducting equilibrium solubility experiments to classify active pharmaceutical ingredients under BCS. The goal is to streamline the regulatory approval process for generic medicines while ensuring they are as safe and effective as the originator products, thus facilitating greater access to essential medicines globally.

Regulatory standards: general guidance

The regulatory standards section on general guidance provides comprehensive guidelines aimed at ensuring the consistent regulation and oversight of pharmaceutical products. This section includes guidelines on good regulatory practices, emphasizing the importance of effective and transparent regulatory frameworks for national and regional authorities. It also covers good review practices to ensure that the evaluation of medical products is thorough, consistent, and based on scientific evidence. Additionally, the implementation of quality management systems for regulatory authorities and inspectorates is addressed, aiming to standardize processes and enhance the overall quality of regulatory activities.

Further, the section includes guidelines on quality risk management, data integrity, and handling variations to multisource pharmaceutical products, ensuring that changes are managed without compromising product quality. It also outlines the WHO pharmaceutical starting materials certification scheme and the WHO Certification Scheme for the quality of pharmaceutical products in international commerce. These guidelines collectively aim to harmonize regulatory practices, ensure high-quality standards for pharmaceuticals, and facilitate international trade and cooperation, ultimately safeguarding public health and ensuring access to safe and effective medicines.

Contract research organizations

This section complements the requirements for marketing authorization of multisource finished pharmaceutical products. It provides additional guidance for contract research organizations (CRO) conducting in vivo bioequivalence studies to support regulatory approval of generic finished pharmaceutical products. The requirements in this section include instructions for conducting in vivo bioequivalence studies, preparation of a CRO master file, and adherence to good clinical practice (GCP) standards. The rationale behind these requirements is to ensure the integrity, reliability, and ethical conduct of research conducted by CROs. By following these guidelines, CROs can uphold high standards of scientific rigor, data accuracy, and well-being of research participants, thus contributing to the ethical development of safe and effective generic medicines.

Prequalification of medicines

Prequalification within the realm of pharmaceuticals encompasses a series of guidelines and procedures established by WHO to evaluate and approve priority medicines for use by United Nations agencies and other international bodies. These include submission guidelines for multisource finished products, assessments of active pharmaceutical ingredients, and procedures for prequalification of pharmaceutical products and quality control laboratories. The rationale behind these requirements is to ensure the availability of safe and effective medicines of good quality, particularly in low- and middle-income countries where regulatory capacity may be limited. By prequalifying products and facilities, WHO aims to streamline procurement processes, facilitate access to affordable, essential medicines, and uphold standards of quality, safety, and efficacy, ultimately contributing to improved public health outcomes worldwide.

Regulatory standards: collaborative procedures and reliance

WHO published a series of guidances and procedures to facilitate regulatory information sharing on marketing authorizations and post-approval changes and promote the concepts of regulatory reliance among regulatory authorities, including on outcomes from WHO prequalification and reference authorities. These include good

practices for national regulatory authorities to implement collaborative registration procedures to accelerate national registration of WHO-prequalified pharmaceutical products and vaccines, products approved by “stringent regulatory authorities,” and guidance on desk assessments of compliance with manufacturing, laboratory, and clinical practices. The rationale behind these requirements is to enhance regulatory capacity, streamline assessment processes, and promote reliance on the work of trusted regulatory authorities. By fostering collaboration and reliance among regulatory bodies, these standards aim to expedite the availability of safe, quality medical products while ensuring regulatory oversight and adherence to international standards. This approach ultimately supports global access to essential medicines and contributes to improved public health outcomes.

Procurement, storage, and distribution

The section on procurement, storage, and distribution covers guidelines and procedures aimed at ensuring the safe and efficient handling of medical products. This includes import procedures for medical products, setting appropriate shelf-life upon delivery, and establishing a model quality assurance system for procurement agencies. Additionally, it outlines good trade and distribution practices for pharmaceutical starting materials and good storage and distribution practices for medical products. The section also provides model guidance and technical supplements for the storage and transport of time- and temperature-sensitive pharmaceutical products. The rationale for these requirements is to maintain the integrity, quality, and efficacy of medical products throughout the supply chain, from procurement to final distribution. By adhering to these guidelines, organizations can ensure that medical products are consistently safe and effective when they reach the end user, thereby safeguarding public health and optimizing therapeutic outcomes.

Good pharmacy practices

Good pharmacy practice encompasses a framework of guidelines jointly developed by the International Pharmaceutical Federation (FIP) and WHO to ensure high standards in pharmacy services. This includes the 2011 standards for quality of pharmacy services, which guide the ethical and professional responsibilities of pharmacists. Additionally, the 2016 technical guidelines address the provision of children-specific preparations by healthcare professionals when authorized products are unavailable. The rationale for these guidelines is to promote safe, effective, and patient-centered pharmaceutical care, ensuring that all patients, including vulnerable populations such as children, receive appropriate medication management. By adhering to these standards, pharmacy practices can enhance medication safety, improve health outcomes, and maintain public trust in pharmaceutical services.

Post-marketing surveillance

Post-marketing surveillance refers to the monitoring of pharmaceutical products after they have been released to the market to ensure their continued safety, efficacy, and quality. This section includes guidelines on conducting quality surveys of medicines, sampling pharmaceutical products, considerations for analyzing medicine samples, and testing "suspect" falsified medicines. The rationale for these requirements is to identify and address any issues that may arise post-approval, such as adverse drug reactions, quality defects, or the presence of substandard or falsified products. By implementing these guidelines, regulatory authorities aim to protect public health by ensuring that medicines remain safe and effective throughout their lifecycle, maintaining high standards of quality control, and promptly addressing any potential risks associated with pharmaceutical products. This ongoing vigilance helps build public trust in healthcare systems and pharmaceutical products.

Quality control

This section includes guidelines and best practices to ensure the reliability and accuracy of pharmaceutical testing and quality assurance processes. This encompasses good practices for pharmaceutical and microbiology laboratories, preparation of laboratory information files, and good pharmacopoeial practices, including chapters on monographs for compounded preparations and herbal medicines. It also covers guidelines for chromatography practices, model certificates of analysis, and selecting marker substances for quality control of herbal medicines. The rationale for these requirements is to maintain high standards in the testing, analysis, and quality assurance of pharmaceutical products, ensuring their safety, efficacy, and consistency. These guidelines aim to standardize laboratory practices globally, enhance the credibility of laboratory results, and support regulatory compliance, ultimately contributing to the protection of public health by ensuring that medicines meet the required quality standards.

Changes in the tenth edition

The Revision History at the end of this document provides an overview of the main changes in the tenth edition of the Compendium. The tenth edition of the Compendium has 61 WHO guidelines and related texts, of which seven are new guidelines published for the first time, nine are revisions or updates of existing guidelines, and the rest remain unchanged from the ninth edition. One text, "*Basic tests for drugs: pharmaceutical substances, medical plant materials, and dosage forms, 1998*", is withdrawn as it is considered obsolete and no longer represents the current thinking of WHO.

Revisions and updates to published WHO guidelines

Since the last publication, several texts have been revised to ensure they remain current and relevant. These updates align with technological advancements, regulatory changes, and industry best practices.

The updated WHO Biowaiver List, BCS-based biowaiver requirements, and guidelines on registration requirements to establish interchangeability, Annexes 6, 7, and 8, TRS 1052, 2024, respectively, reflect current scientific understanding and regulatory expectations, facilitating the development and approval of high-quality generic medicines. The BCS-based biowaiver requirements are updated and published as a separate text (Annex 7) from the main text (Annex 8) compared to the consolidated version from 2017 (Annex 6, TRS 1003, 2017).

The requirements for national inspectorates (Annex 5, TRS 1025, 2020) have been revised from the 2002 version to incorporate contemporary quality systems and inspection methodologies, ensuring robust regulatory oversight. The updated guideline on data integrity (Annex 4, TRS 1033, 2021) replaces the 2016 version to address the evolving challenges in maintaining accurate and reliable data in a digital environment.

The guidelines on import procedures for medical products (Annex 5, TRS 1019, 2019) and the implementation of the WHO Certification Scheme (Annex 9, TRS 1033, 2021) have been updated from their 1996 versions to streamline import processes and enhance the quality of pharmaceuticals in international trade. Similarly, the updated guidelines on good storage and distribution practices for medical products (Annex 7, TRS 1025, 2020) reflect the advancements in storage technologies and regulatory expectations, ensuring product integrity during distribution.

The revised WHO good practices for pharmaceutical quality control laboratories (Annex 4, TRS 1052, 2024) replaces the 2010 guidelines, emphasizing current standards for laboratory operations and quality management systems.

WHO continues to monitor published guidelines and update them as necessary to ensure the requirements are still current and fit for purpose. The Compendium helps to guide users in this respect so that they always refer to the most up-to-date WHO requirements.

New WHO guidelines

The tenth edition introduces several new guidelines to address evolving needs in pharmaceutical regulation and quality assurance. One key addition is the protocol to conduct equilibrium solubility experiments for the BCS-based classification of active pharmaceutical ingredients for biowaivers (Annex 4, TRS 1019, 2019). This protocol provides a standardized approach to determine the solubility of active pharmaceutical ingredients, facilitating the classification process essential for biowaiver applications. The rationale is to streamline the approval process for generic drugs by leveraging scientific data on solubility, thereby ensuring that high-quality generics can be brought to market more efficiently.

Several new guidelines are introduced to enhance regulatory efficiency, and global collaboration in medical product regulation. First, good regulatory practices in the regulation of medical products (Annex 11, TRS 1033, 2021) and good reliance practices (Annex 10, TRS 1033, 2021) are introduced. These guidances provide frameworks for regulatory authorities to adopt best practices and collaborative approaches in the regulation of medical products. Good regulatory practices focus on establishing robust regulatory systems that ensure the safety, efficacy, and quality of medical products. Good reliance practices encourage regulatory authorities to trust and utilize assessments conducted by trusted counterparts, fostering global collaboration and efficient use of resources. Additionally, good practices of national regulatory authorities in implementing collaborative registration procedures (Annex 6, TRS 1019, 2019) outline strategies for regulatory authorities to work together in the registration of medical products. This collaborative approach is intended to harmonize regulatory requirements and reduce duplication of efforts, speeding up the registration process while ensuring approval of medicines of good quality with a positive benefit-risk ratio in local populations. These guidelines aim to enhance regulatory efficiency and ensure consistent regulatory standards worldwide.

Points to consider for setting the remaining shelf-life of medical products upon delivery (Annex 8, TRS 1044, 2022) guide the determination of appropriate shelf-life in the supply chain to ensure product efficacy and safety up to the point of use. This guide includes emergency health kits for use as part of the humanitarian response. Lastly, good chromatography practices (Annex 4, TRS 1025, 2020) establish standards for chromatographic methods, which are crucial for the accurate analysis of pharmaceutical substances.

In conclusion, Volume 1 of Quality Assurance of Pharmaceuticals: a Compendium of Guidelines and Related Materials is a comprehensive resource for pharmaceutical quality assurance. It combines essential recommendations, guidelines, and other materials in a structured manner to support countries in ensuring the quality, safety, and efficacy of medicines. An alphabetical index of subjects covered in Volume 1 of Quality Assurance of Pharmaceuticals: A Compendium of Guidelines and Related Materials is included at the end of this volume.

1. Pharmaceutical development

1.1 Pharmaceutical development of multisource (generic) finished pharmaceutical products – points to consider

Annex 3, WHO Technical Report Series, 970, 2012

1. Introduction	10
1.1 General principles	10
1.2 Scope	10
2. Predevelopment activities	11
2.1 Desk research	11
2.1.1 Quality risk management	11
2.2 Additional considerations	12
2.2.1 Selection and characterization of comparator finished pharmaceutical product(s)	12
2.2.2 Benchmarking for formulation experiments and stability studies	13
2.2.3 Formulation selection experiments	13
2.2.4 Bioequivalence and dissolution studies	14
3. Pharmaceutical development	14
3.1 Components of the finished pharmaceutical product	16
3.1.1 Active pharmaceutical ingredient	16
3.1.2 Excipients	17
3.2 Finished pharmaceutical product “3.2.P.2.2”	18
3.2.1 Formulation development	18
3.2.2 Overages	20
3.2.3 Physicochemical and biological properties	20
3.3 Manufacturing process development	20
3.4 Container-closure system	22
3.5 Microbiological attributes	25
3.6 Compatibility	25
4. Glossary	26
References	30
Appendix 1 Examples of presenting quality attributes of active pharmaceutical ingredients	32
Appendix 2 Information on development batches	34

1. Introduction

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies provide scientific understanding to support the establishment of specifications and manufacturing controls.

This document focuses on the development of multisource finished pharmaceutical products (FPPs) which are intended to be bioequivalent to the relevant comparator product. Multisource FPPs should¹ accordingly be therapeutically equivalent to the comparator product.

This document provides a structured approach for industry following the International Conference on Harmonisation (ICH) common technical document (CTD) format, for developing high-quality, multisource FPPs. The ICH-CTD structure for pharmaceutical development information allows for a logical, progressive description of the development process.

The document is also intended to provide assessors and inspectors with a good understanding of best practices in the development of multisource FPPs and their manufacturing processes.

Manufacturers who have chosen a more systematic approach to product development would follow the development within the broader context of quality assurance principles, including the use of quality risk management and pharmaceutical quality systems.

This document is designed to be used in conjunction with other WHO guidelines and guidance documents (1).

1.1 General principles

The pharmaceutical development studies and the manufacture of primary batches are essential elements for the science and risk-based approach to establish the critical quality attributes (CQAs) of the FPP and the critical process parameters (CPPs) of the manufacturing process.

1.2 Scope

This document addresses the pharmaceutical development of multisource FPPs containing existing active pharmaceutical ingredients (APIs) of synthetic or semisynthetic origin. For the purposes of this document an existing API is one that has been previously authorized through a finished product by a stringent regulatory

¹ For the purpose of this document the term “should” is generally to be interpreted as “is recommended” or “is usually required”.

authority (SRA) or, for the purposes of a national medicines regulatory authority (NMRA), that has been authorized by that NMRA or for which a monograph exists in the pharmacopoeia(s) recognized by that NMRA. APIs of biological or biotechnological origin are not covered here.

This document provides guidance on the contents of a pharmaceutical development plan for multisource pharmaceutical products for both the applicants for marketing authorizations and NMRAs.

Pharmaceutical development issues depend on the API(s), the excipients, the dosage form, the manufacturing process and the container-closure system.

2. Predevelopment activities

2.1 Desk research

Desk research includes all relevant documentation being collected and evaluated prior to initiation of any laboratory activities. This documentation may include information such as is found in:

- WHO, European Medicines Agency (EMA) and United States Food and Drug Administration (US-FDA) web sites that contain regulatory information, for example, the qualitative composition, mode of administration and the primary packing materials of the innovator and multisource FPPs;
- compendial monographs, scientific literature, patents, technical information typically found in the applicant's (open) part of the API master file (APIMF), technical information on excipients and prior company knowledge.

2.1.1 Quality risk management

An essential part of desk research entails the identification of possible risks prior to the development of a multisource product.

An important consideration when selecting the API manufacturer is the fact that the FPP manufacturer is responsible for the control of the API and as such must have a comprehensive understanding of the API. Analysis of the applicant's part of the APIMF (or drug master file) is, therefore, important.

Poor solubility in aqueous medium is an important quality risk factor for APIs administered in the solid state as there is a high risk that inter-batch variability in physical properties may translate into significant differences in the in vivo performance.

It is recommended that polymorphism, pseudo-polymorphism and the implications of variability in particle size be routinely considered. Variability in any of these key physical properties is likely to be of particular significance for APIs that have low solubility according to the biopharmaceutics classification system (BCS).

The requirement for routine control of polymorphic form and particle size should be considered in accordance with advice in Decision Trees 3 and 4 of ICH Q6A (2). When controls are necessary they should be established based on the results obtained for the API lot(s) used in the biostudies.

For example, *The International Pharmacopoeia* (Ph. Int.) (3) restricts the polymorphic form of mebendazole API to form C and furthermore states that the formulation, manufacturing process and product packaging of chewable mebendazole tablets are designed and controlled so as to minimize the conversion of the polymorphic form of mebendazole from C to A.

The initial risk assessment of potential CQAs and CPPs of a multisource product should be based on desk research and the applicant's own experience with the manufacture of the dosage form.

Literature, preferably peer-reviewed, may contain risk information essential for predevelopment. For example, the presence of meso-ethambutol hydrochloride in commercial ethambutol hydrochloride API material has been demonstrated in the literature (4), although some pharmacopoeial monographs do not clearly reveal the presence of this impurity. Recently a specific test was included in the *European Pharmacopoeia* (Ph. Eur.) (5) for control of this impurity.

The least risky strategy for multisource product development is to use the same qualitative and, where possible, quantitative formula as that of the comparator FPP – so long as this does not lead to the possibility of patent infringement – in order to minimize the risks related to compatibility, stability and bioequivalence.

Accompanying reconstitution diluents should also be included in the development strategy where appropriate. This topic is discussed further in section 3.

2.2 Additional considerations

2.2.1 Selection and characterization of comparator finished pharmaceutical product(s)

In many countries the NMRA provides a list of comparator products. Alternatively, references are available from WHO (Prequalification of Medicines Programme), and in international lists of comparator products. Note that for a dossier to be submitted to the Prequalification of Medicines Programme the comparator must be selected from the published lists. Guidance regarding Prequalification of Medicines Programme comparator products is available under Guidance on bioequivalence studies on the Prequalification of Medicines Programme web site (apps.who.int/prequal/).

In the case of fixed-dose combination (FDC) FPPs, there will be instances when a combination of APIs is recommended for clinical use but an innovator FDC FPP containing these APIs, whose approval was based on clinical trial data, will not be available as a comparator product. FDCs approved based on data such as bioequivalence data are not typically used as comparators, as the original safety and efficacy data

are linked to the monocomponent products and not the FDC FPP. For FDC FPPs, the development strategy should take into account the formulas of the individual component comparator FPPs. If the innovator FDC exists this should be the target product for the FDC multisource product development – even if the individual comparator tablets could also be used in the bioequivalence study (see also WHO *Guidelines for registration of fixed-dose combination medicinal products* (6)).

The comparator product batch may be selected by dissolution profile testing (see WHO's *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (7)). Ideally a batch which shows intermediate dissolution under the most discriminative condition (where the difference in dissolution between the fastest and slowest batches studied is the largest) should be selected as the reference product for pharmaceutical equivalence studies and bioequivalence studies.

2.2.2 Benchmarking for formulation experiments and stability studies

The comparator sample should be thoroughly examined for parameters such as physical properties, shelf-life, including in-use stability information, storage instructions and details of the container-closure system in comparison to the outcome of the desk research and the requirements for marketing the new multisource product in the intended market.

All the relevant quality attributes of the dosage form should be analysed, e.g. assay, related substances, dissolution rate, pH, preservative concentrations, water content, total mass, mass variation, resistance to crushing, friability and disintegration of tablets.

The information obtained forms the basis for the development of the new multisource FPP.

2.2.3 Formulation selection experiments

Based on the outcome of the desk research and the national requirements for marketing authorization, formulation experiments will be conducted to develop the quality target product profile (QTPP) of the FPP.

Experiments may include determining the qualitative and quantitative composition of the comparator product. The qualitative information on the comparator product may be available in the public domain, e.g. in its summary of product characteristics (SmPC) or package leaflet. Screening different formulations to match the comparator dissolution profile is the best method to select the final formula for scale-up from laboratory to pilot batch.

Selected formulations may be stress-tested to challenge CQAs and to establish tentative acceptance limits for their control.

Any special design features of the pharmaceutical product (e.g. tablet score-line, overfill, or anti-counterfeiting measure) should be identified as such features affect the

pharmaceutical product and a rationale for their use should be provided in the product dossier (PD).

2.2.4 Bioequivalence and dissolution studies

Bioequivalence and comparative dissolution studies should be conducted with samples from a batch of the FPP of at least pilot size. The dissolution conditions and acceptance criteria should be derived from the dissolution profiles obtained for the biobatch.

Where an *in vivo* bioequivalence study could be waived, similarity of the formulations may be required, in particular with respect to excipients that may have an influence on the extent and rate of absorption, e.g. sorbitol in liquid formulations or mannitol in solid dosage forms. For instance, when considering a biowaiver for an immediate-release solid oral dosage form containing a BCS class 3 API, the risk of reaching an inappropriate biowaiver decision needs to be critically evaluated, especially when the extent of absorption (f_{abs}) is less than 50%. As part of the risk assessment the excipients used will also need to be scrutinized carefully in terms of both qualitative and quantitative composition – the greater the deviation from the comparator composition, the greater the risk of an inappropriate biowaiver decision.

Inclusion of summaries of all bioequivalence studies (passed and failed) on the final formulation in the PD may be required.

3. Pharmaceutical development

It is recommended to use an internationally harmonized structure when submitting a dossier for obtaining a marketing authorization. This section therefore follows the ICH-CTD structure according to ICH M4 (8).

The text of the M4Q (CTD-Q) guideline (9) is reproduced verbatim in this document in *italic* text, with minor modifications to accommodate WHO terminology and to include certain changes to the text that would be appropriate for multisource pharmaceutical products, notably:

- drug substance is replaced with active pharmaceutical ingredient or API;
- drug product is replaced with finished pharmaceutical product or FPP;
- application is replaced with product dossier or PD;
- combination product is replaced with fixed-dose combination or FDC;
- clinical batches is replaced with comparative bioavailability or biowaiver batches.

Following the *italic* text of the M4Q (CTD-Q) guideline (9), additional guidance by WHO is added in normal type to enable it to be easily distinguishable from the ICH text. This additional text is included to further clarify WHO's expectations and requirements. This approach is intended to facilitate the identification and origin of the text in the document (i.e. whether from ICH or WHO).

In section 3.2.P.2 below, reference may be made to CTD sections that are not discussed in this document. This is done to guide the manufacturer in completing the PD according to national or regional requirements.

3.2.P.2 *The Pharmaceutical development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container-closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the product dossier. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and FPP quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the product dossier.*

Pharmaceutical development information usually includes, at a minimum:

- the definition of the QTPP as it relates to quality, safety and efficacy, considering, for example, the route of administration, dosage form, bioavailability, strength and stability;
- identification of the potential CQAs of the FPP so as to adequately control product characteristics that could have an impact on quality;
- discussion of the potential CQAs of the API(s), excipients and container-closure system(s) including the selection of the type, grade and amount necessary to deliver the product of the desired quality;
- discussion of the selection criteria for the manufacturing process and the control strategy required to manufacture commercial lots meeting the QTPP in a consistent manner.

These features should be discussed as part of the product development, using the principles of risk management over the entire life-cycle of the product (ICH Q8 (10)). The information gained through the predevelopment activities may already have disclosed some of these features and could form an integral part of pharmaceutical development.

For a discussion of additional pharmaceutical development issues specific to the development of FDCs, reference can be made to WHO Technical Report Series, No. 929, Annex 5, section 6.3.2 (6).

Reference documents for pharmaceutical development include ICH guidelines Q6A, Q8, Q9 and Q10 (2, 10–12).

3.1 Components of the finished pharmaceutical product

3.2.P.2.1 The components of the FPP are the ingredients listed under section 3.2.1.P.1 (Description and composition of the FPP in the PD). The components thus include the API(s) and all the excipients, as well as those excipients that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. water for granulation) and any others (e.g. nitrogen or silicone for stoppers).

3.1.1 Active pharmaceutical ingredient

3.2.P.2.1.1 *The compatibility of the API with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g. water content, solubility, particle size distribution, polymorphic or solid state form) of the API that can influence the performance of the FPP should be discussed. For FDCs, the compatibility of APIs with each other should be discussed.*

Physicochemical characteristics of the API may influence both the manufacturing capability and the performance of the FPP.

Information on the intrinsic physicochemical properties of the molecule, e.g. solubility, solid-state properties, including polymorphism and habit, melting range, pKa and hygroscopicity, is needed for the development of the product to allow the manufacturer of the FPP to take full responsibility for the quality and quality control (QC) of the API and the FPP.

Additionally, the manufacturer will need information (either from the API manufacturer, or gathered by another party, or by itself) on potentially critical properties of the API, together with specifications, as applicable, e.g. solubility at 37 °C at relevant physiological pH values to permit BCS classification of the API, partition coefficient (octanol/water) at 37 °C and particle size distribution, which may affect dissolution rate and bioavailability, as well as density, bulk and tapped density, flowability, compressibility, and other factors which may influence processability. The above-mentioned properties of the API should usually be supported by experimental data (or by information from peer-reviewed literature) and discussed with respect to CQAs and CPPs.

The specifications of the API manufacturer and the retest period or expiry date derived from formal regulatory stability studies should also be available to the manufacturer of the FPP.

Guidance on compatibility studies is provided in Appendix 3 of the WHO *Guidelines for registration of fixed-dose combination medicinal products* (6). In addition to

visual examination, chromatography results (assay, purity) are required to demonstrate API-API and API-excipient compatibility. In general, API-excipient compatibility is not required to be established for specific excipients when evidence is provided (e.g. in the SmPC or product leaflet) that the excipients are present in the comparator product.

Stress testing of the API should be designed to include simulation, as far as possible, of the conditions that may be encountered during the manufacturing process of the FPP. An example is provided in Appendix 1.

3.1.2 Excipients

“3.2.P.2.1.2 The choice of excipients listed in 3.2.P.1, their concentration and their characteristics that can influence the FPP performance should be discussed relative to their respective functions.”

When choosing excipients, those with a compendial monograph are generally preferred and may be required in certain jurisdictions. Other resources are available for information on acceptable excipients and their concentrations such as the US-FDA IIG (13) list and the *Handbook of pharmaceutical excipients* (14). Use of excipients at concentrations outside the established ranges is discouraged and generally requires justification. In addition, available guidelines which address particular excipients to be avoided should usually be consulted, for example, azo colourants as listed in EMA guideline CPMP/463/00 (15). Other guidelines such as WHO's *Development of paediatric medicines: points to consider in pharmaceutical development* (16) may provide useful general guidance in this regard.

The characteristics and amounts of excipients that can influence the performance of the pharmaceutical product or its manufacturing capability should usually be discussed relative to the respective function. The ability of functional excipients, e.g. pH-adjusting agents, buffers, stabilizers (such as antioxidants and chelating agents), preservatives and dissolution modifiers (such as surface active agents), to perform throughout the intended shelf-life of the FPP should usually be demonstrated.

Antimicrobial preservatives are discussed in 3.2.P.2.5.

Many excipients such as povidone, microcrystalline cellulose and lactose are by nature multifunctional. The chemically identical excipients may have different grades (physical properties) with different functional characteristics; therefore, conformance to pharmacopoeial specifications does not always provide sufficient confidence that an excipient will perform according to its intended purpose.

When an excipient is critical for manufacturing capability of the FPP, batch or batch variations should be minimized by including user requirements additional to those specified in the pharmacopoeia, e.g. particle size distribution.

Ranges or alternatives for excipients are normally not accepted unless supported by appropriate process validation data. Where relevant, compatibility study results (e.g. compatibility of a primary or secondary amine API with lactose) should be included

to justify the choice of excipients. Specific details should usually be provided in the PD where necessary (e.g. on use of potato or corn starch).

3.2 Finished pharmaceutical product “3.2.P.2.2”

3.2.1 Formulation development

3.2.P.2.2.1 *A brief summary describing the development of the FPP should be provided, taking into consideration the proposed route of administration and usage. The differences between the comparative bioavailability or biowaiver formulations and the formulation (i.e. composition) described in 3.2.P.1 should be discussed. Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo studies (e.g. bioequivalence) should be discussed when appropriate.*

When preparing the PD for submission, the data requirements of the NMRA regarding formulation development may depend on whether the multisource product has been newly developed by the applicant or manufacturer or whether it is an established multisource product.

The WHO Prequalification of Medicines Programme defines an established multisource product as one that has been marketed by the applicant or manufacturer associated with the dossier for at least five years and for which at least 10 production batches were produced over the previous year or, if less than 10 batches were produced in the previous year, not less than 25 batches were produced in the previous three years. For products that meet the criteria of an established multisource product, all sections of P.2.2.1 of the dossier should usually be completed with the exception of P.2.2.1 (a). In addition, a product quality review should usually be provided in the PD as outlined in Appendix 2 of the WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part (1).

The requirements for bioequivalence studies should be taken into consideration, for example, when formulating multiple strengths and/or when the product(s) may be eligible for a biowaiver. WHO reference documents (e.g. *WHO guidelines on registration requirements to establish interchangeability for multisource (generic) pharmaceutical products* (7)) can be consulted.

Tablet scoring may be recommended or required in certain jurisdictions or, for example, when scoring is indicated in the WHO invitation for expression of interest, or is specified for an invited FPP in the listing of recommended comparator products, or when division into fractional doses may be necessary according to approved posology.

If the proposed FPP is a functionally scored tablet a study should be undertaken to ensure the uniformity of dose in the tablet fragments. The data provided in the PD should usually include a description of the test method, individual values, mean and relative standard deviation of the results. Uniformity testing (i.e. content uniformity or mass variation, depending on the requirement for the whole tablet) should be performed

on each split portion from a minimum of 10 randomly selected whole tablets. As an example the number of units (i.e. the splits) would be 10 halves for bisected tablets (one half of each tablet is retained for the test) or 10 quarters for quadrisectioned tablets (one quarter of each tablet is retained for the test). At least one batch of each strength should be tested. Ideally the study should cover a range of the hardness values. The splitting of the tablets should be performed in a manner that would be representative of that used by the consumer (e.g. manually split by hand). The uniformity test on split portions only needs to be demonstrated once and does not need to be added to the FPP specification(s). The tablet description in the FPP specification and in the product information (e.g. SmPC, labelling or package leaflet) should reflect the presence of a score line.

If a paediatric dose is to be obtained by splitting a tablet, a demonstration of content uniformity of tablet fragments may be required.

For modified-release tablets designed to be divided into equal halves, demonstration of dissolution profile similarity of the tablet halves against the whole tablet may be required.

Where relevant, labelling should state that the score line is only intended to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses. In this case a demonstration of uniformity is unlikely to be required.

In vitro dissolution or drug release

A discussion should usually be included as to how the development of the formulation relates to development of the dissolution method(s) and the generation of the dissolution profile.

The results of studies justifying the choice of in vitro dissolution or drug release conditions (e.g. apparatus, rotation speed and medium) are usually required in the PD. Data should also usually demonstrate whether the method is sensitive to changes in manufacturing processes and/or changes in grades and/or amounts of critical excipients and particle size where relevant. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters.

Recommendations for conducting and assessing comparative dissolution profiles can be found in Appendix 1 of the WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part (1).

In the case of rapidly dissolving FPPs containing highly soluble APIs (BCS classes 1 and 3), a single-point dissolution test limit of 80% in 30 minutes or less is considered sufficient as a routine QC test for batch-to-batch uniformity. For slowly dissolving or poorly water-soluble APIs (BCS classes 2 and 4) in immediate-release products, a two-point dissolution range (a dissolution window), one at an early time-point (e.g. Q = 60% in 45 minutes) and the other at a later point (e.g. Q = 80% in 90 minutes), is recommended to characterize the quality of the product. Note that in some cases the later point may be lower than 80% if a plateau is reached.

Modified-release FPPs should have a meaningful in vitro release rate (dissolution) test that is used for routine QC. Preferably, this test should possess in vitro–in vivo correlation. Results demonstrating the effect of pH on the dissolution profile are usually required, if appropriate for the type of dosage form.

For extended-release FPPs the testing conditions should be set to cover the entire period of expected release (e.g. at least three test intervals chosen for a 12-hour release and additional test intervals for longer duration of release). One of the test points should be at the early stage of drug release (e.g. within the first hour) to demonstrate absence of dose dumping. At each test period, upper and lower limits should be set for individual units. Generally the acceptance range at each intermediate test point should not exceed 25% or $\pm 12.5\%$ of the targeted value. Dissolution results are usually required for several lots including those used for pharmacokinetic and bioavailability or biowaiver studies.

The dissolution acceptance limit(s) should also be incorporated into the stability programmes.

Where there are scientific grounds that the defined release characteristics of oral pharmaceutical products may be adversely affected by the presence of alcohol, e.g. for modified-release products containing opiates, 5%, 10% and 20% ethanol should be added to the dissolution medium proposed for routine testing in order to demonstrate that no dose dumping will occur through intake with alcoholic beverages.

3.2.2 Overages

3.2.P.2.2.2 *Any overages in the formulation(s) described in 3.2.P.1 should be justified.*

Justification of an overage to compensate for loss during manufacture should usually be provided in the PD, including the step(s) where the loss occurs, the reasons for the loss and batch analysis release data (assay results).

Overages for the sole purpose of extending the shelf-life of the FPP are generally not acceptable.

3.2.3 Physicochemical and biological properties

3.2.P.2.2.3 *Parameters relevant to the performance of the FPP, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency and/or immunological activity, should be addressed.*

3.3 Manufacturing process development

3.2.P.2.3 *The selection and optimization of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.*

For products that meet the criteria of an established multisource product, in order to fulfil the requirements of section P.2.3, section P.2.3 (b) of the dossier should

be completed and a product quality review should usually be submitted as outlined in Appendix 2 of the WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part (1). The guidance below applies to all other products, for which section P.2.3 should be completed in its entirety.

The rationale for choosing the particular pharmaceutical product (e.g. dosage form, delivery system) should be provided in the PD. The scientific rationale for the choice of the manufacturing, filling and packaging processes that can influence quality and performance of the FPP should usually be explained (e.g. wet granulation using high-shear granulator). The results of an API stress study may be included in the rationale. Any developmental work undertaken on protecting the FPP from deterioration (e.g. protection from light or moisture) should also be included.

The manufacturing process of the multisource FPP should be appropriate for the product that is in development. It does not need to be the same as that of the comparator FPP.

Efforts should be primarily directed towards reducing variability in process and product quality. In order to achieve this, all critical sources of variability should be identified and explained and the sources of variability should be minimized and controlled.

Process development studies should provide the basis for process improvement, process validation and any process control requirements. All CPPs should usually be identified, monitored or controlled to ensure that the product is of the desired quality.

For sterile products an appropriate method of sterilization for the pharmaceutical product and primary packaging material should be chosen. Where relevant, justification for the selection of aseptic processing or other sterilization methods over terminal sterilization should be provided in the PD.

Differences between the manufacturing process(es) used to produce comparative bioavailability or biowaiver batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.

The scientific rationale for the selection, optimization and scale-up of the manufacturing process described in 3.2.P.3.3 should usually be explained, in particular the CPPs (e.g. rate of addition of granulating fluid, massing time, and granulation endpoint). A discussion of the CPPs, controls and process robustness with respect to the QTPP and CQA of the product should usually be included (10).

Based on close monitoring of the manufacturing process in the pilot batches, provisional acceptance ranges should be proposed for the CQAs of intermediates and CPPs that impact on downstream processing. Interim acceptance criteria may be approved until enough knowledge is available to finalize CQAs of intermediates and CPPs for production batches.

The manufacturing process used for pilot batches should be the same as the one proposed to be applied to production batches and should provide product of the same quality and meeting the same specifications as that intended for marketing.

3.4 Container-closure system

3.2.P.2.4 *The suitability of the container-closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the FPP should be discussed. This discussion should consider, e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction and performance (such as reproducibility of the dose delivery from the device when presented as part of the FPP).*

The properties of the container-closure systems should be defined by the characteristics of the FPP and the conditions prevailing in the intended market (e.g. climatic zone IVb).

Stability testing of primary batches of the FPP is conducted on samples packaged in the container-closure system selected for marketing in order to confirm compatibility and product stability to support PDs for marketing authorization.

When the container-closure system is a critical factor for FPP stability, batch or supplier variations need to be minimized through tight specifications and extended sampling plans for QC testing.

To facilitate the visual identification of spuriously or falsely-labelled, falsified or counterfeit (SFFC) medicines (including by the public) the description needs to be completely detailed in the product information. Details may include information on the container-closure system, such as “round, white opaque, high- density polyethylene (HDPE) bottles fitted with white opaque, polypropylene continuous thread closures with induction sealing liner”, or “a blister package comprising clear transparent polyvinyl chloride (PVC) film with a backing of aluminium foil coated with heat-seal lacquer”.

Primary packing materials, particularly plastics, should comply with relevant pharmacopoeial and food contact regulations.

Testing requirements to verify the suitability of the container-closure system contact material(s) depend on the dosage form and route of administration and possibly, the manufacturing process. The pharmacopoeias provide standards that are required for packaging materials; examples include the following:

- glass containers (17, 18);
- plastic containers (19, 20);
- rubber/elastomeric closures (21, 22).

Table 1 outlines the general recommendations for the various dosage forms for once-only studies to establish the suitability of the container-closure system contact materials.

Table 1
Studies to establish the suitability of the container-closure system contact materials

	Solid oral products	Oral liquid and topical products	Sterile products (including ophthalmic preparations)
Description of any additional treatments ^a	×	×	× (sterilization and depyrogenation of the components)
Extraction studies	–	×	×
Interaction studies (migration/sorption)	–	×	×
Moisture permeability	× (uptake)	× (usually loss)	× (usually loss)
Light transmission	× ^b	×	×

× Information should usually be submitted.

– Information does not need to be submitted.

^a E.g. coating of tubes, siliconization of rubber stoppers, sulfur treatment of ampoules or vials.

^b Not required if product has been shown to be photostable.

The suitability of the container-closure system used for the storage, transportation (shipping) and use of any intermediate or in-process products (e.g. premixes, bulk FPP) should also be discussed.

Devices

There are certain situations in which pharmaceutical dosage forms are developed in association with specific devices. The device might be critical to enabling delivery of the medicine or it might be included in order to facilitate administration.

Where the device is critical to drug delivery and fully integrated with the product formulation, this product formulation–device combination should be considered as the primary product for the purposes of regulatory submission. Examples of such products include metered dose inhalers (MDIs), dry powder inhalers, intranasal sprays and ready-made intravenous infusions. For these products the data necessary to support a regulatory submission would include:

- physical and chemical stability data for the product formulation– device combination in its primary pack in order to support the claimed shelf-life and storage conditions;
- relevant data on extractables and leachables;
- for multidose products, demonstration of accurate dose delivery over the shelf-life of the product under the registered storage conditions;

- for multidose products with a dose-counting mechanism, stability data to demonstrate reliable performance of that mechanism over the shelf-life of the product under the registered storage conditions;
- specification control and secure sourcing of all device components;
- relevant information on any secondary device associated with the FPP, such as a spacer device sometimes associated with inhaled products such as MDIs and nebulizers. This device enables dose delivery in situations where the patient cannot easily use the primary product to inhale the dose, particularly where administration to children is involved. The device acts as a temporary reservoir for the dose which can then be inhaled more easily by the patient. There will be some variability inherent to a spacer device but, nevertheless, an acceptable accuracy of dose delivery when using this device needs to be demonstrated.

Alternatively, the co-developed device may be intended to facilitate measurement of the prescribed dose prior to administration; this is particularly important for paediatric products where flexibility of dose may also be a requirement. Examples include spoons, cups, syringes or droppers for oral delivery and droppers for nasal or aural delivery. A device is required to be included with the container-closure system for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders or granules), whenever the package provides for multiple doses.

In accordance with the Ph. Int. (3) general chapter *Liquid preparations for oral use*:

“Each dose from a multidose container is administered by means of a device suitable for measuring the prescribed volume. The device is usually a spoon or a cup for volumes of 5 ml or multiples thereof, or an oral syringe for other volumes or, for oral drops, a suitable dropper.”

In these cases the following data would be required to support a regulatory submission:

- for a device accompanying a multidose container, the results of a study demonstrating the reproducibility of the device (e.g. consistent delivery of the intended volume), generally at the lowest intended dose;
- specifications for the device materials, including specific identification testing of the material which will be in contact with the FPP.

When the intention is to submit a PD in CTD format a sample of the device should usually be provided with Module 1 of the PD.

3.5 Microbiological attributes

3.2.P.2.5 *Where appropriate the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products the integrity of the container-closure system to prevent microbial contamination should be addressed.*

Where an antimicrobial preservative is included in the formulation the amount used needs to be justified by submission of results of studies of the product formulated with different concentrations of the preservative(s) to demonstrate the lowest necessary but still effective concentration. The effectiveness of the agent needs to be justified and verified by appropriate studies (e.g. national, regional or international pharmacopoeial general chapters on antimicrobial preservatives) using a batch of the FPP. If the lower limit for the proposed acceptance criterion for the assay of the preservative is less than 90.0%, the effectiveness of the agent has to be established with a batch of the FPP containing a concentration of the antimicrobial preservative corresponding to the lower proposed acceptance criteria.

As outlined in the WHO guidelines on *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (23), a single primary stability batch of the FPP should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) for the duration of the proposed shelf-life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

3.6 Compatibility

3.2.P.2.6 *The compatibility of the FPP with reconstitution diluent(s) or dosage devices (e.g. precipitation of API in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labelling.*

Where a device is required for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders or granules for reconstitution), which are intended to be administered immediately after being added to the device, the compatibility studies mentioned in the following paragraphs are not required.

Where sterile, reconstituted products are to be further diluted, compatibility will have to be demonstrated with all diluents over the range of dilution proposed in the labelling. These studies should preferably be conducted on aged samples. Where the labelling does not specify the type of containers, compatibility (with respect to parameters such as appearance, pH, assay, levels of individual and total degradation products, subvisible particulate matter and extractables from the packaging components) should be demonstrated in glass, PVC and polyolefin containers. However, if one or more containers are identified in the labelling, compatibility of admixtures needs to be demonstrated only in the specified containers.

In the case of infusion sets where a product formulation is added to an infusion vehicle in an intravenous administration set (giving set) immediately prior to administration, the following data would be required:

- physical and chemical stability data for the prepared infusion to support the claimed in-use shelf-life and storage conditions;
- compatibility data to support the claimed in-use shelf-life and storage conditions;
- specification control and secure sourcing of all giving set contact materials.

Studies are usually required to cover the duration of storage reported in the labelling (e.g. 24 hours under controlled room temperature and 72 hours under refrigeration). Where the labelling specifies co-administration with other FPPs, compatibility should be demonstrated with respect to the principal FPP as well as the co-administered FPP (i.e. in addition to the other, aforementioned parameters for the mixture, the assay and degradation levels of each co-administered FPP should be reported).

In some cases when a pharmaceutical product is developed for global marketing there may also be a need to consider alternative diluents or liquids for dispersion and/or in-use reconstitution for a product, and compatibility with these diluents or liquids may be required to be established.

4. Glossary

The definitions given below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

active pharmaceutical ingredient

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

comparator product

The comparator product is a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established. The selection of the comparator product is usually made at the national level by the medicines regulatory authority. (For the WHO Prequalification of Medicines Programme, the selection of the comparator product is based on the information presented under Guidance on bioequivalence studies available on the Prequalification web site.)

control strategy

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to active pharmaceutical ingredient and finished pharmaceutical product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

critical process parameter (CPP)

A process parameter whose variability has an impact on a critical quality attribute and, therefore, should be monitored or controlled to ensure the process produces the desired quality.

critical quality attribute (CQA)

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality.

finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labelling.

fixed-dose combination finished pharmaceutical product (FDC-FPP)

A finished pharmaceutical product that contains two or more active pharmaceutical ingredients.

formal experimental design

A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as “design of experiments”.

generic product

See *multisource (generic) pharmaceutical products*.

life-cycle

All phases in the life of a product from the initial development through marketing until the product's discontinuation.

multisource (generic) pharmaceutical products

Multisource pharmaceutical products are pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

pharmaceutical alternatives

Products are pharmaceutical alternative(s) if they contain the same molar amount of the same active pharmaceutical moiety(s) but differ in dosage form (e.g. tablets versus capsules), and/or chemical form (e.g. different salts, different esters). Pharmaceutical alternatives deliver the same active moiety by the same route of administration but are otherwise not pharmaceutically equivalent. They may or may not be bioequivalent or therapeutically equivalent to the comparator product.

pharmaceutical equivalence

Products are pharmaceutical equivalents if they contain the same molar amount of the same active pharmaceutical ingredient(s) in the same dosage form, if they meet comparable standards, and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the excipients and/or the manufacturing process and some other variables can lead to differences in product performance.

pharmaceutical product

Any preparation for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

pilot-scale batch

A batch of an active pharmaceutical ingredient or finished pharmaceutical product manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger; unless otherwise adequately justified.

primary batch

A batch of an active pharmaceutical ingredient or finished pharmaceutical product used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf-life, as the case may be.

process robustness

Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality.

production batch

A batch of an active pharmaceutical ingredient or finished pharmaceutical product manufactured at production scale by using production equipment in a production facility as specified in the application.

quality

The suitability of either an active pharmaceutical ingredient or a pharmaceutical product for its intended use. This term includes such attributes as the identity, strength and purity.

quality target product profile (QTPP)

A prospective summary of the quality characteristics of a finished pharmaceutical product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the finished pharmaceutical product.

stringent regulatory authority (SRA)

For the purpose of this document, a stringent regulatory authority (SRA) is the medicines regulatory authority in a country which is:

- (a) a member of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (European Union, Japan and the United States of America (USA)); or (b) an ICH Observer, being the European Free Trade Association as represented by SwissMedic and Health Canada (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time);
- only in relation to good manufacturing practices inspections: a medicines regulatory authority that is a member of the Pharmaceutical Inspection Co-operation Scheme as specified at <http://www.picscheme.org>.

therapeutic equivalence

Two pharmaceutical products are considered to be therapeutically equivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and after administration in the same molar dose, their effects, with respect to both efficacy and safety, are essentially the same when administered to patients by the same route under the conditions specified in the labelling. This can be demonstrated by appropriate bioequivalence studies, such as pharmacokinetic, pharmacodynamic, clinical or in vitro studies.

References

1. WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-sixth report*. Geneva, World Health Organization, 2012, Annex 4 (WHO Technical Report Series, No. 970; https://iris.who.int/bitstream/handle/10665/75168/WHO_TRS_970.pdf?sequence=1&isAllowed=y).
2. Q6A: *Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1999; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6A/Step4/Q6Astep4.pdf.
3. *The International Pharmacopoeia, 4th ed., Vol. 1. General notices; monographs for pharmaceutical substances (A–O) and Vol. 2: Monographs for pharmaceutical substances (P–Z); monographs for dosage forms and radiopharmaceutical preparations; methods of analysis; reagents*. Geneva, World Health Organization, 2006, also available in CD-ROM format and online.
The International Pharmacopoeia, 4th ed., First supplement. Geneva, World Health Organization, 2008 (<http://apps.who.int/phint/en/p/docf/>).
The International Pharmacopoeia, 4th ed., Second supplement, 2011, available on CD-ROM.
4. Prasad B. et al. A new validated differential scanning calorimetric procedure for monitoring the less active R,S isomer of ethambutol dihydrochloride in bulk drug samples and anti-tuberculosis formulations. *Pharmaceutical Forum*, 2007, 33: 326–333.
5. *European pharmacopoeia, 7th ed*. Strasbourg, European Directorate for the Quality of Medicines, 2010.
6. Guidelines for registration of fixed-dose combination medicinal products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report*. Geneva, World Health Organization, 2005, Annex 5 (WHO Technical Report Series, No. 929; https://iris.who.int/bitstream/handle/10665/43157/WHO_TRS_929_eng.pdf?sequence=1&isAllowed=y).
7. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization, 2006, Annex 7 (WHO Technical Report Series, No. 937; https://apps.who.int/iris/bitstream/handle/10665/43443/WHO_TRS_937_eng.pdf?sequence=1).
8. M4: *ICH Harmonised Tripartite Guideline – Organisation of the common technical document for the registration of pharmaceuticals for human use*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2004.
9. M4Q: *ICH Harmonised Tripartite Guideline – The common technical document for the registration of pharmaceuticals for human use: quality*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2000.
10. Q8: *Pharmaceutical development*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2009.
11. Q9: *Quality risk management*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2005 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf).

12. Q10: *Pharmaceutical quality system*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2008 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf).
13. *Inactive ingredient guide*. US Food and Drug Administration.
14. Rowe RC, Sheskey PJ, Quinn ME, eds. *Handbook of pharmaceutical excipients*, 6th ed. London, Pharmaceutical Press, 2009.
15. Excipients in the label and package leaflet of medicinal products for human use. Committee for Proprietary Medicinal Products, 2003 (CPMP/463/00Final).
16. Development of paediatric medicines: points to consider in pharmaceutical development. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-sixth report*. Geneva, World Health Organization, 2012, Annex 5 (WHO Technical Report Series, No. 970; https://iris.who.int/bitstream/handle/10665/75168/WHO_TRS_970.pdf?sequence=1&isAllowed=y).
17. Containers – glass. In: *United States Pharmacopeia*, 2nd suppl. Rockville, MD, 2007.
18. Glass containers for pharmaceutical use. In: *European Pharmacopoeia*. Strasbourg, European Directorate for the Quality of Medicines, 2010: 303–307
19. Plastic containers and closures for pharmaceutical use. In: *European Pharmacopoeia*. Strasbourg, European Directorate for the Quality of Medicines, 2010: 308–309.
20. Containers – plastic. In: *United States Pharmacopeia*, 2nd suppl. Rockville, MD, 2007.
21. Elastomeric closures for injections, In: *United States Pharmacopeia*, 2nd suppl. Rockville, MD, 2007: 144–145.
22. Rubber closures for containers. In: *European Pharmacopoeia*. Strasbourg, European Directorate for the Quality of Medicines, 2010: 316–317.

Appendix 1

Examples of presenting quality attributes of active pharmaceutical ingredients

Physicochemical characteristics of the active pharmaceutical ingredient (API) that can influence manufacturing capability and the performance of the finished pharmaceutical product (FPP) should be tabulated and discussed, for example, as in the following tables.

pH (of the buffer)	Solubility (mg/ml)
1.2	
4.5	
6.8	
pKa of API	

Method (compendial):

Particle size of API used in relevant laboratory and pilot-scale batches					
Measured data (µm)	Batch number (and use)				Proposed acceptance range (µm)
	<API batch no.>	<API batch no.>	<API batch no.>	<API batch no.>	
	<FPP batch no.> (design)	<FPP batch no.> (final laboratory)	<FPP batch no.> (stability)	<FPP batch no.> (bioequivalence)	
D 10					
D 50					
D 90					
Add rows as needed. Change data range as relevant					

Method (compendial):

Apparent density of API used in relevant laboratory and pilot-scale batchess					
	<API batch no.> <FPP batch no.> (design)	<API batch no.> <FPP batch no.> (final laboratory)	<API batch no.> <FPP batch no.> (stability)	<API batch no.> <FPP batch no.> (bioequivalence)	Proposed acceptance range (µm)
Bulk Tapped					

Method (compendial):

Stress Condition	Treatment	Observations
None	Initial values of the API	Assay: S1: <i>Insert as many rows as necessary</i> D1: <i>Insert as many rows as necessary</i> Total unspecified: Total impurities:
Temperature	A thin layer of the API is kept at 80 °C for 4 weeks in a Petri dish (open system) with sampling once a week	Assay: S1: D1: Total unspecified: Total impurities:
Humidity	A thin layer of the API is kept at 40 °C /100% relative humidity for 4 weeks in a Petri dish (open system) with sampling once a fortnight	Assay: S1: D1: Total unspecified: Total impurities:
Oxidation	Oxygen is bubbled slowly through the oxygen-saturated aqueous solution/suspension (under constant mixing) of the API for 24 hours with sampling every 8 hours	Assay: S1: D1: Total unspecified: Total impurities:

S1, S2, etc., are synthesis impurities (as in API specifications).
D1, D2, etc., are degradation products.

Appendix 2

Information on development batches

Table 1
Screening laboratory batches with different proportions of excipients to match comparator dissolution

Composition of formulation development experiments								
Ingredients	Lab01		Lab02		Lab03		Lab04	
	Grams	%	Grams	%	Grams	%	Grams	%
active pharmaceutical								
ingredient (API) 1								
API 2								
API 3								
Excipient 1								
Excipient 2								
Excipient 3								
Excipient 4								
Excipient 5								
Dissolution, % at pH ...								

Table 2
Example table for developmental multipoint dissolution profiles (hypothetical example – Ph. Int., paddle, 75 rpm, 900 ml)

	Percentage API dissolved	Percentage API dissolved	Percentage API dissolved
Time (min)	pH 1.2 buffer	pH 4.5 buffer	pH 6.8 buffer
5			
10			
15			
20			
30			
45			
60			
90			

Repeat the table as needed, for example, for comparator product and development batch chosen for scale-up.

When comparing dissolution profiles of products, for example, comparator and test products or different strengths of the same product, the dissolution conditions and sampling intervals must be the same.

Graphical presentation and summary evaluation of the results of comparative dissolution studies of the test (samples taken from the bioequivalence batch no. ...) and comparator products:

1.2 Development of paediatric medicines: points to consider in formulation

Annex 5, WHO Technical Report Series, 970, 2012

General note

The “points to consider” document should not contain detailed instructions for development but rather it should make reference to relevant literature. Some matters dealt with in the draft on development of multisource products have, therefore, been omitted in this proposal.

1. Introduction	38
2. Glossary	39
3. Paediatric dosage forms	39
3.1 Convenient, reliable administration	40
3.2 Acceptability and palatability	41
3.3 Minimum dosing frequency	41
3.4 End-user needs	42
4. Particular dosage forms to be considered	42
4.1 Flexible solid dosage forms	42
4.2 Oral medicines	43
4.3 Medicines for severe conditions	43
4.4 Rectal preparations	43
5. Formulation design	43
5.1 Quality	44
5.2 Biopharmaceutics classification system	44
5.3 Excipients	45
5.4 Colouring agents	46
5.5 Antimicrobial preservatives	46
5.6 Sweetening agents	47
5.7 Taste masking	47
5.8 Solubility enhancers	48
6. Oral administration	48
6.1 Oral liquid preparations	49
6.2 Administration through feeding tubes	51
6.3 Oral solid dosage forms	51

7. Rectal administration	55
7.1 Suppositories	55
7.2 Rectal liquids (enemas)	56
8. Parenteral administration	56
8.1 Formulation	57
8.2 Additional points to consider for parenteral preparations	57
9. Dermal and transdermal administration	58
9.1 Transdermal patches	58
10. Inhalations	59
11. Packaging and labelling	60
References	60

1. Introduction

Safe and effective pharmacotherapy for paediatric patients requires the timely development of medicines and information on their proper use appropriate to the age, physiological condition and body size of the child. Formulations developed specifically for children are often needed. The use of unlicensed and off-label medicines for treating children is widespread. Their effects on children have not been properly studied, age-appropriate formulations are generally not available, and the medicines are not licensed for use in children.

Pharmacists, parents or caregivers are often faced with the need to manipulate an adult medicine in a way that is not described in the Summary of product characteristics. This manipulation can be simple, e.g. breaking tablets that do not have a score line with a tablet splitter, or complex, e.g. using tablets as a source for an active pharmaceutical ingredient (API) to prepare a suspension.

Pharmacists may also be faced with the need to compound a medicine on the basis of the API.

The manipulation process itself can increase the potential for inaccurate dosing and in general can increase the variability of the product. Such handling may be potentially hazardous for the patient as it may affect the stability, bioavailability and accuracy of dosing of a finished pharmaceutical product (FPP), in particular for controlled-release preparations. The use of such medicines may expose children to overdosing and unintended side-effects or to underdosing and a resultant reduction in efficacy. Moreover, excipients that are safe for adults may not necessarily be so for children.

In December 2007 WHO launched its initiative “Make medicines child size” in order to raise awareness of and accelerate action to meet the need for improved availability and access to child-specific medicines. The WHO Model Formulary for children, 2010, provides independent prescriber information on dosage and treatment guidance for medicines based on the WHO Model List of essential medicines for children, first developed in 2007 and reviewed and updated every two years.

Among actions to support the “Make medicines child size” initiative is the present “Points to consider” document on the formulation of paediatric medicines. The objective is to inform regulatory authorities and manufacturers on issues that require special attention in pharmaceutical formulation. Its focus is on the conditions and needs in developing countries. The guidance does not provide exhaustive information and does not exclude the possibility that other aspects may be relevant to the development of paediatric medicines.

It is not within the scope of this document to address extemporaneous preparations and compounding. A separate interim document entitled *Provision by health-care specialists of patient-specific preparations that are not available as authorized products – points to consider (1)* will deal with such preparations.

2. Glossary

The definitions given below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

child-resistant container

A form of packaging difficult for young children to open but not unduly difficult for adults to open properly.

flexible dosage form

A solid dosage form that can be administered to patients in more than one manner, e.g. may be dispersed or taken orally as a whole.

labelling information

Information to the user provided on the package label or in the patient information leaflet.

mini-tablet

A tablet of no more than 4 mm diameter.

off-label use

Use of a medicine outside the scope of regulatory authorization.

platform technology

Technique, including formulation and related processes, which can be used to obtain different dosage forms, different strengths and/or accommodate different APIs.

3. Paediatric dosage forms

The paediatric population is a heterogeneous group ranging from newborns to adolescents with wide physical and developmental differences regarding pharmacokinetics and pharmacodynamics. Organ maturation, metabolic capacity, skin maturation and other factors may change with age, especially in early infancy (2). The age groups identified by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (3) have been derived mainly from physiological and pharmacokinetic differences from birth to adulthood:

- preterm newborn infants
- term newborn infants (0–27 days)
- infants and toddlers (28 days–23 months)
- children (2–11 years)
- adolescents (12 to 16–18 years (dependent on region)).

It is a challenge to find one formulation appropriate for all age groups. The aim should be to safely cover as wide an age range as possible with a single formulation. The guiding principle for selecting paediatric dosage forms should be – as for adults – the balance of risks and benefits taking into account the specific needs of this vulnerable population (4).

During the development of pharmaceutical products, the assessment of individual risks related to specific products and starting materials, and the recognition of hazards at specific stages of production or distribution, will enable further enhancement of the usual quality assurance mechanisms, such as implementation of good manufacturing practices (GMP), by increasing the effectiveness of the activities of all parties involved, within the limits of the available resources. Manufacturers who have chosen a more systematic approach to product development would follow the stages of development within the broader context of quality assurance principles, including the use of quality risk management and pharmaceutical quality systems (4, 5).

Current use of medicines for the paediatric population reflects the full range of dosage forms and routes of administration used for adult medicines. Common routes of administration in paediatric patients include oral, parenteral, dermal, pulmonary, nasal, rectal and ocular. There is, however, limited information on the acceptability of different paediatric dosage forms in relation to age and therapeutic needs and on the safety of excipients in relation to the development of the child. A European Medicines Agency (EMA) reflection paper on paediatric formulations (6) provides background information on these issues. Reviews by Ernest et al. (7) and Krause and Breitkreutz (8) discuss the needs and challenges in developing paediatric medicines.

The desirable features of high-quality paediatric medicines common to all dosage forms are outlined below. Further information on specific dosage forms is given in the following sections.

3.1 Convenient, reliable administration

The administered dose should contain an amount of API adjusted to the age and needs of the child. The implication is that more than one dosage form of the API or more than one strength of a dosage form may be needed to cover different age groups. The intended dose volume or size should be appropriate for the target age group.

Paediatric medicines should preferably be presented as formulations that are ready to administer. The need for health professionals, parents or caregivers to manipulate the dose prior to administration should be kept to a minimum. However, there might be situations, depending on the formulation properties and the dose range to be covered, where this cannot be avoided.

Alternatively, to enable accurate dosing, the dosage form should be designed to subdivide into smaller, uniform doses of appropriate size and, for liquid forms, the dose volume should be accurately measured.

3.2 Acceptability and palatability

Acceptability is the overall acceptance of the dosage form regardless of the mode of its administration. Acceptability of a dosage form depends on a variety of factors such as:

- suitability of the dosage form for the particular age group
- the dosing device used for a liquid medicine
- palatability of an oral medicine
- dose volume or size to be administered
- appropriateness of packaging
- clarity and accuracy of labelling information
- directions for use.

Acceptance of parents and caregivers is also a relevant issue, and the cultural setting may influence the understanding of and expectations of the therapy.

Palatability is the overall acceptance of the taste, flavour, smell, dose volume or size, and texture of a medicine to be administered by mouth or to be swallowed. Palatability can be crucial to adherence. Palatability of the API may influence the choice of dosage form and its design, which may include taste-masking ingredients. The dosage form should not, however, be made too attractive to the child (e.g. it should not be in the form of a sugar-coated tablet resembling a sweet or candy) in order to avoid increasing the risk of accidental poisoning.

It is preferable that the dosage form is palatable in itself without any need for further modification. The caregiver may, however, attempt to improve the ease of administration and acceptance of the patient by mixing the dose with food or a beverage. Such mixing should not be encouraged unless it can be done in such a small volume that ingestion of the full dose can be guaranteed and if there are no undesirable physical or chemical interactions between the food and the medicine. If mixing with food or a beverage (including breast milk) is foreseen, this eventuality should be evaluated by appropriate compatibility studies. Information should be provided in the patient information leaflet by the manufacturer, as supported by evidence-based studies.

3.3 Minimum dosing frequency

Parents and caregivers take care of the administration of medication to young children, whereas schoolchildren and adolescents can often manage their medication themselves. In both cases minimal dosing frequency should be aspired to. Instructions on the dosing frequency are based on the pharmacokinetic and pharmacodynamic properties of the API, but may be influenced by the design of the dosage form.

Frequent dosing, i.e. more than twice daily, may have a negative impact on adherence to the dosing scheme both by caregivers and by older children, in particular

when medicines are taken in settings where a trained caregiver is not available, e.g. at school. Moreover, frequent dosing may conflict with the lifestyle of older children.

3.4 End-user needs

In addition to maximizing the acceptability and palatability of paediatric medicines it is important that they are convenient to produce and affordable. It is also important to bear in mind supply-chain considerations, such as ease of transportation and storage requirements. It is not always possible for the user to store medicines in a refrigerator.

Depending on the age and clinical condition of the child, there are restrictions to the applicable dose volume or size. Generally, when developing the product, minimum dose volume and size should be the goal.

Lack of access to clean water is an important issue to take into consideration in the development of medicines that need to be dissolved, diluted or dispersed prior to administration, as it may compromise the quality of an FPP. It may be necessary to educate patients on how to obtain water of suitable quality, e.g. by supplying instructions on boiling or filtering. Provision of the liquid vehicle as a part of the package may be an option, or the dose may be dispersed or dissolved in a suitable food or beverage prior to administration. Some instructions on such use should be included on the label or package insert. Regional and cultural differences with regard to preferred tastes may need to be considered.

4. Particular dosage forms to be considered

4.1 Flexible solid dosage forms

Dosage forms that, in general, are likely to prove most suitable for global use, including for developing countries, and which should be prioritized, are flexible solid dosage forms such as tablets that are orodispersible and/or can be used for preparation of oral liquids suitable also for the younger age groups, e.g. dispersible and soluble tablets. The flexible dosage form design may be used for various APIs but may not be suitable for medicines requiring a precise dose titration.

Provided that the medicine can be dispersed in breast milk from the mother, it could potentially be used in very young children (< 6 months). When recommending mixing medicines with breast milk, the effect on the taste should be taken into account, as unpleasant tasting medicine may cause aversion in breastfed children. In addition, the compatibility of the API with breast milk will need to be considered. The same considerations apply whenever medicines are mixed with other food.

It is necessary to identify appropriate product strengths and ratios of active ingredients for each medicine as well as to ensure that package sizes will allow optimal use under public health programmatic conditions.

4.2 Oral medicines

For oral medicines that require precise dose measurement or titration, suitable dosage forms could be based on a platform technology to produce multiparticulate solids, e.g. mini-tablets or spherical granules (pellets), that allow production of dosage forms of varying strength as well as different dosage forms like tablets and capsules, and dosage forms to be dispersed to form a liquid dose or to be sprinkled onto food. Platform technology has potential flexibility for manufacturing appropriate fixed-dose combination products (FDCs). Breakable solid dosage forms specially designed to provide the appropriate dose may also serve the same purpose (1, 9).

4.3 Medicines for severe conditions

For severe disease conditions, e.g. neonatal sepsis, the use of alternative dosage forms should be carefully considered. Some alternatives may be easier for untrained caregivers to administer, e.g. a rectal preparation or a spray under the tongue. For some conditions, parenteral formulations may be the best existing option; however, their use requires a trained caregiver.

4.4 Rectal preparations

As an alternative to parenteral preparations for severely ill children or children who are unable to swallow, the use of rectal preparations for indications of severe malaria, pain, infection and also nausea and vomiting may be appropriate. There may, however, be cultural barriers to the use of rectal preparations.

5. Formulation design

When designing paediatric medicines, the route of administration, dosage form and dose of the API are decided on the basis of the disease state, API properties such as taste, aqueous solubility, pharmacokinetic and pharmacodynamic properties and stability during manufacture, storage and use of the chosen dosage form (10). The age, size and condition of the child (e.g. critical illness, concomitant medication, or inability to swallow a dose), and the expected duration of the therapy must be taken into account. Selection of the most appropriate dosage form is, therefore, based on case-by-case considerations.

Most medicines are formulated as single compounds. FDCs are chosen only when the combination has a proven advantage over single compounds administered separately, for example, to achieve compliance in multidrug regimens for treating human immunodeficiency virus (HIV) and/or tuberculosis (TB). The development of FDCs may be more complex than for single compounds; guidance is provided in WHO guidelines (11).

5.1 Quality

In the pharmaceutical development of paediatric medicines attention should be paid to current quality guidelines, especially those provided by WHO (1).

The acceptable level of impurities in APIs and degradation products in finished dosage forms should be qualified and controlled according to regulatory guidelines, e.g. ICH guidelines (12–14). Safety margins established during toxicological studies on an API and finished dosage form usually apply to a worst-case level in adults. Such limits typically apply to both adults and children; although a child would receive a smaller dose, the exposure per kilogram is likely to be similar. Term and preterm neonates have to be considered specifically, and establishment of safety limits may require safety studies in juvenile animals. Additional guidance may be found on the EMA web site (15–17).

The final product should comply with the requirements in relevant pharmacopoeial monographs, preferably those in *The International Pharmacopoeia*.¹ With regard to dissolution testing, dissolution media should be carefully reconsidered in view of the different gastric pH of children from that of adults. Testing at other pHs should be considered in relevant cases. For dissolution testing of special dosage forms, such as chewable tablets, suspensions and patches, see the International Pharmaceutical Federation/American Association of Pharmaceutical Scientists (FIP/AAPS) guidelines for dissolution testing of special dosage forms (18).

5.2 Biopharmaceutics classification system

The biopharmaceutics classification system (BCS) is a scientific framework for classification of APIs for oral administration. The BCS is based upon aqueous solubility and intestinal permeability. An API is considered highly soluble when the highest dose is soluble in 250 ml or less of aqueous media at 37 °C over the pH range 1.2–6.8. The volume estimate of 250 ml is derived from typical bioequivalence study protocols that prescribe administration of a medicine together with a glass of water to fasting human volunteers. A highly permeable API is absorbed orally to an extent of 85% or more of the administered dose based on a mass-balance determination or in comparison to an intravenous dose (19).

Hence an API can be classified as belonging to one of four classes:

- class 1 (high solubility, high permeability);
- class 2 (low solubility, high permeability);
- class 3 (high solubility, low permeability);
- class 4 (low solubility, low permeability).

¹ *The International Pharmacopoeia*, 4th ed. First and Second Supplements (available online and on CD-ROM). Geneva, World Health Organization, 2011 (<http://www.who.int/medicines/publications/pharmacopoeia/overview/en/index.html>).

Classification of APIs included in the WHO Model List of essential medicines is provided in the WHO Technical Report Series (20).

The BCS may be particularly helpful to assess the importance of aqueous solubility since it relates the solubility of the API to the unit dose. Aqueous solubility should not be a concern in the formulation of immediate-release dosage forms containing class 1 and 3 substances.

For class 2 substances, the effect of particle size, polymorphic form, and solubility enhancers, among others, should be considered, as the absorption of these substances may be limited by dissolution rate. The same applies to class 4 substances, although factors other than dissolution may also govern the oral absorption. However, overall the BCS classification can be used as a basis when estimating the likelihood of different absorption of paediatric medicines when the dosage form and/or excipients used in adult medicines differ from those used for paediatric medicines.

In addition, for BCS class 3 and 4 substances, where the absorption process and/or intestinal first pass also restrict bioavailability, the possibility of excipients affecting transit time (efflux), transporter function and metabolic enzymes (typically CYP3A4) should be taken into consideration.

5.3 Excipients

The use of excipients in paediatric medicines is driven by functional requirements and should be justified through a risk-based assessment, taking into account factors such as the paediatric age group, frequency of dosing and duration of treatment.

The added challenge for paediatric medicines compared to adult medicines is that excipients may lead to adverse reactions in children that are not experienced by adults or are not seen to the same extent. Reviews of the literature on adverse reactions attributed to excipients show that the available data on excipient safety are limited in quantity and variable in quality.

Major problems with excipients in paediatric medicines, especially when used to treat infants and neonates, have been reported (21), e.g. medicines with benzyl alcohol, azo-dyes, propylene glycol, ethanol and propyl paraben. A study on the exposure to benzyl alcohol and propylene glycol of neonates receiving parenteral medication demonstrated a potential risk of toxic doses, especially for neonates receiving continuous infusion (22). The toxicity of excipients to newborns and infants can be explained by factors related to their physiological and metabolic development (2). Information on the safety of some excipients may be found, for example, in reviews published by the American Academy of Pediatrics (23). Alternative sources of information should also be consulted, e.g. the WHO Technical Report Series on Evaluation of certain food additives (24).

In the development of paediatric medicines, the number of excipients and their quantity in a formulation should be the minimum required to ensure an appropriate

product with respect to performance, stability, palatability, microbial control, dose uniformity and other considerations necessary to support product quality. Risks for adverse reactions are mostly associated with excipients used for liquid dosage forms.

In the choice of excipients consideration should be given to:

- the safety profile of the excipient for children of the target age groups;
- the route of administration;
- the single and daily dose of the excipient;
- duration of the treatment;
- acceptability for the intended paediatric population;
- potential alternatives;
- regulatory status in the intended market.

Potential alternatives to excipients which pose a significant risk to children should always be considered. Another dosage form or even a different route of administration might be necessary to avoid significant risk. Although well-known excipients with well-defined safety profiles are preferred, new excipients cannot be excluded. Novel excipients should only be used when their safety, quality and appropriateness for use in children have been established. It may also be necessary to look at alternative excipients because of different cultural attitudes or for religious reasons, e.g. the use of gelatin may not be acceptable for all patients.

5.4 Colouring agents

The use of colouring agents in paediatric medicines is generally discouraged, in particular in medicines for infants and young children. Their use may, however, be justified in certain cases, e.g. to avoid accidental dosing errors in connection with medicines produced in several strengths. In this case, a solid dosage form of the types mentioned in section 3 may be preferred because size, shape and embossing can facilitate identification of different strengths of the preparation.

Some colouring agents used in paediatric medicines have been associated with hypersensitivity (25). The number of colouring agents that are acceptable for use in medicines is limited. Azo-dyes should be avoided in children's medicines and attention should be paid to the risk of allergic reactions associated with natural colourants (26).

5.5 Antimicrobial preservatives

FPPs may require antimicrobial preservatives to avoid microbial proliferation during storage, in particular under in-use conditions. Preservatives are needed in particular for aqueous multidose preparations and semi-solid preparations and may also be needed for other aqueous preparations. Usually solid dosage forms do not require preservatives.

Preservatives may have a potential to cause adverse reactions, in particular in infants and neonates, and should be avoided where possible. Furthermore, complex preservative systems should be avoided.

Ophthalmic preparations without preservatives are strongly recommended for use in children, especially neonates. Therefore, preparations without preservatives should be developed wherever possible in order to cater for the diversity of patients' needs. When preservatives are required, their concentration should be the minimum level consistent with satisfactory antimicrobial function in each individual preparation and a thorough justification for the choice of the preservative should be established. Ophthalmic preparations without any mercury-containing preservatives, e.g. thiomersal, should also be considered. Further details on this topic are provided in a public statement (27) published on the EMA web site.

5.6 Sweetening agents

Oral paediatric medicines often use sweetening agents to make them palatable. These may be either cariogenic or non-cariogenic sweeteners. In addition to the considerations listed in section 4.3, attention should be paid to:

- safety of the sweetening agent in relation to specific conditions of the child, e.g. diabetes, fructose intolerance, and avoiding use of aspartame in patients with phenylketonuria;
- the laxative effect of poorly absorbed or non-digestible sweeteners in high concentrations;
- the severity of the condition to be treated, i.e. are potential adverse reactions of the sweetening agent secondary to patient adherence?

5.7 Taste masking

Taste masking in medicines for oral use or for use in the mouth is often needed to improve palatability of the medicine. Children have a well-developed sensory system for detecting tastes, smells and chemical irritants. They are able to recognize sweetness and saltiness from an early stage and are also able to recognize a sweet taste in oral liquids and the degree of sweetness (28). Children seem to prefer sweeter tastes than adults do. The unpleasant taste of an API, e.g. bitterness or a metallic taste, is, therefore, often masked in an oral liquid by the use of sweetening agents and flavours. Additional use of colouring agents that match the flavour is discouraged (see section 4.4) unless this is necessary to disguise an unpleasant colour related to the API. Some successful approaches to taste masking are discussed by Ernest et al. (7).

A child's preference for particular flavours is determined by individual experiences and culture. The target for taste masking need not necessarily be good-tasting medicines; it should simply be a taste that is acceptable in as many countries as possible taking into account cultural differences.

An example of a “qualitative evaluation of the taste by a taste panel” for zinc formulations can be found in the United Nations Children’s Fund (UNICEF)/WHO publication on production of zinc formulations (29, 30).

Consideration should be given to the items listed in sections 4.3 and 4.6.

Taste masking for orodispersible tablets and chewable tablets is in principle similar to taste masking for oral liquids. Non-cariogenic sweeteners and flavours are preferred.

5.8 Solubility enhancers

The aqueous solubility of the API may limit the concentration achievable in formulated solutions and, hence, the desirable dose volume. In many cases an acceptable solution requires solubility enhancing methods, e.g. use of non-ionic surfactants and of co-solvents such as glycerol, liquid macrogols and ethanol. If solubility enhancers are to be used, consideration should be given to the safety of both the agent and the formulation, for example, the risk of irritation and damage of intestinal tissues in neonates caused by hyperosmolality or other local toxicity. Risks associated with the use of solubility enhancers are higher when they are included in parenteral preparations than when used in oral preparations.

Ethanol, especially in large amounts, should not be administered to children (aged 0–17 years) through FPPs without a clear demonstration of benefit.

Although it is recognized that ethanol may not always be eliminated from FPPs, and replacements may raise other issues, the smallest possible amount should be used. When ethanol is used, adequate development data demonstrating that the lowest possible concentration of ethanol is used should be established.

Children, especially under the age of 6 years, are more vulnerable to the effects of ethanol. Adverse effects on the central nervous system are already evident at blood ethanol concentrations of 10 mg/100 ml in children. Higher peak ethanol blood concentrations are also observed in children than in adults for a similar intake. Chronic exposure to ethanol (> 1 week), even to small doses, through FPPs is, in principle, contraindicated in children aged less than 6 years and should be limited to 2 weeks in children aged over 6 years, if a positive risk–benefit balance is not demonstrated. Toxic effects on brain maturation in young children are highly probable and also supported by non-clinical data. Additionally, chronic exposure has been shown to be linked to ethanol dependence in adults and adolescents.

6. Oral administration

The oral route is the preferred and most appropriate route of administration to paediatric patients. This route is generally acceptable in all age groups if the medicine is administered in a suitable dosage form, e.g. in liquid form for children in the youngest

age groups who have difficulty in swallowing solid dosage forms. Strictly speaking, the choice of dosage form for oral administration depends on the gut function and, thus, on both age and clinical condition.

Consideration should be given to the effects of increased gastric pH and intestinal mobility at birth and in early infancy (2). In addition, gastric emptying of sick newborns is most erratic and can be delayed. Further information can be found in an EMA guideline on medicines for term and preterm neonates (31).

Mixing oral dosage forms with food or a beverage is not recommended, but may be performed to enhance compliance (see section 2.2). Potential effects of foods on bioavailability should be considered. When recommending mixing medicines with food, attention should be paid to the effect on the taste, as an unpleasant taste of medicine may cause aversion in children.

6.1 Oral liquid preparations

Oral liquid preparations include aqueous solutions, suspensions, emulsions and syrups. They are most appropriate for children in the youngest age groups who are unable to swallow solid dosage forms. The advantage of oral liquid preparations is that variable dose volumes can be measured and administered. The need for stabilizing agents, e.g. antimicrobial preservatives, is a major drawback as is the potential chemical instability, which may lead to a requirement for controlled storage conditions during distribution and use. Oral liquid preparations are less transportable than solid-dose preparations because of their relatively high bulk volume.

The dose volume is important for the acceptability of the preparation. High-dose volumes pose a risk of incomplete ingestion and, thus, underdosage. Efforts should, therefore, be made during pharmaceutical development to minimize the dose volume while recognizing the need to ensure accurate measurements of the dose over the anticipated range. Typical target dose volumes are 5 ml or less for children under 5 years and 10 ml or less for children of 5 years and older (32). There is some uncertainty about these limits because the more palatable the formulation, the higher the dose volume that will be accepted by the child. Target volumes and electrolyte contents are critical for neonates, especially in cases of immature renal function.

Oral liquid preparations may be supplied in multidose containers or single-dose containers. Usually, both forms require antimicrobial preservatives. Special attention has to be paid to the in-use stability of multidose preparations, both microbial and physicochemical.

Multidose preparations should be packaged together with an appropriate dosing device. The correct graduation of the device and the accuracy of the volumes measured must be checked by the manufacturer. Generally, oral syringes are preferable because of the flexibility in dose measurement and superior accuracy compared to other devices such as graduated pipettes or plastic spoons. The accuracy in measuring and delivering

a volume of liquid is influenced by the liquid's physical characteristics, especially its viscosity.

The risks associated with incorrect dosing should be considered. If correct dosing is critical, a single-dose preparation, e.g. a pre-filled oral syringe, should be considered.

Drops

Some liquids are administered as drops in small volumes using a dropper or a graduated pipette to measure a volume to be dissolved or dispersed in water or another diluent before the dose is swallowed. The use of this dosage form should be evaluated using a risk-based approach to ensure it is suitable given the medicine's potency and side-effect profile and the potential for dosing errors. The in-use performance of the dose-measuring device is critical for this dosage form.

Oral suspensions

Formulation of an oral suspension may be dictated by the aqueous solubility of the API and the balance between the dose of API and the dose volume. In certain cases, the unpleasant taste of an API can be reduced by choosing the suspended form.

Oral suspensions must be shaken before use to ensure a homogeneous liquid when the dose volume is measured. There might in some instances be a significant risk of dosing errors due to sedimentation or caking of the suspension during storage; therefore, resuspendability should be a stability parameter. The control strategy for oral suspensions includes dissolution testing (18) unless otherwise justified.

Powders and granules for reconstitution

Solid preparations for reconstitution as solutions or suspensions should be considered, especially when the liquid preparation has a short shelf-life due to instability (chemical, physical or microbiological). Powders and granules for reconstitution are produced as single-dose sachets or multidose preparations, usually provided in containers that can hold the reconstituted multidose preparation. The liquid vehicle can be provided together with the dry preparation, especially when the product is intended for markets where access to clean water may be difficult. Alternatively, manufacturers can recommend on the product labels and summary of product characteristics (SmPCs) how to reconstitute the product, e.g. with boiled and cooled water.

To ensure their proper use, the solids must be easily wetted and dispersed or dissolved within a short time once the vehicle is added.

The major drawbacks of this type of formulation are the bulk volume of the preparation, i.e. it is less transportable, and the in-use microbial stability of multidose preparations, which may require use of antimicrobial agents. For these reasons, single-dose preparations of the flexible types mentioned in section 3.1 are preferable.

6.2 Administration through feeding tubes

For neonates and seriously ill infants, enteral administration of liquids via feeding tubes is used. Hence the preparation will not be subject to the normal effects of saliva and/or gastric juice, which may affect its bioavailability.

Dosing accuracy should be considered, taking into account the ease of transfer along the feeding tube (including viscosity, particle size and amount of suspended components), potential absorption of the API into the tube material and rinsing by flushing of the tube. The rinsing volume should be appropriate to the target age group and an acceptable fluid intake.

These considerations should be highlighted in the SmPCs.

6.3 Oral solid dosage forms

Oral solid dosage forms include a variety of final forms from powders to coated tablets intended to be swallowed directly or after application to the mouth (chewable tablets, orally dissolving tablets or orodispersible tablets). Some are intended for swallowing after dissolution, dispersion in water or other suitable liquids. Their advantages over oral liquid preparations are improved stability, good dosage uniformity and options for different doses. The ease of administration depends on the child and the particular dosage form. These forms are convenient for packaging and ease of transport.

While powders and multiparticulate preparations mixed with food or beverages may be acceptable from the moment when the infant is able to accept solid food, i.e. about 6 months, there are uncertainties with regard to the age at which intact tablets and capsules are acceptable. It has been thought generally that even small tablets and capsules to be taken whole are not acceptable for children below the age of 6 years. However, no good scientific evidence exists to support this notion. Recent preliminary evidence indicates that mini-tablets (with a diameter of less than 4 mm) may be acceptable even by the majority of small children (2–4 years old) (33).

Powders and multiparticulate preparations

Powders and multiparticulates are provided in sachets or in hard capsules that allow the contents to be taken directly or after manipulation, e.g. following preparation of oral liquids or to be sprinkled on to food or liquids.

Multiparticulate preparations are granules, rounded granules of uniform size (often called pellets) and mini-tablets. Pellets are often prepared by extrusion/spheronization technology, which produces uniform particles within the size range 0.5–2 mm. Mini-tablets are prepared by compression into units with a diameter of not more than 4 mm. Especially when only a portion of the provided dose is administered, the particle size distribution of the API may be critical to dosing accuracy. Control of dose uniformity should be performed on a level corresponding to the dose to be taken by the target age group.

Multiparticulate preparations offer the same advantages as conventional tablets and capsules with regard to the use of excipients, opportunities for taste masking (e.g. by coating), stability and opportunities for modifying the release profile. Furthermore, they possess great flexibility. An age-related dose may be obtained by taking an appropriate number of pellets or mini-tablets. A counting device may be necessary when a large number of pellets or minitables is required. In addition, pellets and mini-tablets are suited for the platform technology mentioned in section 3.2.

Immediate-release tablets

Conventional tablets are either uncoated, film-coated or sugar-coated and are intended for immediate disintegration, release and absorption when swallowed. The coating may cover an unpleasant taste and smell and will, in general, improve palatability. Film-coating is preferable because sugar-coated tablets resemble sweets or candies and hence may be too attractive to the child. It is critical to differentiate the appearance of tablet packs from that of confectionery packs.

Break-marks intended to enable accurate subdivision of the tablet to provide doses of less than one tablet should be proven to result in parts that comply with the requirements for uniformity of mass or uniformity of content, as appropriate. The decision whether or not to provide scored tablets will depend on a risk analysis, taking into account the safety and dose of the API. A suitable test is provided in the monograph on tablets in *The International Pharmacopoeia* (34). It is preferable that the single part of the broken tablet contains the amount of API suited to the youngest intended age group. Specially designed tablets and tablet punches may be needed.

Caregivers often crush tablets to increase user-friendliness and adherence. Crushing may, however, affect the bioavailability of some medicines. The effect of crushing of tablets should be investigated by the manufacturer and this information should be provided in the patient information leaflet.

Tablets should not be crushed unless instructions allowing crushing are provided on the label by the manufacturer. Generally a multiparticulate formulation supplied in sachets, hard capsules or blister packs is preferred.

Chewable tablets

Chewable tablets are intended to be chewed and swallowed. They should possess good organoleptic properties including a good mouth feel, which is influenced by the solubility, particle size and shape of the API, and they should not leave a bitter or unpleasant aftertaste. They are usually formulated with a high content of a water-soluble sweetener, such as mannitol, which provides a sweet, cooling taste, and microcrystalline cellulose, which assists in obtaining a good mouth feel and reduces grittiness. Other sweetening agents such as sorbitol and xylitol suitable for direct compression are also used.

A potential problem with chewable tablets is that they may be swallowed by a patient before being properly chewed or without being chewed at all. It is, therefore,

strongly recommended that chewable tablets are formulated so that they may be swallowed whole and, thus, labelled as “tablets that may be chewed or swallowed whole”, or “tablets that may be chewed, swallowed or crushed and mixed with food or liquid”.

It is a consequence of the above that tablets that may be chewed or swallowed whole should meet the quality requirements for conventional tablets, including dissolution testing. Where applicable, dissolution test conditions should be the same as used for conventional tablets of the same API, but because of their non-disintegrating nature it may be necessary to alter the test conditions (18).

Effervescent dosage forms

Effervescent dosage forms are tablets, granules or powders that are dissolved in water prior to administration. The use of these dosage forms usually requires a relatively large volume of water, the intake of which may be problematic for children. It is helpful when an indication of the minimum volume of water is given on the label. Furthermore, the label should give instructions that the solution is not to be drunk before effervescence has subsided, in order to minimize ingestion of hydrogen carbonate. Effervescent tablets require continuous attention to levels of moisture and humidity during manufacture, packaging and storage.

The drawbacks of effervescent dosage forms are the need for clean water for dissolution and the ingestion of potassium or sodium, which may make them unsuitable for patients with renal insufficiency.

Dispersible and soluble tablets

Dispersible and soluble tablets are intended to be used in the same way as effervescent tablets. Their advantage is that problems with hydrogen carbonate, potassium and sodium are avoided. For the convenience of users, the formulations should disintegrate or dissolve within a short time of being added to water. It is helpful when an indication of the minimum volume of water is provided on the label.

Dispersible and soluble tablets are flexible dosage forms, the formulation of which may be suited for several water-soluble APIs (see section 3.1).

Sustained-release formulations

Sustained-release formulations are designed to slow the rate of release of the API in the gastrointestinal fluids. They may be provided in a variety of formulations, e.g. as multiparticulate solids provided with a barrier coating, in sachets, hard capsules or in quickly disintegrating tablets, coated tablets and matrix tablets. Among the advantages of the sustained-release design is the reduced dosing frequency compared to conventional formulations of the same API, a feature which may improve adherence (see section 2.3). Not all APIs can be formulated as sustained-release products. This will also depend on other factors such as aqueous solubility, intestinal permeability and plasma elimination half-life, which may differ between children and adults.

In the development of sustained-release formulations for paediatric use, special attention must be given to the physiological conditions of the child to be treated and their variability, e.g. gastric pH and emptying rate and intestinal mobility.

The majority of sustained-release formulations, especially coated tablets and matrix tablets, must not be broken or chewed and some will not withstand being mixed with food or a beverage. It is, therefore vital that clear instructions on the proper use of the formulation are included on the label.

Capsules

Capsule formulations are provided either as soft capsules, usually with a liquid or semi-solid content or as hard capsules containing powder or a multiparticulate formulation.

Capsules may be taken whole. The limitations mentioned for tablets apply with regard to the ability of the child to swallow them (see introduction to section 5.3). Hard capsules may be opened and their contents taken as such or taken after mixing with food or sprinkling on to food, but this is not always appropriate.

Instructions on the proper use of a capsule formulation should be provided on the label, e.g. whether the capsule has to be taken whole or whether the capsule contents can be mixed with food to facilitate intake and improve palatability.

Orodispersible dosage forms

Orodispersible dosage forms are orodispersible tablets, oral lyophilisates and thin films, to be placed on the tongue where they disperse rapidly into small-sized particles or “melt” by dissolution in the saliva, after which the dose is swallowed.

Orodispersible tablets designed to disintegrate rapidly are prepared by compression of a formulation containing, for example, mannitol, a superdisintegrant, and a flavouring agent. The amount of API that can be incorporated depends on its physical properties. The product may be moisture-sensitive.

Orodispersible tablets are flexible dosage forms (see section 3.1), particularly well-suited for highly water-soluble APIs.

Oral lyophilisates are prepared by freeze-drying of aqueous liquids into porous units shaped like tablets. Typical excipients are gelatin or alginate, which act as structure-forming agents, and mannitol, which facilitates formation of the porous structure and contributes to palatability. Instead of mannitol, sorbitol may be used as a crystallization inhibitor. The amount of water-soluble API to be incorporated is limited (35). Oral lyophilisates are sensitive to moisture and require a vapour-tight package.

Thin, flat films (wafers) to be placed in the oral cavity are prepared by casting water-soluble polymers containing the API in dissolved or dispersed form. The amount of dissolved API that can be incorporated is limited. The release profile depends on the polymer, film thickness and API solubility. The so-called flash-release wafers may have dissolution times of less than 30 seconds.

Orodispersible and orosoluble dosage forms are attractive for several reasons. They may be acceptable to the same age groups as liquid preparations, and it is possible for children who cannot swallow a whole tablet to take an orodispersible dosage form. In some situations, especially with younger children, the orodispersible dosage form may need to be dissolved in a small volume of liquid prior to administration.

Orodispersible dosage forms are intended for systemic effect after being swallowed but absorption may also take place in the mouth and pharynx. Taste masking may be necessary using water-soluble sweeteners and flavourings.

7. Rectal administration

Rectal administration is an important route that can be used for both local (e.g. laxative and anti-inflammatory) and systemic effects (e.g. antipyretic and anticonvulsive) in all age groups. This route of administration is especially valuable when oral administration is not possible because of the condition of the child and palatability issues. In certain cases it is possible to obtain immediate systemic effect by rectal administration of solutions. There is, however, limited absorption and bioavailability for many APIs. Erratic absorption due to faecal contents in the rectum may unpredictably delay absorption.

Dosage forms for rectal administration are primarily suppositories, rectal capsules and rectal liquids (enemas). Other dosage forms are available, e.g. rectal foams provided in pressurized containers.

When suppositories and rectal capsules are administered to paediatric patients there is a risk of premature expulsion, especially when the dosage form constituents have an irritating effect. Rectal dosage forms should be used with extreme caution in premature infants, as they can tear very delicate tissues and, thus, introduce infection.

Adherence for rectal preparations may be lower than for oral dosage forms. There are barriers to rectal administration for both caregivers and patients in some regions and cultures. Generally their acceptability among children of any age is poor.

7.1 Suppositories

Suppositories for use in paediatric patients must be tailored to the age or size of the child. Cutting of suppositories into halves should be avoided unless they are designed to be cut. The majority of suppositories contain APIs as solid particles, which may be unevenly distributed in the suppository base as a result of the manufacturing technique of moulding a molten formulation. However, it is also possible to prepare suppositories which can be cut in smaller portions, ensuring delivery of an appropriate dose. Information on acceptability of cutting suppositories should be provided. When designed to be cut, information on the technique should be provided in the patient leaflet.

Two types of suppository base are available: one is insoluble in water, e.g. hard fat, which melts below body temperature. With suppository melt formulations, special

consideration has to be given to storage temperature. The other type of suppository is soluble or miscible with water, e.g. macrogols, which are dissolved in or mixed with the rectal liquid. Both types may be irritants.

7.2 Rectal liquids (enemas)

Rectal liquids are solutions, suspensions or emulsions based on water or vegetable oil. Any volume to be administered should be appropriate to the size of the child. For systemic therapy, the volume to be administered should be as small as possible to achieve accurate delivery, good absorption and to avoid irritation. Volumes of 1–5 ml may be acceptable.

The rectal tube should be of a length appropriate to the size of the child and should not cause injury. Use of pre-filled syringes equipped with a rectal tube facilitates individual dosing and may reduce the need for several strengths of the formulation.

Formulation of aqueous rectal liquids is similar to the formulation of other aqueous liquids regarding use of stabilizing agents, including surfactants and antimicrobial agents. Non-ionic surfactants are preferred because ionic surfactants are frequently irritating to the rectal mucosa. The need for stabilizing agents, in particular antimicrobial agents, may be reduced by the formulation of rectal tablets to be dispersed or dissolved in water immediately before administration.

8. Parenteral administration

Parenteral administration by the intravenous route is preferred for seriously ill children and for clinically unstable term and preterm neonates (in developed country settings). Some parenteral preparations are administered by the subcutaneous and intramuscular routes. The limited muscle mass of newborns and, in particular of preterm infants, constrains the use of intramuscular injections. Other routes of administration, e.g. intraosseous, are used in emergency cases.

Most children have a fear of injection needles. Possible alternatives, especially suited for children undergoing frequent or long-duration treatment, such as needle-free injection devices (jet injectors), that drive small droplets through the skin by high pressure, could be considered, e.g. for subcutaneous administration. However, experience of their use in paediatric populations, especially in smaller children is limited.

Repeated injections should be avoided for children unless they can be given intravenously via catheter or injection ports that can remain in place for the length of the treatment. Reducing the number of injections by formulation of sustained-release preparations requires consideration of increased blood perfusion in children, usually increasing absorption from tissue depots. The clinical need to limit fluid uptake, especially in very young children, must also be taken into account.

Age- and weight-related preparations (injection volume and strength) are preferred in order to provide an acceptable injection volume, and to avoid dosing errors

due to improper use of multidose preparations and errors in calculation of the dilution required to obtain measurable volumes. It is helpful to state on the label the size of syringe that permits accurate administration.

The size of the presentation should not allow significant overdosage if the dose or volume is miscalculated. In general the volume in the vial should be no greater than 10 times the smallest dose to be measured.

8.1 Formulation

Aqueous preparations (solutions or suspensions) must be adapted to the physiological conditions on the application site. The tolerances for deviations in pH and osmolality are dependent on the route of administration. In particular, subcutaneous administration is highly sensitive because dilution of the injected volume and its escape from the injection site proceed slowly. Hyperosmolar injections and injections with extreme pH may cause pain and irritate peripheral veins.

Formulations for neonatal patients are usually aqueous solutions intended for intravenous administration. Target volumes and electrolyte contents are important for all paediatric patients; however, these are critical for neonates (19).

It is crucial to consider the safety profile of each excipient and its suitability for the intended use (see section 4.3).

Attention should be paid to the potential adsorption of the API on to the surfaces of plastic containers and catheters, and to leaching of plasticizers from containers and catheters to the parenteral preparation.

Some APIs are presented as powders or lyophilisates to be reconstituted before administration. It is important that clear instructions on the reconstitution and information on storage conditions and duration appear on the label or product information.

8.2 Additional points to consider for parenteral preparations

- There should be a minimal need for complex calculations for prescribing, dispensing and administration (e.g. dose in micrograms/kg/hour prescribed to be converted to volume per hour administered; conversion between mmol prescribed and mg on the label; conversion between mg prescribed and percentage concentration on the label; and decimal points).
- The need for additional steps in the preparation of the product for administration should be minimized, for example, by developing ready-to-use preparations.
- Measurement of volumes smaller than 0.1 ml should not be required. Dose volumes in hundredths of a millilitre should be avoided. Tables should be included in the product information clearly stating the dose and the volume to be measured, and how this can be achieved safely and accurately.

- Miscalculation can lead to overdose and the amount of the API in the presentation should not allow administration of a critical overdose to the smallest patient for whom the presentation is intended.
- Using several vials per dose or large vials that may contain several doses should be avoided if possible.
- Other methods of preventing overdose of critical medicines can be explored and presented for consideration, e.g. tables of weight, dose (mass) and volume (ml) of preparation required.
- Safety measures and restrictions on administration via central or peripheral cannula should be provided, including advice on maximum and minimum dilutions for safe administration.
- Consideration should be given to the contribution to the child's fluid and electrolyte balance due to the medicine administration volume and/or electrolyte content.
- Compatibility with other medicines that are part of a standard care plan should be investigated.
- Information on pH of the FPP needs to be provided in the product information.

9. Dermal and transdermal administration

Preparations for dermal (or cutaneous) administration include liquid preparations (lotions and shampoos), semi-solid preparations (ointments and creams) and solid preparations (powders). They are used to obtain local effects.

Unintended systemic absorption through the dermis is a potential risk with many APIs. The stratum corneum is deficient in preterm neonates. Children have a lower volume of distribution per unit area of skin.

Depending on the dosage form, various excipients are needed. The safety profile of each must be considered (see section 4.3) including the risk of sensitization of the skin. Preparations containing ethanol should be avoided in very young children because ethanol may dehydrate the skin and cause pain.

Liquid suspensions, semi-solid preparations and patches should be subject to dissolution testing (18).

9.1 Transdermal patches

Transdermal patches are used for systemic delivery of APIs which are capable of diffusion through the stratum corneum and are therapeutically active at the low plasma concentrations that can be achieved. The manufacture of transdermal patches of the “drug-in-adhesive” type is now well developed and less problematic than the earlier

“drug-in-reservoir” type; the API is dispersed in a suitable polymeric adhesive to be fixed in a thin layer on a backing and covered by a removable liner.

The size and shape of a transdermal patch should be adapted to fit the child's body. It should stick firmly to the skin and not be too difficult to remove. Application sites which cannot easily be reached by the child should be chosen to avoid removal of the patch by the child. The risk of deliberate removal and its consequences for therapy must be considered. The increased systemic absorption through the skin, for the reasons mentioned above, may increase the systemic delivery from transdermal patches, in particular in newborns and young infants.

When designed to be cut, information on the cutting technique should be provided in the patient leaflet and facilitated by the presence of cutting lines to ensure equal division. Reservoir systems should never be cut.

Adhesives should have a low allergenic potential to avoid irritation and infection. Local tolerance and acceptability should be tested.

10. Inhalations

Pulmonary administration of medicines by inhalation has traditionally been used to obtain a local effect. This route of administration also has a potential for systemic delivery. Preparations for inhalation include liquids for nebulization, pressurized metered dose inhalers (MDIs) and dry powder inhalers (DPIs).

The implications of the physiology of children of different ages and their ability to use the devices correctly should be considered in the development of paediatric inhalations (8). Depending on their age, children may have more or less difficulty with some of the devices. Problems with the coordination of the inhalation for MDIs and the ability to inhale strongly enough for DPIs determine the effectiveness of getting the medicine into the lung.

The total lung deposition is important for the clinical efficacy of preparations for inhalation. Generally it is affected by the formulation and delivery device controlling size distribution of the aerosol and patient-related factors such as the current disease state. The diameter of the airways is smaller in children than in adults; hence deposition by impact in the upper and central airways may be significantly higher in children (36). The particle size of the aerosol produced by the delivery device needs to be explored during development.

Nebulized liquids are potentially suitable for young children who cannot use MDIs and DPIs. Their use, however, requires nebulizing devices and access to electricity.

MDIs may be suitable for children from birth when combined with a spacer. A spacer eliminates the need for coordinating the MDI actuation and the start of inhalation. For children younger than 2–3 years a facemask is also required. This can be replaced by a mouthpiece when the child is able to manage the system.

DPIs may be used for children from the age of 4–5 years, as minimum inspiratory flow is required. DPIs and MDIs are preferred for older children because of their portability and convenience.

11. Packaging and labelling

Container-closure systems for paediatric medicines are designed and constructed from materials meeting relevant regulatory requirements, and taking into account the stability of the medicine during transport, storage and use. In addition they are designed to ensure that they:

- permit accurate dosing and convenient administration;
- are robust and convenient for the supply chain, i.e. transportable;
- are tailored to the target age group;
- contribute to in-use stability;
- provide appropriate information on the use of the medicine.

In cases where the paediatric medicine is significantly different from a similar adult medicine, it would be important to have noticeably different product packaging for the two products. It is necessary that consideration be given to whether the medicine is to be packed in a child-resistant container, i.e. a packaging that is difficult for young children to open, but not unduly difficult for adults to open properly.

Self-administration of medicine by schoolchildren and adolescents is facilitated when:

- the medicine is easy to use;
- separation of the day dose pack is facilitated; this should be easily carried by the patient in his or her bag;
- clear instructions for use are contained with the medicine.

Adequate information about the medicine and how to use it is important. Information about the dosage should be clearly spelt out, e.g. as milligrams per weight. Specific instructions about how to measure and administer a precise dose should be provided. Drawings or pictograms showing time, method and route of administration are strongly recommended.

References

1. *Provision by health-care professionals of patient-specific preparations for children that are not available as authorized products – points to consider*. Geneva, World Health Organization, 2010 (working document QAS/11.399/Rev. 1).
2. Kearns GL et al. Developmental pharmacology – drug disposition, action and therapy in infants and children. *New England Journal of Medicine*, 2003, 349:1157–1167.

3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Clinical investigation of medicinal products in the paediatric population. Implementation: EU, MHLW, FDA. Adopted by CPMP, July 2000, issued as CPMP/ICH/2711/99; adopted 15 December 2000, PMSB/ELD Notification No. 1334. *Federal Register*, 12 April 2000, 65(71): 19777–19781.
4. *WHO draft guideline on quality risk management*. Geneva, World Health Organization, 2010 (working document QAS/10.376).
5. *Pharmaceutical development for multisource (generic) pharmaceutical products*. Geneva, World Health Organization, 2010 (working document QAS/08.251/Rev.1).
6. Committee for Medicinal Products for Human Use (CHMP). *Reflection paper: formulations of choice for the paediatric population*. London, EMEA, 2006 (EMA/CHMP/PEG/196810/2005).
7. Ernest TB et al. Developing paediatric medicines: identifying the needs and recognizing the challenges. *Journal of Pharmacy and Pharmacology*, 2007, 59: 1043–1055.
8. Krause J, Breitzkreutz J. Improving drug delivery in paediatric medicine. *Pharmaceutical Medicine*, 2008, 22: 41–50.
9. Zhao N et al. Tablet splitting: product quality assessment of metoprolol succinate extended release tablets. *International Journal of Pharmaceutics*, 2010, 401: 25–31.
10. Allen LV. Dosage form design and development. *Clinical Therapeutics*, 2008, 30: 2102–2111.
11. Guidelines for registration of fixed-dose combination medicinal products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report*. Geneva, World Health Organization, 2005, Annex 5 (WHO Technical Report Series, No. 929; https://iris.who.int/bitstream/handle/10665/43157/WHO_TRS_929_eng.pdf?sequence=1&isAllowed=y).
12. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Impurities in new drug substances. Implementation: EU, MHLW, FDA. Adopted by CPMP, October 2006, issued as CPMP/ICH/142/95; adopted 4 December 2006, PFSB/ELD Notification No. 1204001. *Federal Register*, June 2008.
13. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Impurities in new drug products. Implementation: EU, MHLW, FDA. Adopted by CPMP, June 2006, issued as CPMP/ICH/2738/99; adopted 3 July 2006, PFSB/ELD Notification No. 0703004. *Federal Register*, 2003, 68: 64628–64629 with the revised attachment 2.
14. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Impurities: guideline for residual solvents. Implementation: EU, MHLW, FDA. Core Guideline adopted by CPMP, September 1997, issued as CPMP/ICH/283/95; Core Guideline adopted March 1998, PMSB/ELD Notification No. 307; Core Guideline published in the *Federal Register*, 24 December 1997, 62(247):67377; Q3C Tables and list published in *Federal Register*, 2003, 68: 64352–64353.
15. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). *Guideline on the limits of genotoxic impurities*. London, 28 June 2006 (CPMP/SWP/51199/02, EMA/CHMP/QWP/251344/2006).
16. European Medicines Agency. *Questions and answers on the “Guideline on the limits of genotoxic impurities”*. London, EMEA, 2010 (EMA/CHMP/SWP/431994/2007).
17. European Medicines Agency. *Guideline on the specification limits for residues of metal catalysts or metal reagents*. London, 21 February 2008 (EMA/CHMP/SWP/QWP/4446/2000).

18. Siewert M et al. FIP/AAPS guidelines to dissolution/in vitro release testing of novel/special dosage forms. *AAPS PharmSciTech*, 2003, 4:Article 7 (<http://www.aapspharmscitech.org/view.asp?art=pt040107>).
19. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report*. Geneva, World Health Organization 2006, Annex 7 (WHO Technical Report Series, No. 937; https://apps.who.int/iris/bitstream/handle/10665/43443/WHO_TRS_937_eng.pdf?sequence=1).
20. Proposal to waive in vivo bioequivalence requirements for WHO Model List of essential medicines immediate-release, solid dosage forms. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report*. Geneva, World Health Organization, 2006, Annex 8 (WHO Technical Report Series, No. 937; https://apps.who.int/iris/bitstream/handle/10665/43443/WHO_TRS_937_eng.pdf?sequence=1).
21. Breitkreutz J, Boos J. Paediatric and geriatric drug delivery. *Expert Opinion on Drug Delivery*, 2007, 4: 37–45.
22. Shehab N et al. Exposure to the pharmaceutical excipients benzyl alcohol and propylene glycol among critically ill neonates. *Pediatric Critical Care Medicine*, 2009, 10(2): 256–259.
23. American Academy of Pediatrics. “Inactive” ingredients in pharmaceutical products: update (subject review). *Pediatrics*, 1997, 99:268–278 (<http://www.pediatrics.org/cgi/content/full/99/2/268>).
24. WHO Technical Report Series on evaluation of certain food additives. *List of publications*.
25. Pollock I et al. Survey of colourings and preservatives in drugs. *BMJ*, 1989, 299: 649–651.
26. Pefferi G, Restani P. The safety of pharmaceutical excipients. *Il Farmaco*, 2003, 58: 541–550.
27. European Medicines Agency. *EMA Public Statement on antimicrobial preservatives in ophthalmic preparations for human use*. London, EMA, 2009 (EMA/622721/2009).
28. Mennella JA, Beauchamp GK. Optimizing oral medications for children. *Clinical Therapeutics*, 2008, 30: 2120–2132.
29. *Production of zinc tablets and zinc oral solutions: guidelines for programme managers and pharmaceutical manufacturers*, Annex 7. Geneva, World Health Organization, 2007.
30. Cram A et al. Challenges of developing palatable oral paediatric formulations. *International Journal of Pharmaceutics*, 2009, 365: 1–3.
31. Committee for Medicinal Products for Human Use. *Guideline on the investigation of medicinal products in the term and preterm neonate*. London, European Medicines Agency, 2007 (EMA/566810/2008).
32. Strickly RG et al. Paediatric drugs – a review of commercially available oral formulations. *Journal of Pharmaceutical Sciences* 2007, 97: 1731–1774.
33. Thomson SA et al. Mini-tablets: new modality to deliver medicines to preschool-aged children. *Paediatrics*, 2009, 123:e235–e238.
34. *The International Pharmacopoeia*, 4th ed. First and Second Supplements (available online and on CD-ROM). Geneva, World Health Organization, 2011.
35. Seager H. Drug-delivery products and the zydys fast-dissolving dosage form. *Journal of Pharmacy and Pharmacology*, 1998, 50: 375–382.
36. Dolovich M. Influence of inspiratory flow rate, particle size and airway caliber in aerosolized drug delivery to the lung. *Respiratory Care*, 2000, 45: 597–608.

Web sites

WHO World Health Organization: <http://www.who.int>

ICH International Conference on Harmonisation: <http://www.ich.org>

EMA European Medicines Agency: <http://www.ema.europa.eu>

2. Marketing authorization: quality

2.1 Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part

Annex 6, WHO Technical Report Series, 986, 2014

1. Introduction	66
1.1 Background	66
1.2 Objectives	66
1.3 Scope	67
1.4 General principles	67
1.5 Guidance on format	68
2. Glossary	69
3. Quality summaries	71
3.1 Module 2.3: Quality overall summary – product dossiers (QOS-PD)	71
4. Module 3: Quality	71
4.1 Table of contents of Module 3	71
4.2 Body of data	72
3.2.S Drug substance (or active pharmaceutical ingredient (API))	72
3.2.P Drug product (or finished pharmaceutical product (FPP)) (name, dosage form)	99
3.2.A Appendices	125
3.2.R Regional information	125
4.3 Literature references	127
References	127
Appendix 1 Recommendations for conducting and assessing comparative dissolution profiles	131

1. Introduction

1.1 Background

This document is technically and structurally inspired by the generic quality guidelines, WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*, published in WHO Technical Report Series, No. 970, Annex 4 (1). The resulting guidance document is proposed for wider use by national medicines regulatory authorities (NMRAs) throughout WHO regions.

Through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) process, considerable harmonization has been achieved on the organization of the Quality Module of registration documents with the issuance of the Common Technical Document (CTD) – Quality (ICH M4Q) guideline (2). This recommended format in the M4Q guideline for the quality information of registration applications has become widely accepted by regulatory authorities both within and beyond the ICH regions.

This document provides recommendations on the quality information for active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs) that should be submitted to NMRAs to support product dossiers (PDs).

Alternative approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. It is also important to note that the NMRAs may request information or material, or define conditions not specifically described in this guidance, in order to adequately assess the quality of a pharmaceutical product.

1.2 Objectives

These guidelines are intended to:

- assist applicants in the preparation of the *Quality Module* of PDs for multisource products by providing clear general guidance on the format of these dossiers;
- adopt the modular format of the *Common Technical Document – Quality (M4Q)* (2) as developed by ICH;
- provide guidance on the technical and other general data requirements.

These measures are intended to promote effective and efficient processes for the development of these PDs by applicants and the subsequent assessment procedures by NMRAs.

1.3 Scope

These guidelines apply to PDs for multisource pharmaceutical products containing existing APIs of synthetic or semi-synthetic origin. For the purposes of these guidelines, an existing API is one that has been previously approved through a finished product by a stringent regulatory authority (SRA)¹ or WHO. Fermentation, biological, biotechnological and herbal APIs are covered by other guidelines.

1.4 General principles

To facilitate the preparation of the PD, these guidelines are organized in accordance with the structure of the *Common Technical Document – Quality (M4Q) (2)* guideline, as developed by ICH.

The text of the M4Q (CTD-Q) guideline has been restated in these guidelines in bold text, verbatim, with minor modifications to accommodate WHO terminology and include certain text that would be appropriate for multisource pharmaceutical products, notably:

- “drug substance” is replaced with “active pharmaceutical ingredient” or “API”;
- “drug product” is replaced with “finished pharmaceutical product” or “FPP”;
- “application” is replaced with “product dossier” or “PD”;
- “combination product” is replaced with “fixed-dose combination” or “FDC”;
- “clinical batches” is replaced with “comparative bioavailability or biowaiver batches”.

Following the bold text of the M4Q (CTD-Q) guideline, additional guidance is provided in plain text to allow it to be easily distinguished from the ICH text and is included to further clarify the general expectations for the content of PDs. This approach is intended to facilitate the identification of the origin of the text in the guidelines (i.e. from ICH or additional information).

The content of these guidelines should be read in conjunction with relevant information provided in other existing NMRA guidelines, WHO guidelines and/or ICH reference documents and guidelines. The quality of existing APIs and corresponding

¹ Stringent regulatory authority (SRA): a regulatory authority which is: a member of the International Conference on Harmonisation (ICH) (as specified at www.ich.org); or an ICH observer, being the European Free Trade Association (EFTA), as represented by Swissmedic, and Health Canada (as may be updated from time to time); or a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

multisource products should not be inferior to that of new APIs and innovator FPPs. Therefore, the principles of the ICH guidelines that are referenced throughout this and other relevant guidelines may also equally apply to existing APIs and multisource products.

Scientific literature may be appropriate to fulfil the requirements for some of the information or parameters outlined in these guidelines (e.g. qualification of specified identified impurities). Furthermore, the requirements outlined in certain sections may not be applicable to the proposed API or FPP. In these situations, a summary and the full reference to the scientific literature should be provided or the non-applicability of the requested information should be clearly indicated as such with an accompanying explanatory note.

1.5 Guidance on format

Recommendations outlined in the WHO general filing guidelines: *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): preparation of product dossiers (PDs) in common technical document (CTD) format* (3) may be followed for the format and presentation of the PD, with the understanding that Module 1 contains regionally required information and therefore the required contents will vary depending on the NMRA to which the PD is filed.

There may be a number of instances where repeated sections can be considered appropriate. Whenever a section is repeated, it should be made clear what the section refers to by creating a distinguishing title in parentheses following the M4Q (CTD-Q) guideline heading, e.g. 3.2.S Drug substance (or API) (name, Manufacturer A).

The following are recommendations for the presentation of the information in the *Quality Module* for different scenarios that may be encountered.

- The *Open part* (non-proprietary information) of each APIMF² should always be included in its entirety in the PD, as an annex to 3.2.S.
- For an FPP containing more than one API: one complete “3.2.S” section should be provided for one API, *followed by* other complete “3.2.S” sections for each of the other APIs.
- For an API from multiple manufacturers: one complete “3.2.S” section should be provided for the API from one manufacturer, *followed by* other complete “3.2.S” sections for each of the other API manufacturers.
- For an FPP with multiple strengths (e.g. 10, 50, 100 mg): one complete “3.2.P” section should be provided with the information for the different strengths provided *within* the subsections.

² API master file. Note that other global terms include DMF (drug master file) and ASMF (active substance master file).

- For an FPP with multiple container-closure systems (e.g. bottles and unit dose blisters): one complete “3.2.P” section should be provided with the information for the different presentations provided *within* the subsections.
- For multiple FPPs (e.g. tablets and a parenteral product): a separate dossier is required for each FPP.
- For an FPP supplied with reconstitution diluent(s), one complete “3.2.P” section should be provided for the FPP, *followed by* the information on the diluent(s) in a separate part “3.2.P”, as appropriate.
- For a co-blistered FPP, one complete “3.2.P” section should be provided for each product.

2. Glossary

The definitions provided below apply to the words and phrases used in these guidelines. Although an effort has been made to use standard definitions as far as possible, they may have different meanings in other contexts and documents. The following definitions are provided to facilitate interpretation of the guidelines.

active pharmaceutical ingredient (API). Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form, and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body (4).

API starting material. A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house (5, 6).

applicant. The person or company who submits an application for marketing authorization of a new pharmaceutical product, an update to an existing marketing authorization or a variation to an existing market authorization (7).

BCS highly soluble. An API for which the highest dose recommended by WHO (if the API appears on the WHO Model List of essential medicines (EML)) or highest dose strength available on the market as an oral solid dosage form (if the API does not appear on the EML) is soluble in 250 ml or less of aqueous media over the pH range of 1.2–6.8 at 37 °C (8).

commitment batches. Production batches of an API or FPP for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application (9).

comparator product (reference product). A pharmaceutical product with which the generic product is intended to be interchangeable in clinical practice. The

comparator or reference product will normally be the innovator product for which efficacy, safety and quality have been established (8).

existing API. An API that is not considered a new active substance, that has been previously approved through a finished product by an SRA or WHO, but requires the filing of a dossier. This would include, for example, new PDs and variations to multisource products.

finished pharmaceutical product (FPP). A finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labelling (4).

innovator pharmaceutical product. Generally the pharmaceutical product that was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality (8).

intermediate. A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated (5).

manufacturer. A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals (10).

multisource (generic) pharmaceutical products. Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable (8).

national medicines regulatory authority (NMRA). The national authority responsible for the registration of and other regulatory activities concerning medical products, such as medicines, vaccines, blood products and medical devices.

officially recognized pharmacopoeia (or compendium). Those pharmacopoeias whose standards are officially recognized by an NMRA. These may be national, regional or international pharmacopoeias, at the discretion of the NMRA.

ongoing stability study. The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected retest period (or shelf-life) of the API, or confirm or extend the shelf-life of the FPP (9).

pilot-scale batch. A batch of an API or FPP manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger; unless otherwise adequately justified (9).

primary batch. A batch of an API or FPP used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf-life (9).

production batch. A batch of an API or FPP manufactured at production scale by using production equipment in a production facility as specified in the application (9).

3. Quality summaries

3.1 Module 2.3: Quality overall summary – product dossiers (QOS-PD)

The Quality overall summary (QOS) is a summary that follows the scope and the outline of the Body of data in Module 3. The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the CTD.

The QOS should include sufficient information from each section to provide the Quality assessor with an overview of Module 3. The QOS should also emphasize critical key parameters of the product and provide, for instance, justification in cases where guidelines were not followed. The QOS should include a discussion of key issues that integrates information from sections in the Quality Module and supporting information from other Modules (e.g. qualification of impurities via toxicological studies), including cross-referencing to volume and page number in other Modules.

The WHO *Quality overall summary – product dossiers (QOS-PD)* template or the QOS template associated with the intended NMRA, if available, should be completed for multisource pharmaceutical products containing APIs of synthetic or semi-synthetic origin (see 1.3 Scope for further clarification) and their corresponding FPPs. For the sake of simplicity, these guidelines will refer to the QOS-PD, which can be downloaded from the WHO website.

All sections and fields in the QOS-PD template that would be applicable should be completed. It is understood that certain sections and fields may not apply and should be indicated as such by entering “not applicable” in the appropriate area with an accompanying explanatory note.

The use of tables to summarize the information is encouraged, where possible. The tables included in the template may need to be expanded or duplicated (e.g. for multiple strengths), as necessary. These tables are included as illustrative examples of how to summarize information. Other approaches to summarize the information can be used if they fulfil the same purpose.

4. Module 3: Quality

4.1 Table of contents of Module 3

A table of contents for the filed product dossier should be provided.

4.2 Body of data

3.2.S Drug substance (or active pharmaceutical ingredient (API))

The NMRA, at its discretion, may accept API information in one or more of the following four options:

- Option 1: Confirmation of API prequalification document;
- Option 2: Certificate of suitability of the European Pharmacopoeia (CEP); or
- Option 3: API master file (APIMF) procedure; or
- Option 4: Full details in the PD.

The applicant should clearly indicate at the beginning of the API section (in the PD and in the QOS-PD) how the information on the API for each API manufacturer is being submitted. The API information submitted by the applicant/FPP manufacturer should include the following for each of the options used.

Option 1: Confirmation of API prequalification document

API prequalification is a procedure for manufacturers of APIs that are of interest to WHO. The procedure verifies both the quality of the API and that the API is manufactured in compliance with good manufacturing practices (GMP) (ICH Q7) (5). Complementary information regarding a prequalified API is provided on the Prequalification of Medicines website and in the Confirmation of Prequalification document (CPQ).

A complete copy of the Confirmation of API Prequalification document should be provided in Module 1, together with the duly filled out authorization box in the name of the FPP manufacturer or applicant.

The applicant should supply the following information in the dossier, with data summarized in the QOS-PD.

- 3.2.S.1.3 *General properties* – discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the API manufacturer's specifications, e.g. solubilities and polymorphs according to the guidance in this section.
- 3.2.S.2 If the sterility of the FPP is based upon the sterile manufacture of the API then data on the sterilization process together with full validation data should be provided.
- 3.2.S.3.1 *Elucidation of structure and other characteristics* – studies to identify polymorphs and particle size distribution, where applicable, according to the guidance in this section.
- 3.2.S.4.1 *Specification* – the specifications of the FPP manufacturer including all tests and limits of the API manufacturer's specifications and any additional tests and acceptance criteria that are not controlled by the API manufacturer's specifications, such as polymorphs and/or particle size distribution.

- 3.2.S.4.2/3.2.S.4.3 *Analytical procedures and validation* – for any methods used by the FPP manufacturer in addition to those in the API manufacturer's specifications.
- 3.2.S.4.4 *Batch analysis* – results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.
- 3.2.S.5 *Reference standards or materials* – information on the FPP manufacturer's reference standards.
- 3.2.S.7 *Stability* – data to support the retest period if either the proposed retest period is longer or the proposed storage conditions are at a lower temperature or humidity than that of the prequalified API.

Option 2: Certificate of Suitability of the European Pharmacopoeia (CEP)

A complete copy of the CEP (including any annexes) should be provided in Module 1. The declaration of access for the CEP should be duly filled out by the CEP holder on behalf of the FPP manufacturer or applicant to the NMRA who refers to the CEP.

In addition, a written commitment should be included that the applicant will inform the NMRA in the event that the CEP is withdrawn. It should also be acknowledged by the applicant that withdrawal of the CEP would require additional consideration of the API data requirements to support the PD. The written commitment should accompany the copy of the CEP in Module 1.

Together with the CEP, the applicant should supply the following information in the dossier, with data summarized in the QOS-PD.

- 3.2.S.1.3 *General properties* – discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the CEP and *European Pharmacopoeia* (Ph.Eur.) monograph, e.g. solubilities and polymorphs according to the guidance in this section.
- 3.2.S.3.1 *Elucidation of structure and other characteristics* – studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable, according to the guidance in this section.
- 3.2.S.4.1 *Specification* – the specifications of the FPP manufacturer including all tests and limits of the CEP and Ph.Eur. monograph and any additional tests and acceptance criteria that are not controlled in the CEP and Ph.Eur. monograph, such as polymorphs and/or particle size distribution.
- 3.2.S.4.2/3.2.S.4.3 *Analytical procedures and validation* – for any methods used by the FPP manufacturer in addition to those in the CEP and Ph.Eur. monograph.

- 3.2.S.4.4 *Batch analysis* – results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.
- 3.2.S.5 *Reference standards or materials* – information on the FPP manufacturer's reference standards.
- 3.2.S.6 *Container-closure system* – specifications including descriptions and identification of primary packaging components. Exception: where the CEP specifies a container-closure system and the applicant declares the intention to use the same container-closure system.
- 3.2.S.7 *Stability* – exception: where the CEP specifies a retest period that is the same as or of longer duration, and storage conditions which are at the same or a higher temperature and humidity as proposed by the applicant.

In the case of sterile APIs, data on the process for sterilization of the API, including validation data, should be included in the PD.

Option 3: API master file (APIMF) procedure

Full details of the chemistry, manufacturing process, quality controls during manufacturing and process validation for the API may be submitted to the NMRA as an APIMF by the API manufacturer, for example, as outlined in the WHO *Guidelines on active pharmaceutical ingredient master file procedure* (11).

In such cases, the *Open part* (nonproprietary information) needs to be included *in its entirety* in the PD as an annex to 3.2.S. In addition, the applicant/FPP manufacturer should complete the following sections in the PD and QOS-PD *in full* according to the guidance provided unless otherwise indicated in the respective sections:

General information S.1.1–S.1.3

Manufacture S.2

Manufacturer(s) S.2.1

Description of manufacturing process and process controls S.2.2

Controls of critical steps and intermediates S.2.4

Elucidation of structure and other characteristics S.3.1

Impurities S.3.2

Control of the API S.4.1–S.4.5

Reference standards or materials S.5

Container-closure system S.6

Stability S.7.1– S.7.3

It is the responsibility of the applicant to ensure that the complete APIMF (i.e. both the applicant's *Open part* and the API manufacturer's *Restricted part*) is supplied

to the NMRA directly by the API manufacturer and that the applicant has access to the relevant information in the APIMF concerning the current manufacture of the API.

A copy of the letter of access should be provided in the PD Module 1.

APIMF holders can use the guidance provided for the option “Full details in the PD” for preparation of the relevant sections of the *Open* and *Restricted* parts of their APIMFs. Reference can also be made to the APIMF guidelines (11).

Option 4: Full details in the PD

Information on the 3.2.S *Active pharmaceutical ingredient* sections, including full details of chemistry, manufacturing process, quality controls during manufacturing and process validation for the API, should be submitted in the PD as outlined in the subsequent sections of these guidelines. The QOS-PD should be completed according to section 3.1 of these guidelines.

3.2.S.1 General information (name, manufacturer)

3.2.S.1.1 Nomenclature (name, manufacturer)

Information on the nomenclature of the API should be provided. For example:

- (recommended) International Nonproprietary Name (INN);
- compendial name, if relevant;
- chemical name(s);
- company or laboratory code;
- other nonproprietary name(s) (e.g. national name, United States Adopted Name (USAN), British Approved Name (BAN)); and
- Chemical Abstracts Service (CAS) registry number.

The listed chemical names should be consistent with those appearing in scientific literature and those appearing on the product labelling information (e.g. summary of product characteristics, package leaflet (also known as patient information leaflet (PIL)), and labelling). Where several names exist, the preferred name should be indicated.

3.2.S.1.2 Structure (name, manufacturer)

The structural formula, including relative and absolute stereochemistry, the molecular formula and the relative molecular mass should be provided.

This information should be consistent with that provided in Section 3.2.S.1.1. For APIs existing as salts, the molecular mass of the free base or acid should also be provided.

3.2.S.1.3 General properties (name, manufacturer)

A list should be provided of physicochemical and other relevant properties of the API.

This information can be used in developing the specifications, in formulating FPPs and in the testing for release and stability purposes.

The physical and chemical properties of the API should be discussed, including the physical description, solubilities in common solvents (e.g. water, alcohols, dichloromethane, acetone), quantitative aqueous pH solubility profile (e.g. pH 1.2 to 6.8, dose/solubility volume), polymorphism, pH and pKa values, UV absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity, partition coefficient (see table in the QOS-PD). This list is not intended to be exhaustive, but provides an indication as to the type of information that could be included.

Some of the more relevant properties to be considered for APIs are discussed below in greater detail.

Physical description

The description should include appearance, colour and physical state. Solid forms should be identified as being crystalline or amorphous (see 3.2.S.3.1 for further information on API solid forms).

Solubilities/quantitative aqueous pH solubility profile

The following should be provided whichever option is adopted for the submission of API data.

- The solubilities in a number of common solvents (e.g. water, alcohols, dichloromethane, and acetone).
- The solubilities over the physiological pH range (pH 1.2 to 6.8) in several buffered media in mg/ml. If this information is not readily available (e.g. in literature references), it should be generated in-house.
- For solid oral dosage forms, the dose/solubility volume as determined by:

$$\text{dose/solubility volume} = \frac{\text{largest dosage strength (mg)}}{\text{the minimum concentration of the API (mg/ml)}^*}$$

* corresponding to the lowest solubility determined over the physiological pH range (pH 1.2 to 6.8) and temperature (37 ± 0.5 °C).

In line with the Biopharmaceutics Classification System (BCS), *highly soluble* (or *highly water soluble*) APIs are those with a dose/solubility volume of less than or equal to 250 ml.

For example, compound A has as its lowest solubility at 37 ± 0.5 °C, 1.0 mg/ml at pH 6.8 and is available in 100 mg, 200 mg and 400 mg strengths. This API would not be considered a *BCS highly soluble* API as its dose/solubility volume is greater than 250 ml ($400 \text{ mg}/1.0 \text{ mg/ml} = 400 \text{ ml}$).

Polymorphism

As recommended in ICH's *CTD-Q Questions and answers/location issues* document (12), the following refers to where specific data should be located in the PD:

- the polymorphic form(s) present in the proposed API should be listed in section 3.2.S.1.3;
- the description of manufacturing process and process controls (3.2.S.2.2) should indicate which polymorphic form is manufactured, where relevant;
- the literature references or studies performed to identify the potential polymorphic forms of the API, including the study results, should be provided in section 3.2.S.3.1;
- if a polymorphic form is to be defined or limited (e.g. for APIs that are not *BCS highly soluble* and/or where polymorphism has been identified as an issue), details should be included in 3.2.S.4.1–3.2.S.4.5.

Additional information is included in the sections mentioned in the above bullet points of these guidelines. In addition, 3.2.P.2.2.3 discusses considerations for control of the polymorphic form of the API in the FPP.

Particle size distribution

As recommended in ICH's *CTD-Q Questions and answers/location issues* document (12), the studies performed to identify the particle size distribution of the API should be provided in section 3.2.S.3.1 (refer to this section of these guidelines for additional information).

Information from literature

Supportive data and results from specific studies or published literature can be included within or attached to this section.

Reference documents: ICH Q6A (13).

3.2.S.2 Manufacture (name, manufacturer)

3.2.S.2.1 Manufacturer(s) (name, manufacturer)

The name, address and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

The facilities involved in the manufacturing, packaging, labelling, testing and storage of the API should be listed. If certain companies are responsible only for specific steps (e.g. milling of the API), this should be clearly indicated. This includes any manufacturing sites responsible for the preparation and supply of intermediates to the API manufacturer.

The list of manufacturers/companies should specify the actual addresses of production or manufacturing site(s) involved (including block(s) and units(s)), rather than the administrative offices. Telephone number(s), fax number(s) and email address(es) should be provided.

A valid manufacturing authorization for the production of APIs should be provided. If available, a certificate of GMP compliance should be provided in the PD in Module 1. For manufacturers of API intermediates, the basis for establishing that these sites are operating under GMP should be provided.

3.2.S.2.2 *Description of manufacturing process and process controls (name, manufacturer)*

The description of the API manufacturing process represents the applicant's commitment for the manufacture of the API. Information should be provided to adequately describe the manufacturing process and process controls. For example: a flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and API reflecting stereochemistry, and identifies operating conditions and solvents.

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g. temperature, pressure, pH, time).

Alternate processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or filed in 3.2.S.2.5.

Where the APIMF procedure is used, a cross-reference to the *Restricted part* of the APIMF may be indicated for confidential information. In this case, if detailed information is presented in the *Restricted part*, the information to be provided for this section of the PD includes a flow chart (including molecular structures and all reagents and solvents) and a brief outline of the manufacturing process, with special emphasis on the final steps including purification procedures. However, for sterile APIs full validation data on the sterilization process should be provided in the *Open part* (in cases where there is no further sterilization of the final product).

The following requirements apply in cases where the fourth option for submission of API information has been chosen, where full details are provided in the dossier.

As discussed in ICH Q7 (5) and WHO Technical Report Series, No. 957, Annex 2 (6), the point at which the *API starting material* is introduced into the manufacturing process is the starting point of the application of GMP requirements. The *API starting material* itself needs to be proposed and its choice justified by the manufacturer and accepted as such by assessors. The *API starting material* should be proposed, taking into account the complexity of the molecule, the proximity of the *API starting material* to the final API, the availability of the *API starting material* as a commercial chemical and the quality controls placed upon the *API starting material*. This justification should be documented in the dossier and be available for review by WHO GMP inspectors.

In the case where the precursor to the API is obtained by fermentation, or is of plant or animal origin, such a molecule can be considered the API starting material regardless of complexity.

A one-step synthesis may be accepted in exceptional cases, for example, where the API starting material is covered by a CEP, or where the API starting material is an API accepted through the APIMF procedure, or when the structure of the API is so simple that a one-step synthesis can be justified, e.g. ethambutol.

In addition to the detailed description of the manufacturing process according to ICH M4Q, the recovery of materials, if any, should be described in detail with the step in which they are introduced into the process. Recovery operations should be adequately controlled such that impurity levels do not increase over time. For recovery of solvents, any processing to improve the quality of the recovered solvent should be described. Regarding recycling of filtrates (mother liquors) to obtain second crops, information should be available on maximum holding times of mother liquors and maximum number of times the material can be recycled. Data on impurity levels should be provided to justify recycling of filtrates.

Where there are multiple manufacturing sites for one API manufacturer, a comprehensive list in tabular form should be provided comparing the processes at each site and highlighting any differences; this includes preparation of the API intermediates from external suppliers. The manufacturing details described in this section should either be declared to be identical for all intermediate manufacturers involved in the preparation of the API, or each alternative manufacturing process employed should be described in this section, for each intermediate manufacturer, using the same level of detail as that supplied for the primary manufacturing process.

All solvents used in the manufacture (including purification and/or crystallization step(s)) should be clearly identified. Solvents used in the final steps should be of high purity. Use of recovered solvent in the final step or purification is not recommended unless the specification of the recovered solvent is essentially the same as the fresh solvent. It is essential that the quality standard applied to recovered solvents and the use of such solvents is validated thoroughly.

Where polymorphic/amorphous forms have been identified the form resulting from the synthesis should be stated.

Where particle size is considered a critical attribute (see 3.2.S.3.1 for details), the particle size reduction method(s) (milling, micronization) should be described.

Justification should be provided for alternative manufacturing processes. Alternative processes should be explained using the same level of detail as is used to describe the primary process. It should be demonstrated that batches obtained by the alternative processes have the same impurity profile as the principal process. If the impurity profile obtained is different it should be demonstrated to be acceptable according to the requirements described under S.3.2.

It is acceptable to provide information on pilot-scale manufacture, provided it is representative of production scale and scale-up is reported immediately to the NMRA according to the requirements of the associated variation guidelines (e.g. WHO Technical Report Series, No. 981, 2013, Annex 3 (14)).

Reference documents: ICH Q7 (5), Q11 (15)

3.2.S.2.3 *Control of materials (name, manufacturer)*

Materials used in the manufacture of the API (e.g. raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials meet standards appropriate for their intended use should be provided, as appropriate (details in 3.2.A.2).

Where the APIMF procedure is used, a cross-reference to the *Restricted part* of the APIMF is considered sufficient for this section.

The following requirements apply to the fourth option for submission of API information, where full details are provided in the dossier.

The *API starting material* should be fully characterized and suitable specifications proposed and justified, including, at a minimum, control for identity, assay, impurity content and any other critical attribute of the material. For each *API starting material*, the name and manufacturing site address of the manufacturer(s) should be indicated, including of those manufacturers supplying API starting material to an external intermediate manufacturer. A brief description of the preparation of the *API starting material* should be provided for each manufacturer, including the solvents, catalysts and reagents used. A single set of specifications should be proposed for the starting material that applies to material from all sources. Any future changes to the API starting material manufacturers, mode of preparation or specifications should be notified.

In general, the starting material described in the PD should:

- be a synthetic precursor of one or more synthesis steps prior to the final API intermediate. Acids, bases, salts, esters and similar derivatives of the API, as well as the racemate of a single enantiomer API, are not considered final intermediates;

- be a well-characterized, isolated and purified substance with its structure fully elucidated including its stereochemistry (when applicable);
- have well-defined specifications that include, among others, one or more specific identity tests and tests and limits for assay and specified, unspecified and total impurities;
- be incorporated as a significant structural fragment into the structure of the API.

Copies of the specifications for the materials used in the synthesis, extraction, isolation and purification steps should be provided in the PD, including starting materials, reagents, solvents, catalysts and recovered materials. Confirmation should be provided that the specifications apply to materials used at each manufacturing site. A certificate of analysis of the starting material should be provided. A summary of the information on starting materials should be provided in the QOS-PD.

The carry-over of impurities of the starting materials into the final API should be considered and discussed.

A letter of attestation should be provided confirming that the API and the starting materials and reagents used to manufacture the API are *without* risk of transmitting agents of animal spongiform encephalopathies.

When available, a CEP demonstrating TSE compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module 1.

Reference documents: ICH Q6A (13)

3.2.S.2.4 Controls of critical steps and intermediates (name, manufacturer)

Critical steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled should be provided.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Where the APIMF procedure is used, a cross-reference to the *Restricted part* of the APIMF is considered sufficient for this section of the PD, with the exception of information that is also relevant for the applicant (see APIMF guidelines in WHO Technical Report Series, No. 948, Annex 4) (11).

The following requirements apply to the fourth option for submission of API information, where full details are provided in the dossier.

The critical steps should be identified. These can be among others: steps where significant impurities are removed or introduced, steps introducing an essential molecular structural element such as a chiral centre or resulting in a major chemical transformation, steps having an impact on solid-state properties and homogeneity of the API that may be relevant for use in solid dosage forms.

Specifications for isolated intermediates should be provided and should include tests and acceptance criteria for identity, purity and assay, where applicable.

Where API intermediates are sourced externally, these materials should be controlled to a single specification maintained by the API manufacturer. Evidence of the quality of the supplied materials should be provided in the form of certificates of analysis for batches of intermediate, issued by the intermediate supplier and by the API manufacturer upon retesting.

Reference documents: ICH Q6A

3.2.S.2.5 Process validation and/or evaluation (name, manufacturer)

Process validation and/or evaluation studies for aseptic processing and sterilization should be included.

Where the APIMF procedure is used, a cross-reference to the *Restricted part* of the APIMF is considered sufficient for this section of the PD.

The following requirements apply to the fourth option for submission of API information, where full details are provided in the dossier.

The manufacturing processes for all APIs are expected to be properly controlled. If the API is prepared as sterile, a complete description should be provided of the aseptic processing and/or sterilization methods. The controls used to maintain the sterility of the API during storage and transportation should also be provided. Alternative processes should be justified and described (see guidance in 3.2.S.2.2 for the level of detail expected).

3.2.S.2.6 Manufacturing process development (name, manufacturer)

A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the API used in producing comparative bioavailability or biowaiver, scale-up, pilot and, if available, production-scale batches.

Reference should be made to the API data provided in Section 3.2.S.4.4.

Where the APIMF procedure is used, a cross-reference to the *Restricted part* of the APIMF is considered sufficient for this section of the PD.

3.2.S.3 Characterization (name, manufacturer)

3.2.S.3.1 Elucidation of structure and other characteristics (name, manufacturer)

Confirmation of structure based on e.g. synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should also be included.

Elucidation of structure

The PD should include quality assurance-certified copies of the spectra, peak assignments and a detailed interpretation of the data on the studies performed to elucidate and/or confirm the structure of the API. The QOS-PD should include a list of the studies performed and a conclusion from the studies (e.g. if the results support the proposed structure).

For APIs that are not described in an officially-recognized pharmacopoeia, the studies carried out to elucidate and/or confirm the chemical structure normally include elemental analysis, infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR) and mass spectra (MS) studies. Other tests could include X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC), for example, where polymorphism is identified as an issue.

For APIs that are described in an officially-recognized pharmacopoeia, it is generally sufficient to provide copies of the IR spectrum of the API from each of the proposed manufacturer(s) run concomitantly with an officially-recognized pharmacopoeial reference standard. See Section 3.2.S.5 for details on acceptable reference standards or materials.

Isomerism/stereochemistry

When an API is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the comparative biostudies, and information should be given as to the stereoisomer of the API that is to be used in the FPP.

Where the potential for stereoisomerism exists, a discussion should be included of the possible isomers that can result from the manufacturing process and the steps where chirality was introduced. The identity of the isomeric composition of the API to that of the API in the comparator product should be established. Information on the physical and chemical properties of the isomeric mixture or single enantiomer should be provided, as appropriate. The API specification should include a test to ensure isomeric identity and purity.

The potential for interconversion of the isomers in the isomeric mixture, or racemization of the single enantiomer should be discussed.

When a single enantiomer of the API is claimed for non-pharmacopoeial APIs, unequivocal proof of absolute configuration of asymmetric centres should be provided such as determined by X-ray of a single crystal.

If, based on the structure of the API, there is not a potential for stereoisomerism, it is sufficient to include a statement to this effect.

Polymorphism

Many APIs can exist in different physical forms in the solid state. Polymorphism is characterized as the ability of an API to exist as two or more crystalline phases that

have different arrangements and/or conformations of the molecules in the crystal lattice. Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice. Solvates are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent. If the incorporated solvent is water, the solvates are also commonly known as hydrates.

Polymorphic forms of the same chemical compound differ in internal solid-state structure and, therefore, may possess different chemical and physical properties, including packing, thermodynamic, spectroscopic, kinetic, interfacial and mechanical properties. These properties can have a direct impact on API process ability, pharmaceutical product manufacturability and product quality/performance, including stability, dissolution and bioavailability. Unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences.

Applicants and API manufacturers are expected to have adequate knowledge about the polymorphism of the APIs used and/or produced. Information on polymorphism can come from the scientific literature, patents, compendia or other references to determine if polymorphism is a concern, e.g. for APIs that are not *BCS highly soluble*. In the absence of published data for APIs that are not *BCS highly soluble*, polymorphic screening will be necessary to determine if the API can exist in more than one crystalline form. Polymorphic screening is generally accomplished via crystallization studies using different solvents and conditions.

There are a number of methods that can be used to characterize the polymorphic forms of an API. Demonstration of a non-equivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism. XRPD can also be used to provide unequivocal proof of polymorphism. Other complementary methods, including microscopy, thermal analysis (e.g. DSC, thermal gravimetric analysis and hot-stage microscopy) and spectroscopy (e.g. IR, Raman, solid-state nuclear magnetic resonance (ssNMR)) are helpful to further characterize polymorphic forms. Where polymorphism is a concern, the applicants/manufacturers of APIs should demonstrate that a suitable method, capable of distinguishing different polymorphs, is available to them.

Decision tree 4(1) of ICH Q6A (13) can be used where screening is necessary and 4(2) can be used to investigate if different polymorphic forms have different properties that may affect performance, bioavailability and stability of the FPP and to decide whether a preferred polymorph should be monitored at release and on storage of the API. Where there is a preferred polymorph, acceptance criteria should be incorporated into the API specification to ensure polymorphic equivalence of the commercial material and that of the API batches used in the comparative bioavailability or biowaiver studies. The polymorphic characterization of the API batches used in comparative bioavailability or biowaiver studies by the above-mentioned methods should be provided. The method used to control polymorphic form should be demonstrated to be specific for the preferred form.

Polymorphism can also include solvation or hydration products (also known as pseudopolymorphs). If the API is used in a solvated form, the following information should be provided:

- specifications for the solvent-free API in 3.2.S.2.4, if that compound is a synthetic precursor;
- specifications for the solvated API including appropriate limits on the weight ratio of API to solvent (with data to support the proposed limits);
- a description of the method used to prepare the solvate in 3.2.S.2.2.

Particle size distribution

For APIs that are not *BCS highly soluble* contained in solid FPPs, or liquid FPPs containing undissolved API, the particle size distribution of the material can have an effect on the in vitro and/or in vivo behaviour of the FPP. Particle size distribution can also be important in dosage form performance (e.g. delivery of inhalation products), achieving uniformity of content in low-dose tablets (e.g. 2 mg or less), desired smoothness in ophthalmic preparations and stability of suspensions.

If particle size distribution is an important parameter (e.g. as in the above cases), results from an investigation of several batches of the API should be provided, including characterization of the batch(es) used in the comparative bioavailability or biowaiver studies. API specifications should include controls on the particle size distribution to ensure consistency with the material in the batch(es) used in the comparative bioavailability and biowaiver studies (e.g. limits for d10, d50 and d90). The criteria should be established statistically based on the standard deviation of the test results from the previously mentioned studies. The following are provided for illustrative purposes as possible acceptance criteria for particle size distribution limits:

- d10 not more than (NMT) 10% of total volume less than X µm
- d50 XX µm – XXX µm
- d90 not less than (NLT) 90% of total volume less than XXXX µm.

Other controls on particle size distribution can be considered acceptable, if scientifically justified.

Reference documents: ICH Q6A (13)

3.2.S.3.2 Impurities (name, manufacturer)

Information on impurities should be provided.

Details on the principles for the control of impurities (e.g. reporting, identification and qualification) are outlined in the ICH Q3A, Q3B and Q3C impurity guidelines (16–18).

Additional information to provide further guidance on some of the elements discussed in the ICH guidelines is outlined below.

Regardless of whether a pharmacopoeial standard is claimed, a discussion should be provided of the potential and actual impurities arising from the synthesis, manufacture, or degradation of the API. This should cover starting materials, by-products, intermediates, chiral impurities and degradation products and should include the chemical names, structures and origins. The discussion of pharmacopoeial APIs should not be limited to the impurities specified in the API monograph.

The tables in the QOS-PD template should be used to summarize the information on the API-related and process-related impurities. In the QOS-PD, the term *origin* refers to how and where the impurity was introduced (e.g. “Synthetic intermediate from Step 4 of the synthesis”, “Potential by-product due to rearrangement from Step 6 of the synthesis”). If the impurity is a metabolite of the API, this should also be indicated.

The ICH thresholds for reporting, identification (used to set the limit for individual unknown impurities) and qualification are determined on the basis of potential exposure to the impurity, e.g. by the maximum daily dose (MDD) of the API. For APIs available in multiple dosage forms and strengths having different MDD values, it is imperative that the thresholds and corresponding controls for each of the presentations be considered to ensure that the risks posed by impurities have been addressed. This is normally achieved by using the *highest potential daily MDD*, rather than the *maintenance dose*. For parenteral products the maximum hourly dose of the API should also be included.

It is acknowledged that APIs of semi-synthetic origin do not fall within the scope of the ICH impurity guidelines. However, depending on the nature of the API and the extent of the chemical modification steps, the *principles* for the control of impurities (e.g. reporting, identification and qualification) could also be extended to APIs of semi-synthetic origin. As an illustrative example, an API whose precursor molecule was derived from a fermentation process, or a natural product of plant or animal origin that has subsequently undergone *several* chemical modification reactions would generally fall within this scope, whereas an API whose sole chemical step was the formation of a salt from a fermentation product generally would not. It is understood that there is some latitude for these types of APIs.

Identification of impurities

It is recognized by the pharmacopoeias that APIs can be obtained from various sources and thus can contain impurities not considered during the development of the monograph. Furthermore, a change in the production or source may give rise to additional impurities that are not adequately controlled by the official compendial monograph. As a result each PD is assessed independently to consider the potential impurities that may arise from the proposed route(s) of synthesis. For these reasons, the ICH limits for unspecified impurities (e.g. NMT 0.10% or 1.0 mg per day intake

(whichever is lower) for APIs having a maximum daily dose ≤ 2 g/day) are generally recommended, rather than the general limits for unspecified impurities that may appear in the official compendial monograph that could potentially be higher than the applicable ICH limit.

Qualification of impurities

The ICH impurity guidelines should be consulted for options on the qualification of impurities. The limit specified for an identified impurity in an *officially recognized pharmacopoeia* is generally considered to be qualified. The following is an additional option for qualification of impurities in existing APIs:

The limit for an impurity present in an existing API can be accepted by comparing the impurity results found in the existing API with those observed in an innovator product using the same validated, stability-indicating analytical procedure (e.g. comparative high-performance liquid chromatography (HPLC) studies). If samples of the innovator product are not available, the impurity profile may also be compared to a different approved FPP with the same route of administration and similar characteristics (e.g. tablet versus capsule). It is recommended that the studies be conducted on comparable samples (e.g. samples of the same age) to obtain a meaningful comparison of the impurity profiles.

Levels of impurities generated from studies under accelerated or stressed storage conditions of the innovator or approved FPP are not considered acceptable/qualified.

A specified impurity present in the existing API is considered qualified if the amount of the impurity in the existing API reflects the levels observed in the innovator or approved FPP.

Basis for setting the acceptance criteria

The basis for setting the acceptance criteria for the impurities should be provided. This is established by considering the identification and qualification thresholds for API-related impurities (e.g. starting materials, by-products, intermediates, chiral impurities or degradation products) and the concentration limits for process-related impurities (e.g. residual solvents) according to the applicable ICH guidelines (e.g. Q3A (16), Q3C (18)).

The qualified level should be considered as the maximum allowable limit. However, limits which are considerably wider than the actual manufacturing process capability are generally discouraged. For this reason, the acceptance criteria are also set taking into consideration the actual levels of impurities found in several batches of the API from each manufacturer, including the levels found in the batches used for the comparative bioavailability or biowaiver studies. When reporting the results of quantitative tests, the actual numerical results should be provided rather than vague statements such as “within limits” or “conforms”. In cases where a large number of

batches have been tested it is acceptable to summarize the results of the total number of batches tested with a range of analytical results.

If there are identified impurities specified in an official compendial monograph that are not controlled by the proposed routine in-house analytical procedure, a justification for their exclusion from routine analyses should be provided (e.g. “Impurities D, E and F listed in *The International Pharmacopoeia* (Ph.Int.) monograph are not potential impurities from the proposed route of synthesis used by manufacturer X”). If acceptable justification cannot be provided it should be demonstrated that the routine in-house method is capable of separating and detecting the impurities specified in the official compendial monograph at an acceptable level (e.g. 0.10%). If such a demonstration cannot be performed, a one-time study should be conducted applying the pharmacopoeial method to several recent batches to demonstrate the absence of impurities listed in the pharmacopoeial monograph.

ICH class II solvent(s) used prior to the last step of the manufacturing process may be exempted from routine control in API specifications if suitable justification is provided. Submission of results demonstrating less than 10% of the ICH Q3C limit (option I) of the solvent(s) in three consecutive production-scale batches or six consecutive pilot-scale batches of the API or a suitable intermediate would be considered acceptable justification (18). The last-step solvents used in the process should always be routinely controlled in the final API.

For guidance on acceptable residual solvent limits, refer to ICH Q3C (18). The limit for residues of triethylamine (TEA) is either 320 ppm on the basis of ICH Q3C option I or 3.2 mg/day on the basis of permitted daily exposure (PDE).

The absence of known established highly toxic (genotoxic) impurities used in the process or formed as a by-product should be discussed and suitable limits should be proposed where absence cannot be assured. The limits should be justified by appropriate reference to available guidance (e.g. EMEA/CHMP/QWP/ 251344/2006 (19) or USFDA guidance (20) or by providing experimental safety data or published data in peer-reviewed journals.

Residues of metal catalysts used in the manufacturing process and determined to be present in batches of API are to be controlled in specifications. This requirement does not apply to metals that are deliberate components of the pharmaceutical substance (such as a counter ion of a salt) or metals that are used as a pharmaceutical excipient in the FPP (e.g. an iron oxide pigment). The guideline on the specification limits for residues of metal catalysts or metal reagents EMEA/CHMP/SWP/4446/2000 (21) or any equivalent approach can be used to address this issue. The requirement normally does not apply to extraneous metal contaminants that are more appropriately addressed by GMP, GDP or any other relevant quality provision, such as the heavy metal test in monographs of recognized pharmacopoeias that cover metal contamination originating from manufacturing equipment and the environment.

Reference documents: ICH Q3A (16), Q3C (18), Q6A (13)

3.2.S.4 Control of the API (name, manufacturer)

3.2.S.4.1 Specification (name, manufacturer)

The specification for the API should be provided.

As defined in ICH's Q6A guideline, a specification is:

a list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which an API or FPP should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the API and/or FPP, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.

Copies of the API specifications, dated and signed by authorized personnel (e.g. the person in charge of the quality control (QC) or quality assurance (QA) department) should be provided in the PD, including specifications from each API manufacturer as well as those of the FPP manufacturer.

The FPP manufacturer's API specification should be summarized according to the table in the QOS-PD template under the headings: tests, acceptance criteria and analytical procedures (including types, sources and versions for the methods).

- The *standard* declared by the applicant could be an officially recognized compendial standard (e.g. British Pharmacopoeia (BP), Ph.Eur., Ph.Int., Japanese Pharmacopoeia (JP), United States Pharmacopeia (USP)), or an in-house (manufacturer's) standard.
- The *specification reference number and version* (e.g. *revision number and/or date*) should be provided for version control purposes.
- For the analytical procedures, the *type* should indicate the kind of analytical procedure used (e.g. visual, IR, UV, HPLC, or laser diffraction), the *source* refers to the origin of the analytical procedure (e.g. BP, Ph.Eur., Ph.Int., JP, USP, or in-house) and the *version* (e.g. *code number/version/date*) should be provided for version control purposes.

In cases where there is more than one API manufacturer, the FPP manufacturer's API specifications should be one single compiled set of specifications that apply to the API from all manufacturers. It is acceptable to lay down in the specification more than one acceptance criterion and/or analytical method for a single parameter with the statement "for API from manufacturer A" (e.g. in the case of residual solvents).

Any non-routine testing should be clearly identified as such and justified along with the proposal on the frequency of non-routine testing.

The ICH Q6A guideline outlines recommendations for a number of *universal* and *specific* tests and criteria for APIs.

Reference documents: ICH Q3A (16), Q3C (18), Q6A (13), officially-recognized pharmacopoeia

3.2.S.4.2 Analytical procedures (name, manufacturer)

The analytical procedures used for testing the API should be provided.

Copies of the in-house analytical procedures used to generate testing results provided in the PD, as well as those proposed for routine testing of the API by the FPP manufacturer, should be provided. Unless modified it is not necessary to provide copies of officially-recognized compendial analytical procedures.

Tables for summarizing a number of the different analytical procedures and the validation information (e.g. HPLC assay/impurity methods, gas chromatography (GC) methods) can be found in section 2.3.R Regional information, of the QOS-PD (i.e. 2.3.R.2). These tables may be used to summarize the in-house analytical procedures *of the FPP manufacturer* for determination of the residual solvents, assay and purity of the API, in section 2.3.S.4.2 of the QOS-PD. Other methods used to generate assay and purity data in the PD can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the QOS-PD. Officially recognized compendial methods need not be summarized unless modifications have been made.

Although HPLC is normally considered the method of choice for determining API-related impurities, other chromatographic methods such as GC and thin-layer chromatography (TLC) can also be used, if appropriately validated. For determination of related substances, reference standards should normally be available for each of the identified impurities, particularly those known to be toxic and the concentration of the impurities should be quantitated against their own reference standards. Impurity standards may be obtained from pharmacopoeias (individual impurities or resolution mixtures), from commercial sources or prepared in-house. It is considered acceptable to use the API as an external standard to estimate the levels of impurities, provided the response factors of those impurities are sufficiently close to that of the API, i.e. between 80 and 120%. In cases where the response factor is outside this range, it may still be acceptable to use the API, provided a correction factor is applied. Data to support calculation of the correction factor should be provided for an in-house method. Unspecified impurities may be quantitated using a solution of the API as the reference standard at a concentration corresponding to the limit established for individual unspecified impurities (e.g. 0.10%). The test for related substances in the Ph.Int. monograph for lamivudine serves as a typical example.

The system suitability tests (SSTs) represent an integral part of the method and are used to ensure adequate performance of the chosen chromatographic system.

As a minimum, HPLC and GC purity methods should include SSTs for resolution and repeatability. For HPLC methods to control API-related impurities, this is typically done using a solution of the API with a concentration corresponding to the limit for unspecified impurities. Resolution of the two closest eluting peaks is generally recommended. However, the choice of alternative peaks can be used if justified (e.g. choice of a toxic impurity). In accordance with the Ph.Int. section on Methods of analysis, the repeatability test should include an acceptable number of replicate injections. HPLC assay methods should include SSTs for repeatability and, in addition, either peak asymmetry, theoretical plates or resolution. For TLC methods, the SSTs should verify the ability of the system to separate and detect the analyte(s) (e.g. by applying a spot corresponding to the API at a concentration corresponding to the limit of unspecified impurities).

Reference documents: ICH Q2 (22); WHO Technical Report Series, No. 943, 2007, Annex 3 (23)

3.2.S.4.3 *Validation of analytical procedures (name, manufacturer)*

Analytical validation information, including experimental data for the analytical procedures used for testing the API, should be provided.

Copies of the validation reports for the analytical procedures used to generate test results provided in the PD, as well as those proposed for routine testing of the API by the FPP manufacturer, should be provided.

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay/impurity methods, GC methods) can be found in section 2.3.R Regional information, of the QOS-PD (i.e. 2.3.R.2). These tables may be used to summarize the validation information on the analytical procedures of *the FPP manufacturer* for determination of residual solvents, assay and purity of the API, in section 2.3.S.4.3 of the QOS-PD. The validation data for other methods used to generate assay and purity data in the PD can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the QOS-PD.

As recognized by regulatory authorities and pharmacopoeias themselves, verification of compendial methods can be necessary. The compendial methods as published are typically validated based on an API or an FPP originating from a specific manufacturer. Different sources of the same API or FPP can contain impurities and/or degradation products that were not considered during the development of the monograph. Therefore the monograph and compendial method should be demonstrated as being suitable to control the impurity profile of the API from the intended source(s).

In general, verification is not necessary for compendial API *assay* methods. However, specificity of a specific compendial assay method should be demonstrated if there are any potential impurities that are not specified in the compendial monograph.

If an officially-recognized compendial method is used to control API-related impurities that are not specified in the monograph, full validation of the method is expected with respect to those impurities.

If an officially-recognized compendial standard is claimed and an in-house method is used in lieu of the compendial method (e.g. for assay or for specified impurities), equivalency of the in-house and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For impurity methods, the sample analysed should be the API spiked with impurities at concentrations equivalent to their specification limits.

Reference documents: ICH Q2

3.2.S.4.4 *Batch analyses (name, manufacturer)*

Description of batches and results of batch analyses should be provided.

The information provided should include batch number, batch size, date, and production site of relevant API batches used in comparative bioavailability or biowaiver studies, preclinical and clinical data (if relevant), stability, pilot, scale-up and, if available, production-scale batches. These data are used to establish the specifications and evaluate consistency in API quality.

Analytical results should be provided from at least two batches of at least pilot-scale from each proposed manufacturing site of the API and should include the batch(es) used in the comparative bioavailability or biowaiver studies. A pilot-scale batch should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

Copies of the certificates of analysis, both from the API manufacturer(s) and the FPP manufacturer, should be provided for the profiled batches and any company responsible for generating the test results should be identified. The FPP manufacturer's test results should be summarized in the QOS-PD.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “all tests meet specifications”. For quantitative tests (e.g. individual and total impurity tests and assay tests), it should be ensured that actual *numerical results* are provided rather than vague statements such as “within limits” or “conforms”.

A discussion and justification should be provided for any incomplete analyses (e.g. results not tested according to the proposed specification).

Reference documents: ICH Q3A (16), Q3C (18), Q6A (13)

3.2.S.4.5 Justification of specification (name, manufacturer)

Justification for the API specification should be provided.

A discussion should be provided on the inclusion of particular tests, evolution of tests, analytical procedures and acceptance criteria, and differences from the officially-recognized compendial standard(s). If the officially-recognized compendial methods have been modified or replaced, a discussion should be included.

The justification for certain tests, analytical procedures and acceptance criteria may have been discussed in other sections of the PD (e.g. impurities, particle size distribution) and does not need to be repeated here, although a cross-reference to the location should be provided.

Reference documents: ICH Q3A (16), Q3C (18), Q6A (13), officially-recognized pharmacopoeia

3.2.S.5 Reference standards or materials (name, manufacturer)

Information on the reference standards or reference materials used for testing of the API should be provided.

Information should be provided on the reference standard(s) used to generate data in the PD, as well as those to be used by the FPP manufacturer in routine API and FPP testing.

The source(s) of the reference standards or materials used in the testing of the API should be provided (e.g. those used for the identification, purity, and assay tests). These could be classified as *primary* or *secondary* reference standards.

A suitable primary reference standard should be obtained from an officially recognized pharmacopoeial source (e.g. BP, Ph.Eur., Ph.Int., JP, USP) where one exists and the lot number should be provided. Where a pharmacopoeial standard is claimed for the API and/or the FPP, the primary reference standard should be obtained from that pharmacopoeia when available. Primary reference standards from officially-recognized pharmacopoeial sources do not need further structural elucidation.

Otherwise, a primary standard may be a batch of the API that has been fully characterized (e.g. by IR, UV, nuclear magnetic resonance (NMR), and MS analyses). Further purification techniques may be needed to render the material acceptable for use as a chemical reference standard. The purity requirements for a chemical reference substance depend upon its intended use. A chemical reference substance proposed for an identification test does not require meticulous purification, since the presence of a small percentage of impurities in the substance often has no noticeable effect on the test. On the other hand, chemical reference substances that are to be used in assays should possess a high degree of purity (such as 99.5% on the dried or water-/solvent-free basis). Absolute content of the primary reference standard must be declared and should follow the scheme: 100% minus organic impurities (quantitated by an assay procedure, e.g. HPLC or DSC) minus inorganic impurities minus volatile impurities by loss on drying (or water content minus residual solvents).

A secondary (or in-house) reference standard can be used by establishing it against a suitable primary reference standard, e.g. by providing legible copies of the IR of the primary and secondary reference standards run concomitantly and by providing its certificate of analysis, including assay determined against the primary reference standard. A secondary reference standard is often characterized and evaluated for its intended purpose with additional procedures other than those used in routine testing (e.g. if additional solvents are used during the additional purification process that are not used for routine purposes).

Reference standards should normally be established for specified impurities. Refer to section 3.2.S.4.2 for additional guidance.

Reference documents: ICH Q6A (13), WHO Technical Report Series, No. 943, Annex 3, 2007 (23)

3.2.S.6 Container-closure system (name, manufacturer)

A description of the container-closure system(s) should be provided, including the identity of materials of construction of each primary packaging component and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g. those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the API, including sorption to container and leaching, and/or safety of materials of construction.

The WHO *Guidelines on packaging for pharmaceutical products* (24) and the officially-recognized pharmacopoeias should be consulted for recommendations on the packaging information for APIs.

Primary packaging components are those that are in direct contact with the API or FPP. The specifications for the primary packaging components should be provided and should include a specific test for identification (e.g. IR).

The name and address of the manufacturer of the API should be stated on the container, regardless of whether relabelling is conducted at any stage during the API distribution process.

3.2.S.7 Stability (name, manufacturer)

3.2.S.7.1 Stability summary and conclusions (name, manufacturer)

The types of studies conducted, protocols used and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

The WHO *Guidelines on Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (9) should be consulted for recommendations on the core stability data package.

As outlined in the WHO *stability guidelines*, the purpose of stability testing is to:

“provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light.”

The tables in the QOS-PD template should be used to summarize the results from the stability studies and related information (e.g. conditions, testing parameters, conclusions, commitments).

Stress testing

As outlined in the ICH Q1A guidance document, stress testing of the API can help identify the likely degradation products, which in turn can help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability-indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual API and the type of FPP involved.

Stress testing may be carried out on a single batch of the API. For examples of typical stress conditions refer to WHO Technical Report Series, No. 953, Annex 2, section 2.1.2 (9), as well as, “A typical set of studies of the degradation paths of an active pharmaceutical ingredient” in WHO Technical Report Series, No. 929, Annex 5, 2005, Table A.1 (7).

The objective of stress testing is not to completely degrade the API, but to cause degradation to occur to a small extent, typically 10–30% loss of active by assay when compared with non-degraded API. This target is chosen so that some degradation occurs, but not enough to generate secondary products. For this reason, the conditions and duration may need to be varied when the API is especially susceptible to a particular stress factor. If there is total absence of degradation products after 10 days, the API is considered stable under the stress condition under investigation.

The tables in the QOS-PD template should be used to summarize the results of the stress testing and should include the treatment conditions (e.g. temperatures, relative humidities, concentrations of solutions, and durations) and the observations for the various test parameters (e.g. assay, degradation products). The discussion of results should highlight whether mass balance was observed.

Photostability testing should be an integral part of stress testing. The standard conditions are described in ICH Q1B (25). If “protect from light” is stated in one of the officially-recognized pharmacopoeias for the API, it is sufficient to state “protect from light” on labelling, in lieu of photostability studies, when the container-closure system is shown to be light protective.

When available, it is acceptable to provide the relevant data published in the scientific literature (inter alia WHOPARs, EPARs) to support the identified degradation products and pathways.

Accelerated and long-term testing

Available information on the stability of the API under accelerated and long-term conditions should be provided, including information in the public domain or obtained from the scientific literature. The source of the information should be identified.

The storage conditions and the lengths of studies chosen should be sufficient to cover storage and shipment. Refer to the WHO stability guidelines in WHO Technical Report Series, No. 953, Annex 2, 2009 (9).

To establish the retest period, data should normally be provided on not less than three batches of at least pilot scale. The batches should be manufactured by the same synthesis route as production batches and using a method of manufacture and a procedure that simulates the final process to be used for production batches. The stability testing programme should be summarized and the results of stability testing should be summarized in the dossier and in the tables in the QOS-PD.

The information on the stability studies should include details such as storage conditions, batch number, batch size, container-closure system and completed (and proposed) test intervals. The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “all tests meet specifications”. Ranges of analytical results where relevant and any trends that were observed should be included. For quantitative tests (e.g. individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms”. Where different from the methods described in S.4.2, descriptions and validation of the methodology used in stability studies should be provided.

Refer to WHO Technical Report Series, No. 953, Annex 2, 2009 (9), for further information regarding the minimum data required at the time of submitting the dossier, storage conditions, container-closure system, test specifications and testing frequency.

Proposed storage statement and retest period

A storage statement should be established for display on the label based on the stability evaluation of the API. The WHO *stability guidelines* include a number of recommended storage statements that should be used, when supported by the stability studies.

A retest period should be derived from the stability information and the retest date should be displayed on the container label.

After this retest period, a batch of API destined for use in the manufacture of an FPP could be retested and then, if in compliance with the specification, could be used immediately (e.g. within 30 days). If retested and found compliant, the batch does not receive an additional period corresponding to the time established for the retest period. However, an API batch can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For APIs known to be labile (e.g. certain antibiotics), it is more appropriate to establish a shelf-life rather than a retest period (ICH Q1A (26)).

Limited extrapolation of the real-time data from the long-term storage condition beyond the observed range to extend the retest period can be undertaken at the time of assessment of the PD, if justified. Applicants should consult the ICH Q1E guideline for further details on the evaluation and extrapolation of results from stability data (e.g. if significant change was not observed within 6 months in accelerated stability studies and the data show little or no variability, the proposed retest period could be up to two times the period covered by the long-term data, but should not exceed the long-term data by more than 12 months).

Reference documents: ICH Q1A (26), Q1B (25), Q1D (27), Q1E (28), WHO Technical Report Series, No. 953, 2009, Annex 2 (9).

3.2.S.7.2 Post-approval stability protocol and stability commitment (name, manufacturer)

The post-approval stability protocol and stability commitment should be provided.

Primary stability study commitment

When the available long-term data on the stability of primary batches do not cover the proposed retest period granted at the time of assessment of the PD, a commitment should be made to continue the stability studies in order to firmly establish the retest period. A written commitment (signed and dated) to continue long-term testing over the retest period should be included in the dossier when relevant.

Commitment stability studies

The long-term stability studies for the commitment batches should be conducted through the proposed retest period on at least three production batches. Where stability data were not provided for three production batches, a written commitment (signed and dated) should be included in the dossier.

The stability protocol for the commitment batches should be provided and should include, but not be limited to, the following parameters:

- number of batch(es) and different batch sizes, if applicable;
- relevant physical, chemical, microbiological and biological test methods;

- acceptance criteria;
- reference to test methods;
- description of the container-closure system(s);
- testing frequency;
- description of the conditions of storage (standardized conditions for long-term testing as described in these guidelines and consistent with the API labelling should be used);
- other applicable parameters specific to the API.

Ongoing stability studies

The stability of the API should be monitored according to a continuous and appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of degradation products). The purpose of the ongoing stability programme is to monitor the API and to determine that the API remains within specifications and can be expected to remain within the retest period in all future batches.

At least one production batch per year of API (unless none is produced during that year) should be added to the stability monitoring programme and tested at least annually to confirm the stability. In certain situations, additional batches should be included. A written commitment (signed and dated) for ongoing stability studies should be included in the dossier.

Refer to WHO Technical Report Series, No. 953, 2009, Annex 2, Section 2.1.11 for further information on ongoing stability studies (9).

Any differences between the stability protocols used for the primary batches and those proposed for the *commitment batches* or *ongoing batches* should be scientifically justified.

Reference documents: ICH Q1A (26), Q1B (25), Q1D (27), Q1E (28), WHO Technical Report Series, No. 953, 2009, Annex 2 (9)

3.2.5.7.3 Stability data (name, manufacturer)

Results of the stability studies (e.g. forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

The actual stability results used to support the proposed retest period should be included in the dossier. For quantitative tests (e.g. individual and total degradation product tests and assay tests), actual numerical results should be provided rather than vague statements such as “within limits” or “conforms”.

Reference documents: ICH Q1A (26), Q1B (25), Q1D (27), Q1E (28), Q2 (22), WHO Technical Report Series, No. 953, 2009, Annex 2 (9)

3.2.P Drug product (or finished pharmaceutical product (FPP)) (name, dosage form)

3.2.P.1 Description and composition of the FPP (name, dosage form)

A description of the FPP and its composition should be provided. The information provided should include, for example:

- **Description of the dosage form**

The description of the FPP should include the physical description, available strengths, release mechanism if not conventional immediate release (e.g. dispersible, modified (delayed or extended)), as well as any other distinguishing characteristics, e.g.

“The proposed XYZ 50 mg dispersible tablets are available as white, oval, film-coated tablets, debossed with ‘50’ on one side and a break-line on the other side.

The proposed ABC 100 mg tablets are available as yellow, round, film-coated tablets, debossed with ‘100’ on one side and plain on the other side.”

- **Composition, i.e. list of all components of the dosage form and their amount on a per unit basis (including overages, if any), the function of the components and a reference to their quality standards (e.g. compendial monographs or manufacturer’s specifications)**

The tables in the QOS-PD template should be used to summarize the composition of the FPP and express the quantity of each component on a per unit basis (e.g. mg per tablet, mg per ml, mg per vial) and a percentage basis, including a statement of the total weight or measure of the dosage unit. The individual components for mixtures prepared in-house (e.g. coatings) should be included in the tables, where applicable.

All components used in the manufacturing process should be included, including those that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. solvents) and any others (e.g. nitrogen, silicon for stoppers). If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g. “1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride”). All overages should be clearly indicated (e.g. “contains 2% overage of the API to compensate for manufacturing losses”).

The components should be declared by their proper or common names, quality standards (e.g. BP, Ph.Eur., Ph.Int., JP, USP, in-house) and, if applicable, their grades (e.g. “microcrystalline cellulose NF (PH 102)”) and special technical characteristics (e.g. lyophilized, micronized, solubilized, or emulsified).

The function of each component (e.g. diluent/filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent, or antimicrobial preservative) should be stated. If an excipient performs multiple functions, the predominant function should be indicated.

The qualitative composition, including solvents, should be provided for all proprietary components or blends (e.g. capsule shells, colouring blends, or imprinting inks). This information (excluding the solvents) is to be listed in the product information (e.g. summary of product characteristics, labelling, and package leaflet).

- **Description of accompanying reconstitution diluent(s)**

For FPPs supplied with reconstitution diluent(s) that are commercially available or have been assessed and considered acceptable in connection with another approved PD, a brief description of the reconstitution diluents(s) should be provided.

For FPPs supplied with reconstitution diluent(s) that are not commercially available or have not been assessed and considered acceptable in connection with another approved PD, information on the diluent(s) should be provided in a separate FPP portion (“3.2.P”), as appropriate.

- **Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable**

The container-closure used for the FPP (and accompanying reconstitution diluent, if applicable) should be briefly described, with further details provided under 3.2.P.7 Container-closure system, e.g.

“The product is available in high-density polyethylene (HDPE) bottles with polypropylene caps (in sizes of 100s, 500s and 1000s) and in PVC/aluminium foil unit dose blisters (in packages of 100s (cards of 5 × 2, 10 cards per package).”

Reference documents: ICH Q6A (13)

3.2.P.2 Pharmaceutical Development (name, dosage form)

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container-closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the product dossier. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and FPP quality. Supportive data and results

from specific studies or published literature can be included within or attached to the Pharmaceutical Development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the product dossier.

Pharmaceutical development information should include, at a minimum:

- the definition of the quality target product profile (QTPP) as it relates to quality, safety and efficacy, considering for example the route of administration, dosage form, bioavailability, strength and stability;
- identification of the potential critical quality attributes (CQAs) of the FPP so as to adequately control the product characteristics that could have an impact on quality;
- discussion of the potential CQAs of the API(s), excipients and container-closure system(s) including the selection of the type, grade and amount to deliver pharmaceutical product of the desired quality;
- discussion of the selection criteria for the manufacturing process and the control strategy required to manufacture commercial lots meeting the QTPP in a consistent manner.

These features should be discussed as part of the product development using the principles of risk management over the entire lifecycle of the product (ICH Q8) (29).

For a discussion of additional pharmaceutical development issues specific to the development of FDCs, reference should be made to WHO Technical Report Series, No. 929, 2005, Annex 5, section 6.3.2 (7).

Reference documents: ICH Q6A (13), Q8 (29), Q9 (30), Q10 (31)

3.2.P.2.1 Components of the FPP (name, dosage form)

3.2.P.2.1.1 Active pharmaceutical ingredient (name, dosage form)

The compatibility of the API with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g. water content, solubility, particle size distribution, polymorphic or solid state form) of the API that can influence the performance of the FPP should be discussed. For fixed-dose combinations, the compatibility of APIs with each other should be discussed.

Physicochemical characteristics of the API may influence both the manufacturing capability and the performance of the FPP.

Guidance on compatibility studies is provided in appendix 3 of the WHO *Guidelines for registration of fixed-dose combination medicinal products* (WHO Technical Report Series, No. 929, 2005, Annex 5) (7). In addition to visual examination, chromatographic results (assay, purity) are required to demonstrate API-API and API-excipient compatibility. In general, API-excipient compatibility is not required to

be established for specific excipients when evidence is provided (e.g. in the SmPC or product leaflet) that the excipients are present in the comparator product.

3.2.P.2.1.2 Excipients (name, dosage form)

The choice of excipients listed in 3.2.P.1, their concentration, their characteristics that can influence the FPP performance should be discussed relative to their respective functions.

When choosing excipients, those with a compendial monograph are generally preferred and may be required in certain jurisdictions. Other resources are available for information on acceptable excipients and their concentrations, such as the US-FDA IIG list and the *Handbook of pharmaceutical excipients* (32). Use of excipients in concentrations outside established ranges is discouraged and generally requires justification. In addition, available guidelines should be referred to, which address particular excipients to be avoided, for example azo colorants as listed in the EMA Guideline CPMP/463/00 (33). Other guidance such as the WHO *Guidelines on development of paediatric medicines* (WHO Technical Report Series, No. 970, 2012, Annex 5) (34) may provide useful general guidance in this regard.

Ranges or alternatives for excipients are normally not accepted, unless supported by appropriate process validation data. Where relevant, compatibility study results (e.g. compatibility of a primary or secondary amine API with lactose) should be included to justify the choice of excipients. Specific details should be provided where necessary (e.g. on use of potato or corn starch).

Where antioxidants are included in the formulation, the effectiveness of the proposed concentration of the antioxidant should be justified and verified by appropriate studies.

Antimicrobial preservatives are discussed in 3.2.P.2.5.

3.2.P.2.2 Finished pharmaceutical product (name, dosage form)

3.2.P.2.2.1 Formulation development (name, dosage form)

A brief summary describing the development of the FPP should be provided, taking into consideration the proposed route of administration and usage. The differences between the comparative bioavailability or biowaiver formulations and the formulation (i.e. composition) described in 3.2.P.1 should be discussed. Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo studies (e.g. bioequivalence) should be discussed, when appropriate.

The requirements for bioequivalence studies should be taken into consideration for example when formulating multiple strengths and/or when the product(s) may be eligible for a biowaiver. WHO reference documents (e.g. WHO Technical Report Series, No. 937, 2006, Annex 7) (8) may be consulted.

Product scoring may be recommended or required, for example, when division into fractional doses may be necessary according to approved posology.

If the proposed FPP is a functionally scored tablet, a study should be undertaken to ensure the uniformity of dose in the tablet fragments. The data provided in the PD should include a description of the test method, individual values, mean and relative standard deviation (RSD) of the results. Uniformity testing (i.e. content uniformity for split portions containing less than 5 mg or less than 5% of the weight of the dosage unit portion, or mass uniformity for other situations) should be performed on each split portion from a minimum of 10 randomly selected whole tablets. As an illustrative example, the number of units (i.e. the splits) would be 10 halves for bisected tablets (one half of each tablet is retained for the test) or 10 quarters for quadrisectioned tablets (one quarter of each tablet is retained for the test). At least one batch of each strength should be tested. Ideally, the study should cover a range of the hardness values. The splitting of the tablets should be performed in a manner that would be representative of that used by the consumer (e.g. manually split by hand). The uniformity test on split portions can be demonstrated on a one-time basis and does not need to be added to the FPP specification(s). The tablet description in the FPP specification and in the product information (e.g. summary of product characteristics, labelling, package leaflet) should reflect the presence of a score.

If splitting of a tablet is intended for a paediatric dose, a demonstration of content uniformity of tablet fragments may be required.

Where relevant, labelling should state that the score line is only to facilitate breaking for ease of swallowing and not to divide tablets into equal doses.

Additional quality data may be required to support special dosing instructions (for example, crushing) stated in product information.

In vitro dissolution or drug release

A discussion should be included as to how the development of the formulation relates to development of the dissolution method(s) and the generation of the dissolution profile.

The results of studies justifying the choice of in vitro dissolution or drug release conditions (e.g. apparatus, rotation speed, and medium) should be provided. Data should also be submitted to demonstrate whether the method is sensitive to changes in manufacturing processes and/or changes in grades and/or amounts of critical excipients and particle size where relevant. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters. Use of a single point test or a dissolution range should be justified based on the solubility and/or biopharmaceutical classification of the API.

For slower dissolving, immediate-release products (e.g. $Q = 80\%$ in 90 minutes), a second time point may be warranted (e.g. $Q = 60\%$ in 45 minutes).

Delayed release (enteric coated) products are intended to resist gastric fluid but disintegrate in intestinal fluid; therefore dissolution should include acid and buffer phases with separate criteria for each. Refer to compendial monographs for examples.

Modified-release FPPs should have a meaningful *in vitro* release rate (dissolution) test that is used for routine quality control. Preferably, this test should possess *in vitro*–*in vivo* correlation. Results demonstrating the effect of pH on the dissolution profile should be submitted if appropriate for the type of dosage form.

For extended-release FPPs, the testing conditions should be set to cover the entire time period of expected release (e.g. at least three test intervals chosen for a 12-hour release and additional test intervals for longer duration of release). One of the test points should be at the early stage of drug release (e.g. within the first hour) to demonstrate absence of dose dumping. At each test period, upper and lower limits should be set for individual units. Generally, the acceptance range at each intermediate test point should not exceed 20% or $\pm 10\%$ of the targeted value. Dissolution results should be submitted for several lots, including those lots used for pharmacokinetic and bioavailability or biowaiver studies.

Recommendations for conducting and assessing comparative dissolution profiles can be found in Appendix 1.

3.2.P.2.2.2 Overages (name, dosage form)

Any overages in the formulation(s) described in 3.2.P.1 should be justified.

Justification of an overage to compensate for loss during manufacture should be provided, including the step(s) where the loss occurs, the reasons for the loss and batch analysis release data (assay results).

Overages for the sole purpose of extending the shelf-life of the FPP are generally not acceptable.

3.2.P.2.2.3 Physicochemical and biological properties (name, dosage form)

Parameters relevant to the performance of the FPP, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity, should be addressed.

When polymorphism is an issue for the API as discussed in 3.2.S.3.1, it may be necessary to provide information on the form present in the FPP, for example, when the manufacturing process may affect the form. Such studies may not be necessary when sufficient information has been provided on the polymorphism observed during API stability studies.

3.2.P.2.3 Manufacturing process development (name, dosage form)

The selection and optimisation of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.

Where relevant, justification for the selection of aseptic processing or other sterilization methods over terminal sterilization should be provided.

Differences between the manufacturing process(es) used to produce comparative bioavailability or biowaiver batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.

The rationale for choosing the particular pharmaceutical product (e.g. dosage form, delivery system) should be provided. The scientific rationale for the choice of the manufacturing, filling and packaging processes that can influence FPP quality and performance should be explained (e.g. wet granulation using high shear granulator). API stress study results may be included in the rationale. Any developmental work undertaken to protect the FPP from deterioration should also be included (e.g. protection from light or moisture).

The scientific rationale for the selection, optimization and scale-up of the manufacturing process described in 3.2.P.3.3 should be explained, in particular the critical aspects (e.g. rate of addition of granulating fluid, massing time, and granulation end-point). A discussion of the critical process parameters (CPP), controls and robustness with respect to the QTPP and CQA of the product should be included (ICH Q8 (29)).

3.2.P.2.4 Container-closure system (name, dosage form)

The suitability of the container closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the FPP should be discussed. This discussion should consider, e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction and performance (such as reproducibility of the dose delivery from the device when presented as part of the FPP).

Testing requirements to verify the suitability of the container-closure system contact material(s) depend on the dosage form and route of administration. The pharmacopoeias provide standards that are required for packaging materials, including, for example, the following :

Glass containers:	USP <660> Ph.Eur. 3.2.1
Plastic containers:	Ph.Eur. 3.2.2, 3.2.2.1 USP <661>, <671>
Rubber/elastomeric closures:	USP <381> Ph.Eur. 3.2.9

Table A6.1 outlines the general recommendations for the various dosage forms for one-time studies to establish the suitability of the container-closure system contact materials.

Table A6.1

General recommendations for the various dosage forms for one-time studies to establish the suitability of the container-closure system contact materials

	Solid oral products	Oral liquid and topical products	Sterile products (including ophthalmics)
Description of any additional treatments ^a	X	X	X (sterilization and depyrogenation of the components)
Extraction studies	–	X	X
Interaction studies (migration/sorption)	–	X	X
Moisture permeability	X (uptake)	X (usually loss)	X (usually loss)
Light transmission	X ^b	X	X

X, information should be submitted; –, information does not need to be submitted.

^a e.g. coating of tubes, siliconization of rubber stoppers, sulfur treatment of ampoules/vials;

^b not required if product has been shown to be photostable.

For solid oral dosage forms and solid APIs, compliance with regulations on plastic materials that come into contact with food (for example (EU) No. 10/2011) (35) can be considered acceptable in lieu of extraction studies.

The suitability of the container-closure system used for the storage, transportation (shipping) and use of any intermediate/in-process products (e.g. premixes or bulk FPP) should also be discussed.

A dosage device should be included with the container-closure system for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders/granules for such), any time the package provides for multiple doses.

In accordance with the Ph.Int. general chapter Liquid preparations for oral use:

“Each dose from a multidose container is administered by means of a device suitable for measuring the prescribed volume. The device is usually a spoon or a cup for volumes of 5 ml or multiples thereof, or an oral syringe for other volumes or, for oral drops, a suitable dropper.”

For a device accompanying a multidose container, the results of a study should be provided demonstrating the reproducibility of the device (e.g. consistent delivery of the intended volume), generally at the lowest intended dose.

A sample of the device should be provided with Module 1.

3.2.P.2.5 *Microbiological attributes (name, dosage form)*

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container-closure system to prevent microbial contamination should be addressed.

Where an antimicrobial preservative is included in the formulation, the amount used should be justified by submission of results of the product formulated with different concentrations of the preservative(s) to demonstrate the lowest necessary but still effective concentration. The effectiveness of the agent should be justified and verified by appropriate studies (e.g. according to Ph.Eur. or USP general chapters on antimicrobial preservatives) using a batch of the FPP. If the lower limit for the proposed acceptance criterion for the assay of the preservative is less than 90.0%, the effectiveness of the agent should be established with a batch of the FPP containing a concentration of the antimicrobial preservative corresponding to the lower proposed acceptance criterion.

As outlined in the WHO *stability guidelines* (WHO Technical Report Series, No. 953, 2009, Annex 2) (9), a single primary stability batch of the FPP should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf-life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

3.2.P.2.6 *Compatibility (name, dosage form)*

The compatibility of the FPP with reconstitution diluent(s) or dosage devices (e.g. precipitation of API in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labelling.

Where a dosage device is required for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders or granules for reconstitution) that are intended to be administered immediately after being added to the device, the compatibility studies mentioned in the following paragraphs are not required.

Where sterile, reconstituted products are to be further diluted, compatibility should be demonstrated with all diluents over the range of dilution proposed in the labelling. These studies should preferably be conducted on aged samples. Where the labelling does not specify the type of containers, compatibility (with respect to parameters such as appearance, pH, assay, levels of individual and total degradation products, subvisible particulate matter and extractables from the packaging components) should be demonstrated in glass, PVC and polyolefin containers. However, if one or more containers are identified in the labelling, compatibility of admixtures needs to be demonstrated only in the specified containers.

Studies should cover the duration of storage reported in the labelling (e.g. 24 hours under controlled room temperature and 72 hours under refrigeration). Where the labelling specifies co-administration with other FPPs, compatibility should be demonstrated with respect to the principal FPP as well as the co-administered FPP (i.e. in addition to the other aforementioned parameters for the mixture, the assay and degradation levels of each co-administered FPP should be reported).

3.2.P3 Manufacture (name, dosage form)

3.2.P3.1 Manufacturer(s) (name, dosage form)

The name, address and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

The facilities involved in the manufacturing, packaging, labelling and testing should be listed. If certain companies are responsible only for specific steps (e.g. manufacturing of an intermediate), this should be clearly indicated (refer to WHO Good distribution practices for pharmaceutical products (36)).

The list of manufacturers or companies should specify the *actual addresses* of production or manufacturing site(s) involved (including block(s) and unit(s)) if applicable, rather than the administrative offices.

For a mixture of an API with an excipient, the blending of the API with the excipient is considered to be the first step in the manufacture of the final product and therefore the mixture does not fall under the definition of an API. The only exceptions occur in the cases where the API cannot exist on its own. Similarly, for a mixture of APIs, the blending of the APIs is considered to be the first step in the manufacture of the final product. Sites for such manufacturing steps should be included in this section.

A valid manufacturing authorization for pharmaceutical production is generally required and a marketing authorization may be required to demonstrate that the product is registered or licensed in accordance with national requirements (Module 1, 1.2.2).

For each site where the major production step(s) are carried out, when applicable, a WHO-type certificate of GMP may be required, issued by the competent authority in terms of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce (Module 1, 1.2.2).

Justification for any differences to the product in the country or countries issuing the WHO-type certificate(s)

When there are differences between the product for which this application is submitted and that marketed in the country or countries which provided the WHO-type certificate(s), data to support the applicability of the certificate(s) despite the differences should be provided. Depending on the case, it may be necessary to provide validation data for differences, for example, in site of manufacture, specifications, or formulation.

Note that only minor differences are likely to be acceptable. Differences in container labelling need not normally be justified.

Regulatory situation in other countries

A list should be made of countries in which this product has been granted a marketing authorization, this product has been withdrawn from the market and/or this application for marketing has been rejected, deferred or withdrawn (Module 1, 1.2.2).

Reference documents: WHO Technical Report Series, No. 961, 2011, Annex 3 (10) and WHO Technical Report Series, No. 957, 2010, Annex 5 (36)

3.2.P.3.2 Batch formula (name, dosage form)

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

The tables in the QOS-PD template should be used to summarize the batch formula of the FPP for *each proposed commercial batch size* and express the quantity of each component on a per batch basis, including a statement of the total weight or measure (e.g. volume) of the batch.

All components used in the manufacturing process should be included, including those that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. solvents) and any others (e.g. nitrogen, or silicon for stoppers). If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g. “1 kg of active ingredient base = 1.075 kg active ingredient hydrochloride”). All overages should be clearly indicated (e.g. “Contains 5 kg (corresponding to 2%) overage of the API to compensate for manufacturing losses”).

The components should be declared by their proper or common names, quality standards (e.g. Ph.Int., Ph.Eur., BP, USP, JP, in-house) and, if applicable, their grades (e.g. “microcrystalline cellulose NF (PH 102)”) and special technical characteristics (e.g. lyophilized, micronized, solubilized, emulsified).

3.2.P.3.3 Description of manufacturing process and process controls (name, dosage form)

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative description of the manufacturing process, including packaging, that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail.

Equipment should, at least, be identified by type (e.g. tumble blender, in-line homogeniser) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section 3.2.P.3.4. In certain cases, environmental conditions (e.g. low humidity for an effervescent product) should be stated.

The maximum holding time for bulk FPP (product prior to final packaging, e.g. tablets in HDPE drums) should be stated. The holding time should be supported by the submission of stability data, if longer than 30 days. For an aseptically processed FPP, sterile filtration of the bulk and filling into final containers should preferably be continuous; any holding time should be justified.

Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section (3.2.P.3.3).

The information above should be summarized in the QOS-PD template and should reflect the production of the proposed commercial batches.

For the manufacture of sterile products, the class (e.g. A, B, C, etc.) of the areas should be stated for each activity (e.g. compounding, filling, sealing, etc.), as well as the sterilization parameters for equipment, container/closure, terminal sterilization, etc.

Reference documents: ICH Q8 (29), Q9 (30), Q10 (31)

3.2.P.3.4 Controls of critical steps and intermediates (name, dosage form)

Critical steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the manufacturing process, to ensure that the process is controlled.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Examples of applicable in-process controls include:

- granulations: moisture (limits expressed as a range), blend uniformity (e.g. low dose tablets), bulk and tapped densities, particle size distribution;
- solid oral products: average weight, weight variation, hardness, thickness, friability, and disintegration checked periodically throughout compression, weight gain during coating;
- semi-solids: viscosity, homogeneity, pH;
- transdermal dosage forms: assay of API–adhesive mixture, weight per area of coated patch without backing;

- metered dose inhalers: fill weight/volume, leak testing, valve delivery;
- dry powder inhalers: assay of API–excipient blend, moisture, weight variation of individually contained doses such as capsules or blisters;
- liquids: pH, specific gravity, clarity of solutions;
- parenterals: appearance, clarity, fill volume/weight, pH, filter integrity tests, particulate matter, leak testing of ampoules, pre-filtration and/or presterilization bioburden testing.

Reference documents: ICH Q2 (22), Q6A (13), Q8 (29), Q9 (30), Q10 (31); WHO Technical Report Series, No. 970, 2012, Annex 5 (34)

3.2.P.3.5 *Process validation and/or evaluation (name, dosage form)*

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g. validation of the sterilisation process or aseptic processing or filling). Viral safety evaluation should be provided in 3.2A.2, if necessary.

The following information should be provided for all products:

- a) a copy of the *process validation protocol*, specific to this FPP, described below;
- b) a *commitment* that three consecutive, production-scale batches of this FPP will be subjected to *prospective validation* in accordance with the above protocol; the applicant should submit a written commitment that information from these studies will be available for verification after approval by the NMRA inspection team;
- c) if the process validation studies have already been conducted (e.g. for sterile products), a copy of the *process validation report* should be provided in the PD in lieu of (a) and (b) above.

One of the most practical forms of process validation, mainly for non-sterile products, is the final testing of the product to an extent greater than that required in routine quality control. It may involve extensive sampling, far beyond that called for in routine quality control and testing to normal quality control specifications and often for certain parameters only. Thus, for instance, several hundred tablets per batch may be weighed to determine unit dose uniformity. The results are then treated statistically to verify the “normality” of the distribution and to determine the standard deviation from the average weight. Confidence limits for individual results and for batch homogeneity are also estimated. Strong assurance is provided that samples taken at random will meet regulatory requirements if the confidence limits are well within compendial specifications.

Similarly, extensive sampling and testing may be performed with regard to any quality requirements. In addition, intermediate stages may be validated in the same way, e.g. dozens of samples may be assayed individually to validate mixing or granulation stages of low-dose tablet production by using the content uniformity test. Certain product characteristics may occasionally be skip tested. Thus, subvisual particulate matter in parenteral preparations may be determined by means of electronic devices, or tablets or capsules tested for dissolution profile if such tests are not performed on every batch.

Where ranges of batch sizes are proposed, it should be shown that variations in batch size would not adversely alter the characteristics of the finished product. It is envisaged that those parameters listed in the following validation scheme will need to be revalidated once further scale-up is proposed after approval.

The process validation protocol should include, but is not limited to, the following:

- a reference to the current master production document;
- a discussion of the critical equipment;
- the process parameters that can affect the quality of the FPP (critical process parameters (CPPs)) including challenge experiments and failure mode operation;
- details of the sampling: sampling points, stages of sampling, methods of sampling and the sampling plans (including schematics of blender/storage bins for uniformity testing of the final blend);
- the testing parameters/acceptance criteria including in-process and release specifications and including comparative dissolution profiles of validation batches against the batch(es) used in the bioavailability or biowaiver studies;
- the analytical procedures or a reference to appropriate section(s) of the dossier;
- the methods for recording and evaluating results;
- the proposed timeframe for completion of the protocol.

The manufacture of sterile FPPs needs a well-controlled manufacturing area (e.g. a strictly controlled environment, highly reliable procedures and appropriate in-process controls). A detailed description of these conditions, procedures and controls should be provided, together with actual copies of the following standard operating procedures (SOPs):

- washing, treatment, sterilization and depyrogenation of containers, closures and equipment;
- filtration of solutions;

- lyophilization process;
- leaker test of filled and sealed ampoules;
- final inspection of the product;
- sterilization cycle.

The sterilization process used to destroy or remove microorganisms is probably the single most important process in the manufacture of parenteral FPPs. The process can make use of moist heat (e.g. steam), dry heat, filtration, gaseous sterilization (e.g. ethylene oxide) or radiation. It should be noted that terminal steam sterilization, when practical, is considered to be the method of choice to ensure sterility of the final FPP. Therefore, scientific justification for selecting any other method of sterilization should be provided.

The sterilization process should be described in detail and evidence should be provided to confirm that it will produce a sterile product with a high degree of reliability and that the physical and chemical properties as well as the safety of the FPP will not be affected. Details such as Fo range, temperature range and peak dwell time for an FPP and the container closure should be provided. Although standard autoclaving cycles of 121 °C for 15 minutes or more would not need a detailed rationale, such justifications should be provided for reduced temperature cycles or elevated temperature cycles with shortened exposure times. If ethylene oxide is used, studies and acceptance criteria should control the levels of residual ethylene oxide and related compounds.

Filters used should be validated with respect to pore size, compatibility with the product, absence of extractables and lack of adsorption of the API or any of the components.

For the validation of aseptic processing of parenteral products that cannot be terminally sterilized, simulation process trials should be conducted. This involves filling containers with culture media under normal conditions, followed by incubation. Refer to current WHO GMP guidelines for details.

Reference documents: ICH Q8 (29), Q9 (30), Q10 (31), WHO Technical Report Series, No. 961, 2011, Annex 3 (10)

3.2.P.4 Control of excipients (name, dosage form)

3.2.P.4.1 Specifications (name, dosage form)

The specifications for excipients should be provided.

The specifications from the applicant or the FPP manufacturer should be provided for all excipients, including those that may not be added to every batch (e.g. acid and alkali), those that do not appear in the final FPP (e.g. solvents) and any others used in the manufacturing process (e.g. nitrogen, silicon for stoppers).

If the standard claimed for an excipient is an officially-recognized compendial standard, it is sufficient to state that the excipient is tested according to the requirements

of that standard, rather than reproducing the specifications found in the officially-recognized compendial monograph.

If the standard claimed for an excipient is a non-compendial standard (e.g. in-house standard) or includes tests that are supplementary to those appearing in the officially-recognized compendial monograph, a copy of the specification for the excipient should be provided.

In general, excipients with an officially-recognized pharmacopoeial monograph should be used. Exceptions should be justified.

For excipients of natural origin, microbial limit testing should be included in the specifications. Skip testing is acceptable if justified (submission of acceptable results of five production batches).

For oils of plant origin (e.g. soy bean oil, peanut oil) the absence of aflatoxins and biocides should be demonstrated.

The colours permitted for use should be limited to those listed in suitable guidelines such as the Japanese *pharmaceutical excipients directory* (37), the EU “List of permitted food colours”, and the FDA “Inactive ingredient guide”. For proprietary mixtures, the supplier’s product sheet with the qualitative formulation should be submitted in addition to the FPP manufacturer’s specifications for the product, including identification testing.

For flavours the qualitative composition should be submitted, as well as a declaration that the excipients comply with foodstuff regulations (e.g. EU or USA).

Information that is considered confidential may be submitted directly to the NMRA by the supplier with reference to the specific related product.

Other certifications of at-risk components may be required on a case-by-case basis.

If additional purification is undertaken on commercially available excipients, details of the process of purification and modified specifications should be submitted.

Reference documents: ICH Q6A (13)

3.2.P.4.2 Analytical procedures (name, dosage form)

The analytical procedures used for testing the excipients should be provided, where appropriate.

Copies of analytical procedures from officially-recognized compendial monographs do not need to be submitted.

Reference documents: ICH Q2 (22)

3.2.P.4.3 Validation of analytical procedures (name, dosage form)

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.

Copies of analytical validation information are generally not submitted for the testing of excipients, with the exception of the validation of in-house methods where appropriate.

Reference documents: ICH Q2 (22)

3.2.P.4.4 Justification of specifications (name, dosage form)

Justification for the proposed excipient specifications should be provided, where appropriate.

A discussion of the tests that are supplementary to those appearing in the officially-recognized compendial monograph should be provided.

3.2.P.4.5 Excipients of human or animal origin (name, dosage form)

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g. sources, specifications, description of the testing performed, viral safety data) (details in 3.2.A.2.)

The excipients to be addressed in this section may include gelatin, phosphates, stearic acid, magnesium stearate and other stearates. If an excipient is of plant origin a declaration to this effect will suffice.

For excipients of animal origin, a letter of attestation should be provided confirming that the excipients used to manufacture the FPP are without risk of transmitting agents of animal spongiform encephalopathies. Materials of animal origin should be avoided whenever possible.

When available, a CEP demonstrating TSE compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module 1.

Reference documents: ICH Q5A (38), Q5D (39), Q6B (40), WHO Technical Report Series, No. 908, 2003, Annex 1 (41)

3.2.P.4.6 Novel excipients (name, dosage form)

For excipient(s) used for the first time in an FPP or by a new route of administration, full details of manufacture, characterisation, and controls, with cross-references to supporting safety data (nonclinical and/or clinical) should be provided according to the API and/or FPP format (details in 3.2.A.3).

At its discretion an NMRA may choose not to accept the use of novel excipients in submitted PDs. For the purpose of these guidelines, a novel excipient is one that has not been used (at a similar level and by the same route of administration) in a product approved by an SRA or WHO. If novel excipients are accepted, full information should be provided in 3.2.A.3.

3.2.P.5 Control of FPP (name, dosage form)

3.2.P.5.1 Specification(s) (name, dosage form)

The specification(s) for the FPP should be provided.

As defined in ICH's Q6A guideline, a specification is:

“a list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which an API or FPP should conform to be considered acceptable for its intended use. ‘Conformance to specifications’ means that the API and /or FPP, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.”

A copy of the FPP specification(s) from the applicant (as well as the company responsible for the batch release of the FPP, if different from the applicant), dated and signed by authorized personnel (i.e. the person in charge of the quality control or quality assurance department) should be provided in the PD. Two separate sets of specifications may be set out: after packaging of the FPP (release) and at the end of shelf-life.

The specifications should be summarized according to the tables in the QOS-PD template including the tests, acceptance criteria and analytical procedures (including types, sources and versions for the methods):

- the *standard* declared by the applicant could be an officially recognized compendial standard (e.g. BP, Ph.Eur., Ph.Int., JP, USP) or an in-house (manufacturer's) standard;
- the *specification reference number and version* (e.g. *revision number and/or date*) should be provided for version control purposes;
- for the analytical procedures, the *type* should indicate the kind of analytical procedure used (e.g. visual, IR, UV, HPLC), the *source* refers to the origin of the analytical procedure (e.g. BP, Ph.Eur., Ph.Int., JP, USP, in-house) and the *version* (e.g. *code number, version and date*) should be provided for version control purposes.

ICH's Q6A guideline outlines recommendations for a number of universal and specific tests and criteria for FPPs. Specifications should include, at the minimum, tests for appearance, identification, assay, purity, performance tests (e.g. dissolution), physical tests (e.g. loss on drying, hardness, friability, particle size), uniformity of dosage units, and, as applicable, identification and assay of antimicrobial or chemical preservatives (e.g. antioxidants) and microbial limit tests.

The following information provides guidance for specific tests that are not addressed by ICH's Q6A guideline (13):

- fixed-dose combination FPPs (FDC-FPPs):
analytical methods that can distinguish each API in the presence of the other API(s) should be developed and validated,
 - acceptance criteria for degradation products should be established with reference to the API they are derived from. If an impurity results from a chemical reaction between two or more APIs, its acceptance limits should in general be calculated with reference to the worst case (the API with the smaller area under the curve). Alternatively the content of such impurities could be calculated in relation to their reference standards,
 - a test and limit for content uniformity is required for each API present in the FPP at less than 5 mg or less than 5% of the weight of the dosage unit,
 - for the API(s) present at greater than or equal to 5 mg and greater than or equal to 5% of the weight of the dosage unit, a test and limit for weight variation may be established in lieu of content uniformity testing;
- modified-release products: a meaningful API release method;
- inhalation and nasal products: mean delivered dose, consistency of delivered dose (throughout the use of the product), particle or droplet size distribution profiles (comparable to the product used in in vivo studies, where applicable) and if applicable for the dosage form, moisture content, leak rate, microbial limits, preservative assay, sterility and weight loss;
- suppositories: uniformity of dosage units, melting point;
- transdermal dosage forms: peel or shear force, mean weight per unit area, dissolution.

Unless there is appropriate justification, the generally accepted limit for the API content of the FPP in the release specifications is $\pm 5\%$ of the label claim (i.e. 95.0–105.0%).

For products such as tablets, capsules and suppositories where a test for uniformity of single dose preparations is required, a test and limit for content uniformity is required when the API is present in the FPP at less than 5 mg or less than 5% of the weight of the dosage unit. Otherwise, the test for mass uniformity may be applied.

Skip testing is generally acceptable for parameters such as identification of colouring materials and microbial limits, when justified by the submission of acceptable supportive results for five production batches. When skip testing justification has

been accepted, the specifications should include a footnote, stating at a minimum the following skip testing requirements: at a minimum every tenth batch and at least one batch annually is tested. In addition, for stability-indicating parameters such as microbial limits, testing will be performed at release and at the end of the shelf-life during stability studies.

Any differences between release and shelf-life tests and acceptance criteria should be clearly indicated and justified. Note that such differences for parameters such as dissolution are normally not accepted.

Reference documents: ICH Q3B (17), Q3C (18), Q6A (13)

3.2.P.5.2 Analytical procedures (name, dosage form)

The analytical procedures used for testing the FPP should be provided.

Copies of the in-house analytical procedures used during pharmaceutical development (if used to generate testing results provided in the PD) as well as those proposed for routine testing should be provided. Unless modified, it is not necessary to provide copies of officially-recognized compendial analytical procedures.

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay/impurity methods) can be found in section 2.3.R Regional information, of the QOS-PD (i.e. 2.3.R.2). These tables may be used to summarize the analytical procedures used for determination of the assay, related substances and dissolution of the FPP.

Refer to section 3.2.S.4.2 of these guidelines for additional guidance on analytical procedures.

Reference document: ICH Q2 (22)

3.2.P.5.3 Validation of analytical procedures (name, dosage form)

Analytical validation information, including experimental data, for the analytical procedures used for testing the FPP, should be provided.

Copies of the validation reports for the in-house analytical procedures used during pharmaceutical development (if used to support testing results provided in the PD) as well as those proposed for routine testing should be provided.

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay/impurity methods, GC methods) can be found in section 2.3.R Regional information, of the QOS-PD (i.e. 2.3.R.2). These tables may be used to summarize the validation information of the analytical procedures used for determination of the assay, related substances and dissolution of the FPP.

As recognized by regulatory authorities and pharmacopoeias themselves, verification of compendial methods may be necessary. The compendial methods, as

published, are typically validated based on an API or an FPP originating from a specific manufacturer. Different sources of the same API or FPP can contain impurities and/or degradation products or excipients that were not considered during the development of the monograph. Therefore the monograph and compendial method(s) should be demonstrated to be suitable for the control of the proposed FPP.

For officially-recognized compendial FPP *assay* methods, verification should include a demonstration of specificity, accuracy and repeatability (method precision). If an officially-recognized compendial method is used to control related substances that are not specified in the monograph, full validation of the method is expected with respect to those related substances.

If an officially-recognized compendial standard is claimed and an in-house method is used in lieu of the compendial method (e.g. for assay or for related compounds), equivalency of the in-house and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For related compound methods, the sample analysed should be the placebo spiked with related compounds at concentrations equivalent to their specification limits.

Reference document: ICH Q2 (22)

3.2.P.5.4 *Batch analyses (name, dosage form)*

A description of batches and results of batch analyses should be provided.

Information should include strength and batch number, batch size, date and site of production and use (e.g. used in comparative bioavailability or biowaiver studies, preclinical and clinical studies (if relevant), stability, pilot, scale-up and, if available, production-scale batches) on relevant FPP batches used to establish the specification(s) and evaluate consistency in manufacturing.

Analytical results tested by the company responsible for the batch release of the FPP (generally, the applicant or the FPP manufacturer, if different from the applicant) should be provided for not less than two batches of at least pilot scale, or in the case of an uncomplicated³ FPP (e.g. immediate-release solid FPPs (with noted exceptions), non-sterile solutions), not less than one batch of at least pilot scale and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules) of each proposed strength of the FPP. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

³ Examples of products that could be included under the term "complicated FPP" include sterile products, metered dose inhaler products, dry powder inhaler products and transdermal delivery systems, as well as FDC and monocomponent products containing APIs known to be of low solubility, or known to have poor stability or polymorphism issues.

The testing results should include the batch(es) used in the comparative bioavailability or biowaiver studies. Copies of the certificates of analysis for these batches should be provided in the PD and the company responsible for generating the testing results should be identified.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “all tests meet specifications”. This should include ranges of analytical results, where relevant. For quantitative tests (e.g. individual and total impurity tests and assay tests), it should be ensured that actual *numerical results* are provided rather than vague statements such as “within limits” or “conforms” (e.g. “levels of degradation product A ranged from 0.2 to 0.4%”). Dissolution results should be expressed at a minimum as both the average and the range of individual results. Recommendations for conducting and assessing comparative dissolution profiles can be found in Appendix 1.

A discussion and justification should be provided for any incomplete analyses (e.g. results not tested according to the proposed specification).

Reference documents: ICH Q3B (17), Q3C (18), Q6A (13)

3.2.P.5.5 Characterization of impurities (name, dosage form)

Information on the characterization of impurities should be provided, if not previously provided in “3.2.S.3.2 Impurities”.

A discussion should be provided of all impurities that are potential degradation products (including any of the impurities identified in 3.2.S.3.2 as well as potential degradation products resulting from interaction of the API with other APIs (FDCs), excipients or the container-closure system) and FPP process-related impurities (e.g. residual solvents in the manufacturing process for the FPP).

Reference documents: ICH Q3B (17), Q3C (18), Q6A (13)

3.2.P.5.6 Justification of specification(s) (name, dosage form)

Justification for the proposed FPP specification(s) should be provided.

A discussion should be provided on the omission or inclusion of particular tests, evolution of tests, analytical procedures and acceptance criteria, differences from the officially-recognized compendial standard(s). If the officially-recognized compendial methods have been modified or replaced, a discussion should be included.

The justification for certain tests, analytical procedures and acceptance criteria (e.g. degradation products or dissolution method development) may have been discussed in other sections of the PD and does not need to be repeated here, although a cross-reference to their location should be provided.

ICH Q6A (13) should be consulted for the development of specifications for FPPs.

3.2.P.6 Reference standards or materials (name, dosage form)

Information on the reference standards or reference materials used for testing of the FPP should be provided, if not previously provided in “3.2.S.5 Reference standards or materials”.

See Section 3.2.S.5 for information that should be provided on reference standards or materials. Information should be provided on reference materials of FPP degradation products, where not included in 3.2.S.5.

Reference documents: ICH Q6A (13), WHO Technical Report Series, No. 943, 2007 Annex 3 (23)

3.2.P.7 Container-closure system (name, dosage form)

A description of the container-closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g. those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located in 3.2.P.2.

The WHO *Guidelines on packaging for pharmaceutical products* (WHO Technical Report Series, No. 902, Annex 9, 2002) and the officially-recognized pharmacopoeias should be consulted for recommendations on the packaging information for FPPs (24).

Descriptions, materials of construction and specifications (of the company responsible for packaging the FPP, generally the FPP manufacturer) should be provided for the packaging components that are:

- in direct contact with the dosage form (e.g. container, closure, liner, desiccant, filler);
- used for drug delivery (including the device(s) for multidose solutions, emulsions, suspensions and powders/granules for such);
- used as a protective barrier to help ensure stability or sterility;
- necessary to ensure FPP quality during storage and shipping.

Primary packaging components are those that are in direct contact with the API or FPP. The specifications for the primary packaging components should include a specific test for identification (e.g. IR). Specifications for film and foil materials should include limits for thickness or area weight.

Information to establish the suitability (e.g. qualification) of the container-closure system should be discussed in Section 3.2.P.2.4. Comparative studies may be warranted for certain changes in packaging components (e.g. comparative delivery study (droplet size) for a change in manufacturer of dropper tips).

3.2.P.8 Stability (name, dosage form)

3.2.P.8.1 Stability summary and conclusions (name, dosage form)

The types of studies conducted, protocols used, and the results of the studies should be summarised. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life.

The WHO *Guidelines on Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (WHO Technical Report Series, No. 953, 2009, Annex 2) should be consulted for recommendations on the core stability data package (9).

As outlined in the WHO *stability guidelines*, the purpose of stability testing is to provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability programme also includes the study of product-related factors that influence its quality, for example, interaction of API with excipients, container-closure systems and packaging materials.

Stress testing

As outlined in the WHO *stability guidelines*, photostability testing should be conducted on at least one primary batch of the FPP if appropriate. If “protect from light” is stated in one of the officially recognized pharmacopoeias for the API or FPP, it is sufficient to state “protect from light” on labelling, in lieu of photostability studies, when the container-closure system is shown to be light protective. Additional stress testing of specific types of dosage forms may be appropriate (e.g. cyclic studies for semi-solid products, freeze-thaw studies for liquid products).

Accelerated, intermediate (if necessary) and long-term testing

Stability data must demonstrate stability of the medicinal product throughout its intended shelf-life under the climatic conditions prevalent in the target countries. Merely applying the same requirements applicable to other markets could potentially lead to substandard products, e.g. stability studies conducted for countries in Climatic Zone I/II when the products are supplied to countries in Climatic Zones III and IV. Refer to WHO Technical Report Series, No. 953, 2009, Annex 2, Appendix 1, for information on climatic zones (9).

Refer to WHO Technical Report Series, No. 953, 2009, Annex 2 for further information regarding the storage conditions, including the minimum data required at the time of submitting the dossier (9).

To establish the shelf-life, data should be provided on not less than two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g. immediate-release solid FPPs (with noted exceptions), non-sterile solutions), not less than one batch of at least pilot scale and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules) of each proposed strength of the FPP. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. Where possible, batches of the FPP should be manufactured using different batches of the API(s). Stability studies should be performed on each individual strength, dosage form and container type and size of the FPP unless bracketing or matrixing is applied.

The stability testing programme should be summarized and the results of stability testing should be reported in the dossier and summarized in the tables in the QOS-PD. Bracketing and matrixing of proportional strengths can be applied, if scientifically justified.

For sterile products, sterility should be reported at the beginning and end of shelf-life. For parenteral products, subvisible particulate matter should be reported frequently, but not necessarily at every test interval. Bacterial endotoxins need only be reported at the initial test interval. Weight loss from plastic containers should be reported over the shelf-life.

Any in-use period and associated storage conditions should be justified with experimental data, for example after opening, reconstitution and/or dilution of any sterile and/or multidose products or after first opening of FPPs packed in bulk multidose containers (e.g. bottles of 1000s). If applicable, the in-use period and storage conditions should be stated in the product information.

The information on the stability studies should include details such as:

- storage conditions;
- strength;
- batch number, including the API batch number(s) and manufacturer(s);
- batch size;
- container-closure system including orientation (e.g. erect, inverted, on-side) where applicable (e.g. semi-solids and liquids in plastic containers);
- completed (and proposed) test intervals.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “all tests meet specifications”. This should include ranges of analytical results and any trends that were observed. For quantitative tests (e.g. individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms”. Dissolution results should be expressed at a minimum as both the average and range of individual results.

Applicants should consult ICH's Q1E guideline (28) for details on the evaluation and extrapolation of results from stability data (e.g. if significant change was not observed within 6 months at accelerated condition and the data show little or no variability, the proposed shelf-life could be up to two times the period covered by the long-term data, but should not exceed the long-term data by more than 12 months).

Proposed storage statement and shelf-life

The proposed storage statement and shelf-life (and in-use storage conditions and in-use period, if applicable) for the FPP should be provided.

The recommended labelling statements for use, based on the stability studies, are provided in the WHO *stability guidelines* (9).

Reference documents: WHO Technical Report Series, No. 953, 2009, Annex 2 (9), ICH Q1A (26), Q1B (25), Q1C (42), Q1D (27), Q1E (28), Q3B (17), Q6A (43)

3.2.P.8.2 Post-approval stability protocol and stability commitment (name, dosage form)

The post-approval stability protocol and stability commitment should be provided.

Primary stability study commitment

When the available data on long-term stability of primary batches do not cover the proposed shelf-life granted at the time of assessment of the PD, a commitment should be made to continue the stability studies in order to firmly establish the shelf-life. A written commitment (signed and dated) to continue long-term testing over the shelf-life period should be included in the dossier.

Commitment stability studies

The long-term stability studies for the *Commitment batches* should be conducted throughout the proposed shelf-life on at least three production batches of each strength in each container-closure system. Where stability data were not provided for three production batches of each strength, a written commitment (signed and dated) should be included in the dossier.

Ongoing stability studies

As described in the WHO stability guidelines, an ongoing stability programme is established to monitor the product over its shelf-life and to determine that the product remains and can be expected to remain within specifications when kept under the storage conditions on the label. Unless otherwise justified, at least one batch per year of product manufactured, in every strength, and every container-closure system, if relevant, should be included in the stability programme (unless none is produced during that year). Bracketing and matrixing may be applicable. A written commitment (signed and dated) to this effect should be included in the dossier.

Any differences in the stability protocols used for the primary batches and those proposed for the commitment batches or ongoing batches should be scientifically justified.

Reference documents: ICH Q1A (26)

3.2.P.8.3 Stability data (name, dosage form)

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Information on characterization of impurities is located in 3.2.P.5.5.

The actual stability results/reports used to support the proposed shelf-life should be provided in the PD. For quantitative tests (e.g. individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms”. Dissolution results should be expressed at a minimum as both the average and range of individual results.

Reference documents: ICH Q1A (26), Q1B (25), Q1C (42), Q1D (27), Q1E (28), Q2 (22)

3.2.A Appendices

3.2.A.1 Facilities and equipment

Not applicable (i.e. not a biotech product).

3.2.A.2 Adventitious agents safety evaluation

3.2.A.3 Novel excipients

At its discretion an NMRA may choose not to accept the use of novel excipients in submitted PDs. If novel excipients are accepted, full information should be provided in the format of the sections in 3.2.P.

3.2.R Regional information

Refer to 1.5 for additional guidance on regional information.

3.2.R.1 Production documentation

3.2.R.1.1 Executed production documents

A minimum of two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g. immediate-release solid FPPs (with noted exceptions), non-sterile solutions), not less than one batch of at least pilot scale (the batch used in comparative bioavailability or biowaiver studies) and a second batch which may be smaller (e.g. for solid oral

dosage forms, 25 000 or 50 000 tablets or capsules), should be manufactured for each strength. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

For solid oral dosage forms, pilot scale is generally, at a minimum, one-tenth that of full production scale or 100 000 tablets or capsules, whichever is the larger.

Copies of the executed production documents should be provided for the batches used in the comparative bioavailability or biowaiver studies. Any notations made by operators on the executed production documents should be clearly legible.

If not included in the executed batch records through sufficient in-process testing, data should be provided for the batch used in comparative bioavailability or biowaiver studies that demonstrates the uniformity of this batch. The data to establish the uniformity of the biobatch should involve testing to an extent greater than that required in routine quality control.

English translations of executed records should be provided, where relevant.

3.2.R.1.2 Master production documents

Copies of the FPP master production documents should be provided for each proposed strength, commercial batch size and manufacturing site.

The details in the master production documents should include, but not be limited to, the following:

- (a) master formula;
- (b) dispensing, processing and packaging sections with relevant material and operational details;
- (c) relevant calculations (e.g. if the amount of API is adjusted based on the assay results or on the anhydrous basis);
- (d) identification of all equipment by, at a minimum, its type and working capacity (including make, model and equipment number, where possible);
- (e) process parameters (e.g. mixing time, mixing speed, milling screen size, processing temperature range, granulation end-point, tablet machine speed (expressed as target and range));
- (f) list of in-process tests (e.g. appearance, pH, assay, blend uniformity, viscosity, particle size distribution, loss on drying, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity, filter integrity checks) and specifications;
- (g) sampling plan with regard to the:
 - steps where sampling should be done (e.g. drying, lubrication, compression),

- number of samples that should be tested (e.g. for blend uniformity testing of low dose FPPs, blend drawn using a sampling thief from x positions in the blender),
 - frequency of testing (e.g. weight variation every x minutes during compression or capsule filling);
- (h) precautions necessary to ensure product quality (e.g. temperature and humidity control, maximum holding times);
- (i) for sterile products, reference to SOPs in appropriate sections and a list of all relevant SOPs at the end of the document;
- (j) theoretical and actual yield;
- (k) compliance with the GMP requirements.

Reference documents: WHO Technical Report Series, No. 961, 2011, Annex 3 (10) and Annex 6 (44)

3.2.R.2 Analytical procedures and validation information

The tables presented in section 2.3.R.2 in the QOS-PD template may be used to summarize the analytical procedures and validation information from sections 3.2.S.4.2, 3.2.S.4.3, 2.3.S.4.4 (c), 2.3.S.7.3 (b), 3.2.P.5.2 and 3.2.P.5.3, where relevant.

4.3 Literature references

References to the scientific literature relating to both the API and FPP should be included in this section of the PD when appropriate.

References

1. Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-sixth report*. Geneva, World Health Organization, 2012, Annex 4 (WHO Technical Report Series, No. 970; https://iris.who.int/bitstream/handle/10665/75168/WHO_TRS_970.pdf?sequence=1&isAllowed=y).
2. International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: The Common Technical Document for the registration of pharmaceuticals for human use: quality – M4Q*, September 2002.
3. Guidelines on submission of documentation for a multisource (generic) finished product: general format: preparation of product dossiers in common technical document format. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth report*. Geneva, World Health Organization, 2011, Annex 15 (WHO Technical Report Series, No. 961; https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1).

4. Procedure for prequalification of pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2011, Annex 10 (WHO Technical Report Series, No. 961; https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1).
5. International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients – Q7*, November 2000.
6. WHO good manufacturing practices for active pharmaceutical ingredients. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report*. Geneva, World Health Organization, 2010, Annex 2 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y).
7. Guidelines for registration of fixed-dose combination medicinal products. Appendix 3: Pharmaceutical development (or preformulation) studies. Table A1: Typical stress conditions in preformulation stability studies. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report*. Geneva, World Health Organization, 2005, Annex 5 (WHO Technical Report Series, No. 929; https://iris.who.int/bitstream/handle/10665/43157/WHO_TRS_929_eng.pdf?sequence=1&isAllowed=y).
8. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization, 2006, Annex 7 (WHO Technical Report Series, No. 937; https://apps.who.int/iris/bitstream/handle/10665/43443/WHO_TRS_937_eng.pdf?sequence=1).
9. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2009, Annex 2 (WHO Technical Report Series, No. 953; https://iris.who.int/bitstream/handle/10665/44553/WHO_TRS_953_eng.pdf?sequence=1&isAllowed=y).
10. Good manufacturing practices for pharmaceutical products: main principles. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2011, Annex 3 (WHO Technical Report Series, No. 961; https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1).
11. Guidelines on active pharmaceutical ingredient master file procedure. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-second report*. Geneva, World Health Organization, 2008, Annex 4 (WHO Technical Report Series, No. 948; https://iris.who.int/bitstream/handle/10665/43852/WHO_TRS_948_eng.pdf?sequence=1&isAllowed=y).
12. International Conference on Harmonisation *ICH Topic M 4 Q Location issues for Common Technical Document for the Registration of Pharmaceuticals for Human Use – Quality Questions and Answers*. August 2003.
13. International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances – Q6A*, October 1999.
14. WHO guidelines on variations to a prequalified product. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh report*. Geneva, World Health Organization, 2013, Annex 3 (WHO Technical Report Series, No. 981; https://iris.who.int/bitstream/handle/10665/81144/WHO_TRS_981_eng.pdf?sequence=1&isAllowed=y).
15. International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: development and manufacture of drug substances (chemical entities and biotechnological/biological entities) – Q11*, May 2012.

16. International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: impurities in new drug substances – Q3A*, October 2006.
17. International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: impurities in new drug products – Q3B*, June 2006.
18. International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: impurities: guideline for residual solvents – Q3C*, February 2011.
19. European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use (CHMP) *Guideline on the limits of genotoxic impurities* (EMA/CHMP/QWP/ 251344/2006), 2006.
20. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) *Guidance for Industry: Genotoxic and carcinogenic impurities in drug substances and products, recommended approaches*, 2008.
21. European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use (CHMP) *Guideline on the specification limits for residues of metal catalysts or metal reagents* (EMA/CHMP/ SWP/4446/2000), 2008.
22. International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: validation of analytical procedures: text and methodology – Q2*, November 2005.
23. General guidelines for the establishment, maintenance and distribution of chemical reference substances. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report*. Geneva, World Health Organization, 2007, Annex 3 (WHO Technical Report Series, No. 943; https://iris.who.int/bitstream/handle/10665/43632/WHO_TRS_943_eng.pdf?sequence=1&isAllowed=y).
24. Guidelines on packaging for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002, Annex 9 (WHO Technical Report Series, No. 902; https://iris.who.int/bitstream/handle/10665/42424/WHO_TRS_902.pdf?sequence=1&isAllowed=y).
25. International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: stability testing: photostability testing of new drug substances and products – Q1B*, November 1996.
26. International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: stability testing of new drug substances and products – Q1A*, February 2003.
27. International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: bracketing and matrixing designs for stability testing of new drug substances and products – Q1D*, February 2002.
28. International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: evaluation for stability data – Q1E*, February 2003.
29. International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: pharmaceutical development – Q8*, August 2009.
30. International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: quality risk management – Q9*, November 2005.
31. International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: pharmaceutical quality system – Q10*, June 2008.
32. Rowe RC, Sheskey PJ, Quinn ME (eds) *Handbook of pharmaceutical excipients*, 6th ed. London/ Washington, DC, Pharmaceutical Press/American Pharmacists Association, 2009.
33. *Excipients in the label and package leaflet of medicinal products for human use* (EMA Guideline CPMP/463/00), 2003.

34. Development of paediatric medicines: points to consider in formulation. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-sixth report*. Geneva, World Health Organization, 2012, Annex 5 (WHO Technical Report Series, No. 970; https://iris.who.int/bitstream/handle/10665/75168/WHO_TRS_970.pdf?sequence=1&isAllowed=y).
35. Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. *Official Journal of the European Union L 12/1*, 15.1.2011.
36. WHO good distribution practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report*. Geneva, World Health Organization, 2010, Annex 5 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y).
37. *Japanese Pharmaceutical Excipients Directory*, Tokyo, Maruzen International Company, 1996.
38. International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: viral safety evaluation of biotechnology products derived from cell lines of human or animal origin – Q5A*, September 1999.
39. International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: derivation and characterisation of cell substrates used for production of biotechnological/biological products – Q5D*, July 1997.
40. ICH Q6B International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: specifications: test procedures and acceptance criteria for biotechnological/biological products – Q6B*, 10 March 1999.
41. Recommendations on risk of transmitting animal spongiform encephalopathy agents via medicinal products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003, Annex 1 (WHO Technical Report Series, No. 908; https://iris.who.int/bitstream/handle/10665/42613/WHO_TRS_908.pdf?sequence=1&isAllowed=y).
42. ICH Q1C International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: stability testing for new dosage forms – Q1C*, November 1996.
43. ICH Q6A International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline: specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances – Q6A*, October 1999.
44. WHO Good manufacturing practices for sterile pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2011, Annex 6 (WHO Technical Report Series, No. 961; https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1).

Appendix 1

Recommendations for conducting and assessing comparative dissolution profiles¹

The dissolution measurements of the two FPPs (e.g. test and reference (comparator), or two different strengths) should be made under the same test conditions. A minimum of three time points (zero excluded) should be included, the time points for both reference and test product being the same. The sampling intervals should be short for a scientifically sound comparison of the profiles (e.g. 5, 10, 15, 20, 30, 45 (60, 90, 120) minutes). Inclusion of the 15-minute time point in the schedule is of strategic importance for profile similarity determinations (very rapidly dissolving scenario). For extended-release FPPs, the time points should be set to cover the entire time period of expected release, e.g. 1, 2, 3, 5 and 8 hours for a 12-hour release and additional test intervals for longer duration of release.

Studies should be performed in at least three media covering the physiological range, including pH 1.2 hydrochloric acid, pH 4.5 buffer and pH 6.8 buffer. International Pharmacopoeia buffers are recommended; alternative compendia buffers with the same pH and buffer capacity are also accepted. Water may be considered as an additional medium, especially when the API is unstable in the buffered media to the extent that the data are unusable.

If both the test and reference products show more than 85% dissolution in 15 minutes, the profiles are considered similar (no calculations required). Otherwise:

- *similarity* of the resulting comparative dissolution profiles should be calculated using the following equation that defines a similarity factor (f_2):

$$f_2 = 50 \text{ LOG } \{ [1 + 1/n \sum_{t=1}^n (R_t - T_t)^2]^{-0.5} \times 100 \}$$

where R_t and T_t are the mean percentage of API dissolved in reference and test product, respectively, at each time point. An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar:

- a maximum of one time-point should be considered after 85% dissolution of the reference product has been reached. In the case where 85% dissolution cannot be reached due to poor solubility of the API, the dissolution should be conducted until an asymptote (plateau) has been reached;

¹ The information provided is with reference to the quality aspects of the dossier. Refer to relevant bioequivalence documents for guidance specific to the requirements for dissolution studies related to bioequivalence studies.

- at least 12 units should be used for each profile determination. Mean dissolution values can be used to estimate the similarity factor, f_2 . To use mean data, the percentage coefficient of variation at the first time point should be not more than 20% and at other time points should be not more than 10%;
- when delayed-release products (e.g. enteric coated) are being compared, the recommended conditions are acid medium (pH 1.2) for 2 hours and buffer pH 6.8 medium;
- when comparing extended-release beaded capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the API, one condition (normally the release condition) will suffice;
- surfactants should be avoided in comparative dissolution testing. A statement that the API is not soluble in any of the media is not sufficient and profiles in the absence of surfactant should be provided. The rationale for the choice and concentration of surfactant should be provided. The concentration of the surfactant should be such that the discriminatory power of the test will not be compromised.

2.2 Guidelines for the registration of fixed-dose combination medicinal products

Annex 5, WHO Technical Report Series, 929, 2005

Abbreviations	134
Introduction	135
1. Scope	135
2. General considerations	136
3. Definitions	146
4. Scenarios	149
5. Balancing the advantages and disadvantages of a new fixed-dose combination	149
6. Data requirements for marketing authorization of fixed-dose combination finished pharmaceutical products	152
7. Product information (or summary of product characteristics) for fixed-dose combination finished pharmaceutical products	170
8. Postmarketing studies and variations	171
Reference	172
Appendix 1 Guidelines for co-packaged fixed-dose combinations	173
Appendix 2 Principles for determining whether data from the scientific literature are acceptable	174
Appendix 3 Pharmaceutical development (or preformulation) studies	177
Appendix 4 Superiority, equivalence and non-inferiority clinical trials	179

Abbreviations

AIHW	Australian Institute of Health and Welfare
API	active pharmaceutical ingredient
BCS	Biopharmaceutics Classification Scheme
BCS #1	Biopharmaceutics class number 1 (the most favourable)
CHMP	Committee for Medicinal Products for Human Use; <i>see also</i> CPMP
CPMP	Committee for Medicinal Products for Human Use (CHMP), formerly the Committee for Proprietary Medicinal Products
CPP	certificate of pharmaceutical product
EMA	European Medicines Agency, formerly the European Medicines Evaluation Agency
EU	European Union
FDA	Food and Drug Administration of the USA
FDC	fixed-dose combination (<i>see</i> Glossary)
FDC-FPP	fixed-dose combination finished pharmaceutical product (<i>see</i> Glossary)
FPP	finished pharmaceutical product
GCP	good clinical practice
GLP	good laboratory practice
GMP	good manufacturing practice
GTDP	good trade and distribution practice
GSP	good storage practice
ICH	International Conference on Harmonisation
IUTLD	International Union of Tuberculosis and Lung Disease
MIC	minimum inhibitory concentration
PP	per-protocol (a form of clinical trial design and analysis)
SPC	summary of product characteristics (<i>see</i> Glossary)
TGA	Therapeutic Goods Administration
WHO	World Health Organization

Introduction

The development of fixed-dose combinations (FDCs) is becoming increasingly important from a public health perspective. They are being used in the treatment of a wide range of conditions and are particularly useful in the management of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), malaria and tuberculosis, which are considered to be the foremost infectious disease threats in the world today.

FDCs have advantages when there is an identifiable patient population for whom treatment with a particular combination of actives in a fixed ratio of doses has been shown to be safe and effective, and when 96 all of the actives contribute to the overall therapeutic effect. In addition there can be real clinical benefits in the form of increased efficacy and/or a reduced incidence of adverse effects, but such claims should be supported by evidence.

Additionally, in a situation of limited resources, the cost of an FDC finished pharmaceutical product (FDC-FPP) may be less than that of separate products given concurrently, and there are simpler logistics of distribution. Improved patient adherence and reduced development of resistance in the case of antimicrobials can be difficult to prove, but may be additional benefits.

Notwithstanding these potential benefits, FDCs must be shown to be safe and effective for the claimed indications. It should not be assumed that benefits outweigh risks. As for any new medicine, the risks and benefits should be defined and compared.

The World Health Organization has published a series of guidelines relating to marketing authorization of finished pharmaceutical products (FPPs) (see Table 1). Currently there are no specific international guidelines for FDCs. Some national authorities have developed their own guidelines, some for specific classes of medicines (see Table 2). These guidelines are intended to provide advice to those countries that do not, as yet, have guidelines for this type of product. They will also provide guidance to industry when developing new products and when considering the regulatory requirements that will need to be met.

In drafting these guidelines, existing international publications have been taken into account and in some cases text has been copied directly. The various scenarios considered below are essentially the same as those in the draft *Scientific and technical principles for fixed dose combination drug products* that followed a meeting of interested parties held in Botswana in April 2004.

1. Scope

- 1.1 The scope of these guidelines is restricted to medicines that in most jurisdictions would be available only on prescription.

Although similar principles would apply to the registration of non-prescription products, the risk-benefit considerations (and consequently data requirements) may be different.

- 1.2 The principles in these guidelines would also apply to chemical combinations and complexes that comprise more than one active.
- 1.3 Registration of co-packaged medicines is not the primary purpose of these guidelines. However, many of the same considerations apply in balancing the advantages and disadvantages of copackaged medicines, although the quality issues are different (see Appendix 1).

2. General considerations

- 2.1 These are not intended to be stand-alone guidelines.
 - 2.1.1 Many general guidelines are also applicable to FDCs. Table 1 lists some relevant WHO publications.
 - 2.1.2 Other international guidelines that pertain to FDCs in particular are summarized in Table 2, together with brief notes as to their content. Some of these relate to particular therapeutic groups such as antihypertensives, or particular topics such as bioavailability.
 - 2.1.3 Table 3 lists other guidelines that were consulted in preparing this text.
 - 2.1.4 A number of International Conference on Harmonisation (ICH) guidelines are referred to in this text when, as at the date of writing, there was no applicable WHO guideline (see Tables 4 and 5).
 - 2.1.5 When a guideline is cited in the text or tables below, the most recent edition should normally be substituted.
 - 2.1.6 If an applicant makes reference to guidelines not cited here, this may be acceptable depending on the case in point and provided that the applicant justifies the alternative reference.
 - 2.1.7 Appendices 2, 3 and 4 provide guidance on subjects that are not exclusive to FDCs, but are nevertheless important in this context, and for which suitable guidance is not otherwise readily available.
 - 2.1.8 The guidelines in Tables 1–5 may not be a comprehensive list of all relevant guidelines.
- 2.2 It is important that access to useful, new FDCs should not be delayed by unnecessary constraints. These guidelines are not intended to define the only means of demonstrating the advantages and disadvantages of a new FDC. In some cases an alternative approach may be appropriate, for example when:

Table 1
WHO guidelines relevant to marketing authorization

Title	Date
<i>Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for a drug regulatory authority. A general text with relevant annexes (see below). Also known as “the Blue book”^a</i>	1999
<i>National drug regulatory legislation: guiding principles for small drug regulatory authorities. Blue book, Annex 1.</i>	1999
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report (WHO Technical Report Series, No. 863), Annex 10: Guidelines for Implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce and Guidelines for implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. Blue book, Annex 2.</i>	1996
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report (WHO Technical Report Series, No. 863), Annex 9: Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability and</i>	1996
<i>Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Blue book, Annex 3.^a</i>	1999
<i>Model guidelines on conflict of interest and model proforma for a signed statement on conflict of interest. Blue book, Annex 4.</i>	1999
<i>Model contract between a regulatory authority and an external evaluator of chemistry, pharmaceutical and bioavailability data. Blue book, Annex 5.</i>	1999
<i>Model application form for new marketing authorizations, periodic reviews and variations, with notes to the applicant. Blue book, Annex 6.</i>	1999
<i>Detailed advice on evaluation of data by the drug regulatory authority. Blue book, Annex 7.</i>	1999
<i>Ethical criteria for medicinal drug promotion. Blue book, Annex 8.</i>	1999
<i>Model marketing authorization letter. Blue Book, Annex 9.</i>	1999
<i>Model list of variations (changes) to pharmaceutical aspects of registered products which may be made without prior approval. Blue book, Annex 10.</i>	1999

Table 1 *continued*

Title	Date
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.</i> (WHO Technical Report Series, No. 863), Annex 5: Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms	1996
and <i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report</i> (WHO Technical Report Series, No. 908)	2003
and Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms. Blue book, Annex 11. ^a	1999 (and 2001 rev)
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report</i> (WHO Technical Report Series, No. 908), Annex 4: Good manufacturing practices for pharmaceutical products and inspection: main principles	2003
and <i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report</i> (WHO Technical Report Series, No. 929, Annex 2)	2005
and Quality assurance of pharmaceuticals. A compendium of guidelines and related materials, Volume 2, updated edition.	2004
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report</i> (WHO Technical Report Series, No. 917), Annex 2: Good trade and distribution practices for pharmaceutical starting materials.	2004
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report</i> (WHO Technical Report Series, No. 917), Annex 3: WHO pharmaceutical starting materials certification scheme (SMACS): Guidelines on implementation.	2004
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report</i> (WHO Technical Report Series, No. 908), Annex 9: Guide to good storage practices for pharmaceuticals	2003
<i>The importance of pharmacovigilance: safety monitoring of medicinal products</i> ^a	2002
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report</i> (WHO Technical Report Series, No. 902), Annex 11: Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products (under revision).	2002
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report</i> (WHO Technical Report Series, No. 902), Annex 3: Good practices for national pharmaceutical control laboratories.	2002

Table 1 *continued*

Title	Date
<i>Handbook: good laboratory practice: quality practices for regulated non-clinical research and development</i> (WHO document TDR/PRD/GLP/01.2,WHO-TDR) in collaboration with the United Nations and World Bank.	2001
<i>Establishing the bioequivalence of rifampicin in fixed-dose formulations containing isoniazid with or without pyrazinamide and/or ethambutol compared to the single drug reference preparations administered in loose combination: model protocol.</i>	1999
Quality assurance: protocol for assessing the rifampicin bioavailability of combined formulations in healthy volunteers: WHO/IUTLD joint statement. <i>International Journal of Tuberculosis and Lung Disease</i> , 3, S284–S285.	1999
Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. In: <i>The use of essential drugs</i> . WHO Technical Report Series, No. 850.	1995

^a These publications are being further updated.

Table 2

International guidelines that relate directly to fixed-dose combination finished pharmaceutical products

Title, publisher and date	Notes
<i>Fixed dose combination and co-packaged drug products for treatment of HIV.</i> Washington, DC, Food and Drug Administration, May 2004, DRAFT	21 pages
<i>Scientific and technical principles for fixed dose combination drug products.</i> Botswana, 22 April 2004, DRAFT	21 pages
<i>Part 7. Report on bioavailability of oral dosage formulations of drugs used for systemic effects. Report C. Report on bio-availability of oral dosage formulations, not in modified release form, of drugs used for systemic effects, having complicated or variable pharmacokinetics.</i> Canada, Health Protection Branch, December 1992.	Approximately 400 words. Discusses the reporting, statistical analysis and decision criteria for bioequivalence studies on combination drug products. A notice to industry in June 2004 confirmed the decision criteria.
<i>Fixed-combination prescription drugs for humans FDA, 2003</i> 21CFR300.50	Approximately 250 words. In terms of safety and efficacy, describes the circumstances in which actives may be combined in an FDC.

Table 2 *continued*

Title, publisher and date	Notes
<i>Estrogen estrogen/progestin drug products to treat vasomotor symptoms and vulvar vaginal atrophy symptoms recommendations for clinical evaluation.</i> FDA, Jan 2003 DRAFT	Ten pages. This guideline is not restricted to estrogens from a biological source. Approval will be based on two criteria: • that each component contributes to safety and efficacy as defined in 21CFR300.50 and • the FDC contains the lowest effective dose of each of the actives for their respective labelled indication.
Conjugated estrogens, USP-LC-MS method for both qualitative chemical characterization and documentation of qualitative pharmaceutical equivalence. FDA June 2000 DRAFT	Seven pages. This guideline relates only to conjugated estrogens from a biological source, normally urine from gestating mares, which contains multiple estrogens. There have been difficulties in preparing generic equivalents of this type of product. The guideline specifies how chemical equivalence can be demonstrated.
<i>Fixed-combination medicinal products.</i> CPMP Apr 1996 — CPMP/EWP/240/95, III/5773/94 (formerly known as <i>Testing and licensing criteria for fixed combination medicinal products</i>)	Four pages that: • require justification of the particular combination; • give examples of circumstances (safety and efficacy) in which FDCs may be acceptable; • describe principles that define acceptable indications; • require consideration of possible pharmacokinetic and pharmacodynamic interactions; • require evidence as to safety and efficacy (allowing bibliographical data as supportive evidence in certain circumstances); and • require evidence as to safety and efficacy of the doses selected. “This guideline is also applicable to a new chemical substance which dissociates in vivo into two well known active substances.” “Substances having a critical dosage range or a narrow therapeutic index are unlikely to be suitable for inclusion in fixed combinations.”

Table 2 *continued*

Title, publisher and date	Notes
<i>Part 7. Fixed combinations in Note for guidance on clinical investigation of medicinal products in the treatment of hypertension.</i> CPMP Nov 1997 — CPMP/EWP/238/96 Rev1	Three pages that: • describe the circumstances (in terms of safety and efficacy) in which FDCs may be acceptable in the therapy of hypertension; and • provide advice on their clinical development as first- or second-line therapy.
IV.3. The ratio and/or fixed content of one component of a combination drug product. <i>In: Points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products.</i> CPMP Jul 2000 — CPMP/EWP/2655/99	Seven pages. This guideline discusses the relationship between plasma concentration/ time profiles and clinical efficacy. Selection of a suitable ratio of doses for FDCs is discussed in Part IV.3 (approx. 100 words).
5.1.5 Fixed combination products. <i>In Note for guidance on the investigation of bioavailability bioequivalence</i> CPMP July 2001 — CPMP/EWP/QWP/1401/98	Approximately 50 words. States that FDCs should in general be assessed as to the bioavailability and bioequivalence of the individual actives administered either as single entity products given concurrently (in the case of a new combination) or as an existing combination. Studies should be designed to detect any pharmacokinetic drug–drug interaction.
<i>Part 6. Fixed combination products in ICH principles document for clinical evaluation of new antihypertensive drugs.</i> ICH/CPMP/541/00, DRAFT Also issued by CPMP as CPMP/ICH/541/00, DRAFT	Approximately 250 words. Describes two experimental designs for safety and efficacy studies on FDCs of antihypertensives, namely: • factorial studies; and • studies in patients who have failed to respond adequately to each of the drugs given alone.
<i>5.2.1 Fixed-combination products in Australian Guidelines for the Registration of Drugs, Volume 1. Australia, TGA, July 1994.</i>	Approximately 250 words. Discusses justification of the combination in terms of either pharmacodynamics or demonstrated therapeutic effect.

- 2.2.1 Scientific developments allow alternative means of achieving the same goals.
- 2.2.2 A circumstance unique to the product in question can be demonstrated.
- 2.2.3 An original but acceptable approach is devised.
- 2.2.4 Sufficient alternative studies have been conducted which, although not exactly what the guidelines seek, nevertheless satisfy the criteria of quality, safety and efficacy.

When these guidelines (or others referred to herein) describe evidence that is required, applicants may either: provide the requested evidence, or provide an alternative form of evidence that addresses the same issues. In this case, the application should include an explanation and justification of the approach taken.

- 2.3 It is not always necessary to generate new (original) data. Evidence may be obtained from the scientific literature, subject to its being of adequate quality (see Appendix 2 entitled *Principles for determining whether data from the scientific literature are acceptable*).

Table 3

Other guidelines consulted in preparing these guidelines

Title	Publisher	Date
<i>Consort E-checklist</i> . Available at: www.consort-statement.org		2004
<i>The Cochrane Collaboration</i> . Available at: http://www.cochrane.org/index0.htm		2004
<i>Literature-based submissions: points to consider</i> . Available at: http://www.tga.gov.au/docs/html/litbsubs.htm	TGA, Australia	2003
<i>Bioanalytical method validation</i> . Available at: http://www.fda.gov/cder/guidance/index.htm	FDA	2001
<i>Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system</i> . Washington, DC, US Food and Drug Administration. Available at: http://www.fda.gov/cder/guidance/index.htm	FDA	2000
<i>Specifications: test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances</i> . Available at: http://www.ich.org/UrlGrpServer.jsr?@_ID=276&@_TEMPLATE=254	ICH	1999

Table 3 *continued*

Title	Publisher	Date
<i>Points to consider on switching between superiority and non-inferiority.</i> CPMP/EWP/482/99	CPMP	1999
<i>Points to consider on the choice of non-inferiority margins.</i> EMEA, CPMP/EWP/2158/99, DRAFT	CPMP	1999
<i>Statistical principles for clinical trials.</i> EMEA, CPMP/ICH/363/99, DRAFT	CPMP	1998
<i>Development pharmaceuticals and process validation,</i> Eudralex 3AQ1a, http://pharmacos.eudra.org/	CPMP	1988
<i>Impurities in new drug products (revised).</i> Q3B(R)	ICH	2003

An application for a marketing authorization may comprise:

2.3.1 Entirely original data.

2.3.2 Entirely data from the literature.

2.3.3 Both original data and data from the literature (a “hybrid” submission).

For FDC-FPPs, it is likely that hybrid submissions will be the most common type.

The scientific literature rarely contains enough adequately validated information on quality to allow the full quality data set to be based solely on data from the literature. In particular, the complete formulation and method of manufacture are rarely specified. Consequently the quality data set is almost always either totally original or hybrid.

- 2.4 When these guidelines request that an applicant explain and/or justify non-conformity with requirements, a suitable argument should be included in the section that discusses the advantages and disadvantages of the combination (see below), together with cross-references to data elsewhere in the submission.
- 2.5 When an applicant is unsure of registration requirements or wishes to deviate from these guidelines, prior consultation with the relevant regulatory authority may be advantageous. However, applicants should not request advice until they have read all relevant guidelines and WHO’s *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for a drug regulatory authority* (1999) or updates thereof. Not all of the guidelines in Tables 1–5 are necessarily relevant to a particular enquiry; the particulars of each case should be considered.

Table 4

Preclinical guidelines from the International Conference on Harmonisation that may be a source of guidanceAvailable at: www.ich.org (last accessed 03/09/04)

Carcinogenicity studies	
S1A	Guideline on the need for carcinogenicity studies of pharmaceuticals
S1B	Testing for carcinogenicity of pharmaceuticals
S1C	Dose selection for carcinogenicity studies of pharmaceuticals
S1C(R)	Addendum to S1C: addition of a limit dose and related notes
Genotoxicity studies	
S2A	Guidance on specific aspects of regulatory tests for pharmaceuticals
S2B	A standard battery for genotoxicity testing for pharmaceuticals
Toxicokinetics and pharmacokinetics	
S3A	Note for guidance on toxicokinetics: the assessment of systemic exposure in toxicity studies
S3B	Pharmacokinetics: guidance for repeated dose tissue distribution studies
Toxicity testing	
S4	Single dose toxicity tests Agreement was reached, at the time of ICH 1, in 1991, that the determination of the median lethal dose (LD ₅₀) should be abandoned for pharmaceuticals. The recommendation was published in the <i>Proceedings of the First International Conference on Harmonisation</i> , p. 184.
S4A	Duration of chronic toxicity testing in animals (rodent and non-rodent)
Reproductive toxicology	
S5A	Detection of toxicity to reproduction for medicinal products
S5B(M)	An addendum on toxicity to male fertility (amended guideline)
Pharmacology studies	
S7A	Safety pharmacology studies for human pharmaceuticals
S7B	Safety pharmacology studies for assessing the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals
Joint safety/efficacy (multidisciplinary) topic	
M3(M)	Maintenance of the ICH guideline on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals

Table 5

Clinical guidelines from the International Conference on Harmonisation that may be a source of guidanceAvailable at: www.ich.org (last accessed: 03/09/04)

Clinical safety	
<i>E1</i>	The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions
<i>E2A</i>	Clinical safety data management: definitions and standards for expedited reporting
<i>E2B/M2</i>	Maintenance of the clinical safety data management including the maintenance of the electronic transmission of individual case safety reports message specification
<i>E2C</i>	Clinical safety data management: periodic safety update reports for marketed drugs
<i>E2CA</i>	Addendum to E2C: periodic safety update reports for marketed drugs
<i>E2D</i>	Post-approval safety data management: definitions and standards for expedited reporting
<i>E2E</i>	Pharmacovigilance planning
Clinical study reports	
<i>E3</i>	Structure and content of clinical study reports
Dose–response studies	
<i>E4</i>	Dose–response information to support drug registration
Ethnic factors	
<i>E5</i>	Ethnic factors in the acceptability of foreign clinical data
Good clinical practice	
<i>E6</i>	Good clinical practice: consolidated guideline
Clinical trials	
<i>E7</i>	Studies in support of special populations: geriatrics
<i>E8</i>	General considerations for clinical trials
<i>E9</i>	Statistical principles for clinical trials
<i>E10</i>	Choice of control group and related issues in clinical trials
<i>E11</i>	Clinical investigation of medicinal products in the paediatric population
Guidelines for clinical evaluation by therapeutic category	
<i>E12A</i>	Principles for clinical evaluation of new antihypertensive drugs (consensus draft principle)
Clinical evaluation	
<i>E14</i>	The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs

- 2.6 Risk–benefit assessments for FDCs should take into consideration any differences in anticipated patient populations. Consequently decisions on the same data set may vary between different national drug regulatory authorities.

3. Definitions

The definitions given below apply solely to the terms as used in these guidelines. They may have different meanings in other contexts.

Active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form. When so used the API becomes the *active moiety* as defined below, often termed simply the *active*. The API may be a salt, hydrate or other form of the active moiety, or may be the active moiety itself. Active moieties are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Active moiety

The term used for the therapeutically active entity in the final formulation of therapeutic goods, irrespective of the form of the API. The active is alternative terminology with the same meaning. For example, if the API is propranolol hydrochloride, the active moiety (the active) is propranolol.

applicant

The person or company who submits an application for marketing authorization of a new pharmaceutical product, an update to an existing marketing authorization or a variation to an existing market authorization.

certificate of pharmaceutical product

A WHO-type certificate of the form described in *Guidelines for implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce*. Geneva, World Health Organization, 1998.

comparator

The finished pharmaceutical product with which an FDC-FPP is to be compared. The comparison may be by means of bioequivalence studies or clinical studies of safety and/or effectiveness. A single study may use more than one comparator, for example several single entity FPPs. A comparator may be a placebo.

co-packaged product

A product consisting of two or more separate pharmaceutical products in their final dosage form that are packaged together for distribution to patients in the co-packaging.

drug

Any substance or product for human or veterinary use that is intended to modify or explore physiological states for the benefit of the recipient.

finished pharmaceutical product (FPP)

A product that has undergone all stages of production, including packaging in its final container and labelling. An FPP may contain one or more actives.

fixed-dose combination (FDC)

A combination of two or more actives in a fixed ratio of doses. This term is used generically to mean a particular combination of actives irrespective of the formulation or brand. It may be administered as single entity products given concurrently or as a finished pharmaceutical product.

fixed-dose combination finished pharmaceutical product (FDC-FPP)

A finished pharmaceutical product that contains two or more actives.

generic products

The term generic product has somewhat different meanings in different jurisdictions. Use of this term has therefore been avoided as far as possible, and the term *multisource pharmaceutical product* is used instead (see the definition below). Multisource products may be marketed either under the approved nonproprietary name or under a brand (proprietary) name. They may be marketed in dosage forms and/or strengths different to those of the innovator products. Where the term *generic product* is used, it means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of the patent or other exclusivity rights. The term should not be confused with generic names for APIs.

microbiology

A branch of science that refers to microbes of all of types, including bacteria, viruses, rickettsia, protozoa, fungi and prions. Derived words (such as microbiological) have a similar meaning.

multisource (generic) pharmaceutical product

Multisource pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

new chemical (or biological) entities

Actives that have not previously been authorized for marketing as a drug for use in humans in the country in question.

pharmaceutical equivalents

Products are pharmaceutical equivalents if they contain the same amount of the same actives in the same dosage form, if they meet comparable standards, and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the excipients and/or manufacturing process and some other variables can lead to differences in product performance.

pivotal clinical trials

Those clinical studies that provide the significant evidence that is the basis for the decision as to the risk–benefit assessment for a particular FDC.

product information

The information provided by the supplier of an FPP that allows prescribers and consumers to ensure the safe and effective use of drugs. If it is written especially for prescribers, it may be termed *prescribing information*.

reference product

A pharmaceutical product with which the new product is intended to be interchangeable in clinical practice. The reference product will normally be the innovator product for which efficacy, safety and quality have been established. Where the innovator product is not available, the product that is the market leader may be used as a reference product, provided that it has been authorized for marketing and its efficacy, safety and quality have been established and documented.

summary of product characteristics (SPC)

A term used in the European Union. Product information or data sheets in the European Union should be based on the approved SPC.

well-established drugs

Actives that:

- have been marketed for at least 5 years in countries that undertake active postmarket monitoring;
- have been widely used in a sufficiently large number of subjects to permit the assumption that safety and efficacy are well known;
and
- have the same route of administration and strength and the same or similar indications as in those countries.

4. Scenarios

An application to register an FDC-FPP may fall into any one of the following four scenarios. These guidelines are intended to address the different requirements for each scenario.

- 4.1 *Scenario 1.* The new FDC-FPP contains the same actives in the same doses as an existing FDC-FPP; that is it is a “generic” of the existing FDC-FPP; they are “multisource” products. The quality, safety and efficacy of the existing product have been established.
- 4.2 *Scenario 2.* The new FDC-FPP contains the same actives in the same doses as an established regime of single entity products, and the dosage regimen is the same. Alternatively the established regime may involve combinations of single entities and FDCs, for example, a single entity FPP combined with an FDC-FPP that contains two actives. In all cases, the established regime has a well-characterized safety and efficacy profile, and all of the FPPs used in obtaining clinical evidence have been shown to be of good quality.
- 4.3 *Scenario 3*
 - The new FDC-FPP combines actives that are of established safety and efficacy but have not previously been used in combination for this indication.
 - The new FDC-FPP comprises a combination for which safety and efficacy have been established, but that will be used in a different dosage regimen.
- 4.4 *Scenario 4.* The new FDC-FPP contains one or more new chemical entities.

5. Balancing the advantages and disadvantages of a new fixed-dose combination

- 5.1 In determining whether it is rational to combine actives into a single product, there are medical, quality and bioavailability considerations.
 - 5.1.1 *Quality* issues may be addressed by much the same criteria that apply to single-component products and it is difficult to imagine a case in which essentially the same standards would not apply.
 - 5.1.2 *Medical* considerations are more complex and sometimes contradictory, for example, when increased efficacy is accompanied by increased toxicity. The decision as to whether to give marketing approval for a new FDC-FPP

in scenarios 3 and 4 is often based on a consideration of the balance of advantages and disadvantages from the medical perspective.

- 5.1.3 Interpretation of the results of *bioavailability and bioequivalence* tests involves both quality and medical considerations. For example it is not acceptable that bioavailability is reduced or variable, when compared with that of single entity products, because of poor formulation, but an interaction between two actives that leads to an increased bioavailability may be one of the advantages that is taken into account when balancing advantages and disadvantages.

Balancing the advantages and disadvantages of a new FDC-FPP should form a major component of submissions pursuant to this guideline.

- 5.2 Submissions for marketing approval of a new FDC in scenarios 2, 3 and 4 should include a section in which the advantages of the new combination are weighed against the disadvantages. All the possible advantages and disadvantages of the combination should be listed and discussed. The discussion should be based on the available data and on scientific and medical principles. In less well-developed nations, and particularly where there are difficulties with transport and the logistics of distribution, other matters may need to be taken into account, such as:

- 5.2.1 The cost of the combination as compared with the cost of individual components.
- 5.2.2 Evidence as to whether the new FDC will improve the reliability of supply as a result of simplified distribution procedures. Improved patient adherence may result from more reliable (continuing) availability of the FDC-FPP than of all of the components as loose combinations of single entity products.

However, issues of cost and procurement alone are not sufficient reason to approve an FDC if it has not been justified by appropriate data and on scientific and medical principles.

- 5.3 From a scientific or medical perspective, FDCs are more likely to be useful when several of the following factors apply:
 - 5.3.1 There is a medical rationale for combining the actives.
 - 5.3.2 There is an identifiable patient group for which this combination of actives and doses is suitable therapy. The larger the patient group in question, the more significant is this factor. It is not appropriate to combine actives that separately treat conditions that do not commonly coexist.

- 5.3.3 The combination has a greater efficacy than any of the component actives given alone at the same dose.
- 5.3.4 The incidence of adverse reactions in response to treatment with the combination is lower than in that response to any of the component actives given alone, for example as a result of a lower dose of one component or a protective effect of one component, and particularly when the adverse reactions are serious.
- 5.3.5 For antimicrobials, the combination results in a reduced incidence of resistance.
- 5.3.6 One drug acts as a booster for another (for example in the case of some antiviral drugs).
- 5.3.7 The component actives have compatible pharmacokinetics and/or pharmacodynamics. See comments under Pharmacokinetics and pharmacodynamics below (section 6.6.2).
- 5.3.8 Therapy is simplified, particularly when the existing therapy is complex or onerous (e.g. because of a “high tablet load”).
- 5.3.9 One of the ingredients is intended to minimize abuse of the other ingredient (e.g. the combination of diphenoxylate with atropine, or buprenorphine with naloxone).
- 5.3.10 The active pharmaceutical ingredients are chemically and physicochemically compatible, or special formulation techniques have been used that adequately address any incompatibility.
- 5.3.11 Other potential advantages of FDCs over single entity products given concurrently in the same dose may include:
 - 5.3.11.1 Convenience for prescribers and patients.
 - 5.3.11.2 Better patient adherence (but the evidence for this is largely anecdotal) (*1*, and Haynes, RB, personal communication, 2003).
 - 5.3.11.3 Simplified logistics of procurement and distribution.
 - 5.3.11.4 Lower cost.

These factors are important, but there may not necessarily be evidence to support them; they may be more significant when there is specific evidence available to support a particular case.

5.4 From a scientific or medical perspective, FDCs are less likely to be useful when one or more of the following factors apply:

5.4.1 The component actives are normally separately titrated to meet the patient's needs. Consequently:

5.4.1.1 Either the doses of the components, and/or the ratio of doses, typically differ from patient to patient, and/or

5.4.1.2 Patients are likely to be taking different doses at different stages of treatment (for example initial treatment compared with long-term treatment).

These two factors are particularly significant when one or more of the actives has a narrow therapeutic index and/or a steep dose–response curve in the therapeutic range.

5.4.2 There is a higher incidence or greater severity of adverse reactions to the combination than with any of the ingredients given alone, or there are adverse reactions not seen in response to treatment with any of the individual ingredients.

5.4.3 There are unfavourable pharmacokinetic interactions between the ingredients, for example when one drug alters the metabolism, absorption or excretion of another. However, see comments under Pharmacokinetics and pharmacodynamics below (section 6.6.2) concerning circumstances in which such interaction is intended.

5.4.4 Dose adjustment is necessary in special populations, such as in people with renal or hepatic impairment.

5.4.5 The product (tablets or capsules), is so large that patients find it difficult to swallow.

6. Data requirements for marketing authorization of fixed-dose combination finished pharmaceutical products

6.1 General

6.1.1 The framework for issuing a marketing authorization for an FDC-FPP is the same as that for single entity FPPs and is summarized in WHO's *Marketing authorization of pharmaceutical products with special reference*

to multisource (generic) products: a manual for a drug regulatory authority (1999) — the “Blue book”, or updates thereof. Information on the pharmaceutical development of a new product is planned for inclusion in the next edition of the Blue book and is summarized in Appendix 3.

- 6.1.2 Data requirements for marketing authorization of FDC-FPPs depend broadly on the scenario into which the application falls (see sections 4.1–4.4 above). Table 6 summarizes these differences. However, each application should be considered on its own merits using scientific judgement and logical argument.
- 6.1.3 Data requirements for marketing authorization do not differ when the combination is in the *WHO Model list of essential medicines*, i.e. data requirements are the same whether or not the combination or its components are in the *Model list of essential medicines*.
- 6.1.4 Submissions should include a statement of the marketing status of the FDC-FPP in other countries.
- 6.1.5 All applications to register an FDC-FPP should include a draft “product information” or “summary of product characteristics” for indicated diseases, and any package information leaflet or patient information. See the more detailed discussion below (section 7).
- 6.1.6 A full quality data set is required in all scenarios (see 6.3 below).
- 6.1.7 In general, preclinical or clinical safety and efficacy data are not required in *scenario 1*. If the risk–benefit assessment has been found to be acceptable for an FDC, then new brands may be approved on the basis of bioequivalence with the brand(s) used in pivotal clinical trials.

The applicant may, however, be asked to establish that a risk–benefit assessment has been conducted and found acceptable if, for example the drug regulatory authority to which the application is submitted is not convinced that this is the case or does not have access to the data.

- 6.1.8 If the FDC directly substitutes for an established regimen of single entity products, in relation to both actives and doses and for the same indication(s), a bioequivalence study may provide adequate evidence of safety and efficacy. This is *scenario 2*. The established regimen should have well-characterized safety and efficacy, and all of the FPPs should have been shown to be of good quality, including compliance with a suitable code of good manufacturing practice (GMP) during manufacture. Again the applicant may have to establish that this is the case.

Table 6

Summary of requirements for the various scenarios

This table is a list of the most likely set of requirements for marketing authorization of an FDC-FPP in each scenario. However each application should be considered on its own merits in relation to data requirements, using scientific judgement and logical argument. Some of the data may be provided in the form of literature studies, subject to the guidance given in the main text and Appendix 2.

Requirement	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Rationale for the combination	Not usually	Not usually	✓	✓
Balancing advantages and disadvantages of the combination	Not usually	Not usually	✓	✓
Marketing status in other countries	✓	✓	✓	✓
Analysis of literature data in the submission	Possibly for pharmaceutical development	Possibly for pharmaceutical development	✓	✓
Pharmaceutical development studies	✓	✓	✓	✓
GMP certification of sites of manufacture	✓	✓	✓	✓
A full quality data set	✓	✓	✓	✓
Bioavailability data ^a	Not usually	Not usually	Sometimes	✓
Bioequivalence data	✓	✓	Sometimes	Sometimes
Preclinical pharmacology and safety	Not usually	Not usually	Sometimes	✓
Clinical safety and efficacy	Not usually	Not usually	✓	✓
Product information	✓	✓	✓	✓
Plan for passive post-marketing surveillance	✓	✓	✓	✓
Plan for active post-marketing surveillance	Not usually	Not usually	✓	✓
Assurances ^b	✓	✓	✓	✓

Table 6 *continued*

✓ This is a requirement.

^a Normally absolute bioavailability for a new chemical entity, or comparative bioavailability for a new dosage form.

^b The applicant should provide assurances that:

- “The Product Information will not be altered without prior approval from [name of regulatory authority], except for safety updates that further restrict use of the product. Any such safety-related changes should be notified to [name of regulatory authority] within five days of making the change”; and
- “No changes will be made to the product without prior approval, except for changes of the type listed in [name of regulatory authority]’s policy on ‘Changes to pharmaceutical aspects which may be made without prior approval’ and subject to the conditions in that policy.”

6.2 Good manufacturing practice

6.2.1 Application of a suitable and relevant code of GMP is a critical element in assuring the current and continuing quality of medicines. Certification of GMP should be provided for all sites of manufacture of finished products, and preferably also for the sites of manufacture of active pharmaceutical ingredients (APIs). A suitable code of GMP would be the WHO Good manufacturing practices (GMP): main principles for pharmaceutical products, and for Inspection, both in: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials*, Volume 2, updated edition. Geneva, World Health Organization, 2004, and subsequent additions and revisions (e.g. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report*. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 2).

Assurance as to certification of GMP may conveniently be obtained using the WHO Certification Scheme — Guidelines for implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce, and WHO pharmaceutical starting materials Certification Scheme (SMACS) (*WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report*. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 917), Annex 3).

6.2.2 Sites of storage and distribution, including company storage facilities, should also be subject to ongoing audits of GMP. Relevant guidelines include: Guide to good storage practices for pharmaceuticals (*WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908), Annex 9); and Good trade and distribution practices for pharmaceutical starting materials (*WHO Expert Committee*

on Specifications for Pharmaceutical Preparations. Thirty-eighth report. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 917), Annex 2).

6.3 Quality

- 6.3.1 In relation to quality, very similar principles apply to FDC-FPPs as apply to single entity products. However there are additional complexities arising from the need to consider two or more actives instead of one. These complexities are principally, but not exclusively, related to assay, stability, physicochemical properties (for example dissolution rate) and bioavailability/bioequivalence. Consequently the following considerations (and others) may be pertinent.
- 6.3.2 Appendix 3, entitled *Development (or preformulation) studies*, makes some general points about this type of study. Pharmaceutical development studies are especially important for FDC-FPPs because they are technically more demanding than single-component products. Issues that are specific to the development of FDC-FPPs include:
 - 6.3.2.1 Chemical and physicochemical compatibility of the APIs in an FDC with one another as well as with possible excipients.
 - 6.3.2.2 The degradability of each API under stress conditions in the presence of the others.
 - 6.3.2.3 Uniformity of content of each active prior to compression (tablets) or filling (for instance capsules, sachets and suspension dosage forms). This study determines whether mixing during manufacture is adequate.
 - 6.3.2.4 Analytical procedures. These should be validated for each active in the presence of the others during development of analytical methods for quality control of the finished product, stability testing and dissolution testing. Validation should be conducted for each active in the presence of the others and in the presence of related synthesis (process) impurities and potential degradation products. In the case of high-performance liquid chromatography (HPLC) (a common analytical technique), possible interference by degradation products in the assay of the active can usually be controlled by peak purity testing.
 - 6.3.2.5 The dissolution rate of each active in pilot formulations. Multipoint limits should normally be established for routine quality control of

each active. For some FDCFPs, different dissolution media may be acceptable for the different actives.

6.3.2.6 Different assay procedures may be necessary for the different actives in the finished product, and for different purposes (e.g. dissolution testing may be needed rather than stability testing).

6.3.3 For solid dosage forms a test and limit for content uniformity should be applied to any active that is present at a weight of ≥ 25 mg or when the API comprises 25% or less of a dosage unit. Some authorities permit an exception for soft gelatin capsules that contain a solution of the API. Typically, when any one API is present at less than 25 mg or less than 25% of the weight of a dosage unit, all of the actives are subjected to content uniformity testing.

If a solid dosage form is not subject to content uniformity testing, for example because all of the actives are present at a weight of greater than 25 mg and greater than 25% of the weight of a dosage unit, there should be a test and limit for mass variation.

6.3.4 Acceptance criteria for impurities in FDC-FPPs should be expressed with reference to the parent API (and not with reference to the total content of APIs). If an impurity results from reaction between two APIs, its acceptance limits should be expressed in terms of the API that represents the worst case. If available, a reference standard should be used to quantify the degradation product in percentage mass/mass with respect to the parent API. Alternatively, and if justified, other quantitative techniques that are described in *Impurities in new drug products* (revised) ICH-Q3B(R) (2003), may be applied.

Note: there should be an approximate mass balance. Together with the remaining active, degradants expressed with reference to the parent compound should sum to approximately 100% of initial strength.

6.3.5 The specifications and defining characteristics of the product should be based on the most vulnerable active. For example expiry dates should be based on the stability of the least stable active.

6.3.6 In setting specifications, relevant pharmacopoeial monographs, WHO guidelines and ICH guidelines should be taken into account. For example in the absence of a relevant WHO guideline, the ICH guideline *Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances* (1999) is a suitable source of guidance.

- 6.3.7 Specifications in addition to those in pharmacopoeias may be necessary for APIs in some cases, for example for particle size, residual solvents and synthesis-related impurities that are not covered by relevant monographs.

6.4 Bioavailability and bioequivalence

- 6.4.1 Data on bioequivalence provide a bridge between *two pharmaceutical equivalents* (see Glossary) when safety and efficacy data are available for one of the FPPs, but not for the other. By demonstrating that the two products lead to the same profile for plasma concentration over time, available safety and efficacy data for one of the products can be extrapolated to the other. The two products being compared may be different brands, or different batches of the same brand, for example when manufactured by different methods, at different sites or according to different formulations.
- 6.4.2 Data on bioequivalence may also be important when the same FPP is administered under different circumstances, for example before or after food, in different patient populations (such as children versus adults), or by different routes of administration (such as subcutaneous versus intramuscular injection).
- 6.4.3 In the context of these guidelines, an additional application of bioequivalence studies is in scenario 2 in which safety and efficacy data on single entity products given concurrently may be extrapolated to an FDC-FPP, provided that all of the conditions described elsewhere in these guidelines are met.
- 6.4.3 There are two common circumstances in which data on bioequivalence are likely to be generated for *pharmaceutical equivalents*:
- 6.4.3.1 Pivotal clinical trials were generated on one formulation and another is to be marketed by the same company (for example because the second formulation is more stable or more marketable than the first); or
 - 6.4.3.2 A relevant patent has expired and a multisource pharmaceutical equivalent has been developed.
- 6.4.4 Evidence as to bioequivalence is required for *scenarios 1* and *2*, and sometimes for *scenarios 3* and *4*, for example when there are major differences between the formulation and/or method of manufacture of the product to be registered and that used in pivotal clinical trials.
- 6.4.5 If a study of bioequivalence finds that the two treatments are bioequivalent, it may be assumed that any pharmacokinetic interactions between the

actives were the same, even if one treatment comprised an FDC-FPP and the other comprised separate products.

6.4.6 Data on absolute bioavailability are usually required in *scenario 4*, i.e. comparison of the area under the curve for plasma concentration over time after an intravenous injection with that after administration of the dosage form to be marketed, for example a tablet given orally.¹

6.4.7 A decision as to whether it is necessary to conduct a study of the effect of food on the bioavailability of an FDC-FPP should be based on what is known of the effect of food on the individual actives, and any relevant recommendations in the product information for the single entity products.

The effect of food should normally be studied in *scenario 4*.

6.4.8 Recommendations as to the conduct and analysis of bioequivalence studies are provided in the WHO *guidelines, Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (1996, or later updates). Other guidelines may be relevant depending on the jurisdiction in which the application is submitted.

6.4.9 In demonstrating bioequivalence it may not always be necessary to provide in vivo data. The nature of suitable evidence as to bioequivalence differs according to the type of application and the remainder of the data set.¹

6.4.10 During analysis of the results of a bioavailability or bioequivalence study for an FDC-FPP, the parameters to be reported and assessed are those that would normally be required of each active if it were present as a single entity and the same statistical confidence intervals and decision criteria should be applied.

6.4.11 An additional scientific consideration that has been elaborated in recent years is the option for biowaivers based on the Biopharmaceutics Classification Scheme (BCS). This is an area in which further developments are expected. The main relevant publication to date is *Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system*. US Food and Drug Administration (2000). At present, and in the absence of clear

¹ See the WHO guidelines on *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (1996, or later updates) for options to be employed when an intravenous solution cannot be prepared or is unsafe.

guidance for FDCs, it is recommended that biowaivers based on the BCS classification as the sole criterion for a decision be handled cautiously because there is at present no guidance as to how to consider the possibility of a chemical or pharmacokinetic interaction between actives that may affect bioequivalence. However there are circumstances in which the BCS classification may nevertheless be relevant to FDCs. In such a case the BCS classification of all the actives in the FDC should be taken into account. For example:

6.4.11.1 For a new multisource product, if all the actives are in the most favourable biopharmaceutics classification of high solubility and high gastrointestinal permeability (i.e. BCS #1), and the criterion of dissolution of not less than 85% in 30 minutes is met for each active in the requisite media, a biowaiver may be considered.

6.4.11.2 For approval of new strengths when all actives are in BCS #1.

In addition, the BCS classification and in vitro dissolution rates may be factors in marginal cases, for example when considering whether a new study is required in support of a change in site or method of manufacture, or another change that might be considered minor.

Even if one or more of the actives is not in BCS #1, if an in vitro/in vivo correlation has been established, then in vitro comparison of dissolution performance in various media may be an option.

6.4.12 Validation of assays of actives in biological media is crucial in order to generate a meaningful bioavailability and bioequivalence study. See, for example, the guidelines *Bioanalytical method validation*. US Food and Drug Administration (2001).

6.4.13 Selection of a suitable comparator for the purpose of bioequivalence is described in *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products*. World Health Organization (2002). Some additional comments follow.

6.4.13.1 The comparator should be of known quality, safety and efficacy.

6.4.13.2 For applications in scenario 1, the decision as to the comparator depends on whether there is more than one existing brand of the combination whose safety and efficacy is known to be acceptable. If only one brand is known to have acceptable safety and efficacy, this should be used as comparator. In other circumstances,

the decision is more difficult and should be justified by cogent argument and data. The WHO *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products* (2002) may be of assistance.

- 6.4.13.3 For applications in scenario 2, single entity products will have been used in the majority of pivotal clinical trials. The same brands of those single entity FPPs should be the comparator and should be given concurrently as was the case in the pivotal clinical trials.
- 6.4.13.4 For applications in scenarios 3 and 4 (with which evidence as to safety and efficacy will be submitted), the new product should be shown to be bioequivalent to the product(s) that was (were) used in pivotal clinical trials.
 - 6.4.13.4.1 If an FDC-FPP was used in the majority of pivotal clinical trials, then that brand should be the comparator.
 - 6.4.13.4.2 If single entity products were used in the majority of pivotal clinical trials, then they should be the comparator, but should be given as (1) the same brands and (2) concurrently, as in the pivotal clinical trials.
 - 6.4.13.4.3 If approximately equal numbers of pivotal clinical trials used an FDC and single entity products, then in principle either may be used as comparator. However judgement should be applied in deciding which to use, for example if one group of studies was more rigorous than another, or if the conclusions were more definitive in relation to one group.
- 6.4.13.5 If in any of the scenarios, the selection of comparator cannot be made according to the suggestions above (for example because the brand in question is no longer available), the decision is more difficult and should be justified by cogent argument and supporting data. It may be necessary to conduct bridging clinical studies. See the WHO *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products* (2002).

6.5 Preclinical pharmacology and safety

- 6.5.1 Preclinical data are not normally required in scenarios 1 and 2. Data may, however, be required in some circumstances, for example if an unusual excipient is included in the formulation or if the impurity profile differs significantly from that of reference products.
- 6.5.2 Preclinical data will be required in scenario 4 as for any new chemical entity. The standard of evidence should be the same as for any new chemical entity.
- 6.5.3 In scenario 3, preclinical studies may not be required if all the actives have been extensively used in humans in the same combination for a long period and the safety of the combination has been well demonstrated. Bridging studies may be appropriate in some cases, for example for a new ratio of doses.
- 6.5.4 If the safety of the combination in humans has not already been demonstrated (i.e. in scenarios 3 and 4), preclinical studies should be conducted on the actives administered in combination in order to investigate possible additive or synergistic toxicological effects.

The preclinical data that are required in scenarios 3 and 4 will vary according to the data that are already available. For example, by definition in scenario 3, the safety and efficacy of each active will have already been established, but that of the combination will not. In scenario 4, the safety and efficacy of one or more of the actives may already have been established, but not those of all the actives or of the combination.

- 6.5.5 When preclinical data are required, the studies should aim to determine both the pharmacological and the adverse effects that may be expected from the combination of actives during clinical use.
- 6.5.6 As a general rule, preclinical studies on the combination should be performed with the actives in same the ratio as in the FDC-FPP in question. If this is not the case, the applicant should explain and justify the proportions used. A comparison of the systemic exposures in animals and humans will be relevant.
- 6.5.7 In the absence of relevant WHO guidelines, the ICH preclinical guidelines in Table 4 may be used as source of guidance.
- 6.5.8 Preclinical studies should comply with a suitable code of good laboratory practice (GLP); see, for example *Handbook: Good laboratory practice*:

Quality practices for regulated non-clinical research and development. World Health Organization (2001).

6.5.9 Microbiological preclinical studies

In general this section is applicable to scenarios 3 and 4, but not to scenarios 1 and 2. There may be some exceptions, for example microbiological data may be appropriate in scenarios 1 and 2 if a different pathogen or resistance pattern is encountered.

6.5.9.1 In scenarios 3 and 4, when a new combination is proposed for an antimicrobial indication, microbiological studies may be needed to determine the advantage of the FDC over the individual active moieties against relevant pathogen(s), and especially when clinical trials of monotherapy are inappropriate or unethical.

6.5.9.2 Data from microbiological preclinical studies of FDCs are particularly useful when clinical trials of monotherapy are inappropriate or unethical.

6.5.9.3 Data from the following types of study should normally be available for the combination:

6.5.9.3.1 Characterization of microbiological activity in vitro and in vivo against laboratory strains and clinical isolates of the targeted pathogen(s), including those strains in the relevant geographical regions.

6.5.9.3.2 Characterization of microbiological activity in appropriate animal models of infection with the targeted pathogen(s).

6.5.9.3.3 If possible, characterization of the mechanism by which the actives exhibit additive or synergistic microbiological activity against the targeted pathogen(s).

6.5.9.3.4 The potential for antagonistic effects between the actives.

6.5.9.3.5 The potential for development of resistance by target pathogens.

6.6 Clinical efficacy and safety

This section is in general applicable to *scenarios 3* and *4* but not to *scenarios 1* and *2*. Bridging studies may sometimes be appropriate in *scenario 3*, for example for a new ratio of doses or a longer duration of treatment.

6.6.1 General principles

- 6.6.1.1 The risk–benefit assessment for a new combination may be based on data generated using *either* the components given as single entity products concurrently *or* the FDC as a single FPP.
- 6.6.1.2 Any theoretical advantages of a particular combination should be confirmed by means of efficacy studies. The risk–benefit assessment should not be based on theoretical considerations only, or on extrapolation from other data.
- 6.6.1.3 If the actives in an FDC are intended to relieve different symptoms of a disease state, it is a prerequisite that these symptoms commonly occur simultaneously at a clinically relevant intensity and for a period of time such that simultaneous treatment is appropriate. Occurrence of the individual symptoms in isolation should not be indications for the FDC.
- 6.6.1.4 Clinical studies should be designed to determine whether the combination has an advantage over the component actives given alone in a substantial patient population. The data should demonstrate that each active contributes to the therapeutic effect of the combination.

It may not be essential to show that all of the components have efficacy when administered as single entities; for example clavulanic acid has little or no antimicrobial activity when given alone, but it enhances the efficacy of beta-lactam antibiotics.

- 6.6.1.5 In situations where comparative clinical trials are not feasible, for example when monotherapy is inappropriate or is unethical, an aggregate of clinical and preclinical data may be substituted. Such data may include:
 - 6.6.1.5.1 Historical clinical data, preferably at an exposure comparable to that for the proposed FDC.
 - 6.6.1.5.2 Bridging pharmacokinetic data.
 - 6.6.1.5.3 Preclinical pharmacology and/or toxicology data.
 - 6.6.1.5.4 In vitro data (e.g. microbiological studies).

- 6.6.1.6 If the FDC is available in more than one strength or ratio of doses, there should be a risk–benefit assessment for each combination.
- 6.6.1.7 The choice of comparators for the purposes of safety and efficacy studies should be justified. They should normally represent the recognized treatment for the indication in question. As far as possible, comparators should be licensed products with well-established safety and efficacy profiles and of established quality. Unapproved or novel combinations should be avoided as comparators as they may introduce new efficacy or toxicity characteristics and thus complicate assessment of the combination under test.
- 6.6.1.8 If the combination is intended for long-term use, data on safety in patients will normally be required for 6 months or longer.
- 6.6.1.9 If one or more of the component actives has an established use and dosage regimen in indications unrelated to the indications of the FDC, existing experience as to its safety may nevertheless be taken into account, bearing in mind the relative doses for the two sets of indications.
- 6.6.1.10 End-points in clinical trials should be such as to characterize the advantages and disadvantages of the combination. For example, for a combination designed to reduce the development of drug resistance, end-points might include the frequency of new drug resistance as well as the overall clinical outcome.
- 6.6.1.11 Parallel group comparisons are one means of demonstrating a therapeutic effect. A parallel placebo group should be included if feasible and if consistent with the indications under treatment. Multifactorial designs are another means by which it may be possible to demonstrate that a combination is superior to the individual actives.
- 6.6.1.12 In some cases, studies have to be specifically designed to confirm the minimal effective dose and the usual effective dose of the combination. Multiple dose-effect studies may be necessary.
- 6.6.1.13 The design and analysis of studies of efficacy and safety should consider (among other things) whether the combination is indicated as first- or second-line therapy.
- 6.6.1.14 In general, all of the actives in a combination should have a similar duration of action. If this is not the case, the applicant should explain and justify the combination.

- 6.6.1.15 In general, the actives in a combination should have similar pharmacokinetics. If this is not the case, the applicant should explain and justify the combination.
- 6.6.1.16 If there is an increase in the number or severity of adverse reactions to the FDC as compared with those in response to the individual actives given alone, evidence and argument should be presented showing that the advantages of the combination outweigh the disadvantages. These should be included in the section of the submission entitled “Balancing the advantages and disadvantages of a new FDC”.
- 6.6.1.17 Data generated in clinical safety and efficacy studies should comply with the WHO *Guidelines for good clinical practice (GCP) for trials on pharmaceutical products* (1995).

6.6.2 **Pharmacokinetics and pharmacodynamics**

This section is generally applicable to scenarios 3 and 4, but not to scenarios 1 and 2. In scenarios 1 and 2, the information described below will usually already be available.

- 6.6.2.1 In general, it is desirable that there be no pharmacokinetic or pharmacodynamic interactions between the components of a combination. However, there are circumstances in which such an interaction is intentional and may even contribute to the therapeutic outcome. For example:
 - 6.6.2.1.1 Ritonavir boosts the activity of protease inhibitors.
 - 6.6.2.1.2 Carbidopa and benserazide both reduce decarboxylation of levodopa in the gut wall, and consequently reduce the dose of levodopa that should be administered.
 - 6.6.2.1.3 Clavulanic acid reduces bacterial hydrolysis of beta lactam antibiotics and consequently both increases the concentration and prolongs the duration of effectiveness.
- 6.6.2.2 Tests should be conducted to elucidate any pharmacokinetic or pharmacodynamic interaction between the actives in a combination. Some interactions may be predictable from pharmacokinetic and enzyme profiles, but should be confirmed

by experiment. Any interaction should be quantified so that its effect on safety and efficacy is either predictable or (preferably) has been tested in a clinical study. This includes competing metabolic effects and effects on gastrointestinal efflux mechanisms or on renal excretion or reabsorption. Interactions may be additive, synergistic or antagonistic.

- 6.6.2.3 If there is an unintended pharmacokinetic interaction between the actives, it should be demonstrated that the therapeutic advantages of the combination outweigh any disadvantages resulting from the interaction. Relevant argument and cross-references to data should be included in the section that discusses the balance between the advantages and disadvantages of the combination.

6.6.3 ***Additional guidelines for scenario 3***

- 6.6.3.1 The risk–benefit assessment for a new combination may be based (at least in part) on a demonstration of the clinical non-inferiority of the combination to another product licensed for the same indication. See Appendix 4, entitled *Superiority, equivalence and non-inferiority clinical trials*, for more information.
- 6.6.3.2 Pharmacodynamic studies for new combinations should normally be conducted at several dose ratios of the actives unless the applicant can provide justification for not doing so.

6.6.4 ***Additional guidelines for scenario 4***

- 6.6.4.1 When an FDC-FPP contains an active that is a new chemical entity, data requirements are the same as for any new chemical entity. In some circumstances, some of the preclinical and clinical data on safety and/or efficacy may have been generated from studies on the combination rather than on single entities, for example when one active confers a protective effect in relation to adverse reactions or when the actives act synergistically.
- 6.6.4.2 Dose-finding monotherapy studies should normally be conducted for the new chemical entity before commencing studies of combination therapy, unless the new chemical entity is not intended to have activity when used alone (such as clavulanic acid). Alternative approaches may be acceptable if they can be justified.

6.6.4.3 The pharmacokinetics and enzyme profile of any new chemical entity should be fully characterized, including prediction of possible interactions and pharmacokinetics in children if the new chemical entity could be used in that population (see also section 7.6.6 on *Paediatric dosage forms*).

6.6.5 ***Superiority, equivalence and non-inferiority trials and fixed-dose combinations***

Appendix 4 defines superiority, equivalence and non-inferiority trials and makes some general points concerning different types of study. More information can be found in the Committee for Medicinal Products for Human Use (CHMP) guidelines in Table 3.

6.6.5.1 In the context of FDCs, equivalence trials are largely confined to bioequivalence studies.

6.6.5.2 An FDC-FPP should be shown, directly or indirectly, to be superior to the component actives given as single entity treatments. Only a superiority trial can give the necessary statistical confidence. Submissions should discuss both the statistical significance and clinical relevance of the results. Any alternative form of evidence that purports to address the same issues, for example one that concerns a dose–response surface, must be explained and justified with appropriate statistical confidence.

6.6.5.3 In clinical trials that are intended to test for superiority and/or non-inferiority, the choice of comparator should be carefully considered and will depend in part on the medical and ethical circumstances. The comparator may be:

6.6.5.3.1 The treatment whose risk–benefit profile is best supported by evidence or is at least well established.

6.6.5.3.2 One or more of the actives in the FDC given as a single treatment.

6.6.5.3.3 A placebo.

6.6.5.4 Depending on the claim, superiority or non-inferiority should be demonstrated for each specified clinical outcome. For example if the claim is less bone marrow depression, but similar efficacy, a non-inferiority outcome should be demonstrated for efficacy and a superiority outcome for safety.

6.6.6 *Paediatric dosage forms*

- 6.6.6.1 Different FDC-FPPs may be needed in paediatric populations from those needed in adults because of differences in pharmacokinetic and pharmacodynamic profiles of the actives, and for reasons of palatability. The doses of each active may need to be lower or higher, and the appropriate dose ratio may be different.

Scenarios 1 and 2

- 6.6.6.2 In scenarios 1 and 2, when the combination of actives and doses has already been shown to be safe and effective in the paediatric population, a bioequivalence study in adults may be extrapolated to the paediatric population provided that the pharmacokinetics of all actives are well-established in both populations and it is known that there are no differences that could affect the outcome of the bioequivalence study. Extrapolation of bioequivalence data between age groups should be justified in these terms.

Scenarios 3 and 4

- 6.6.6.3 If the FDC is indicated in a paediatric population, but the combination of actives and doses has not been shown to be safe and effective in this population, suitable doses of the actives given in combination should be established. In some cases, it may be necessary to do this in more than one age group (see the table below).

Paediatric populations	
<i>Neonate</i>	Birth to under 1 month
<i>Infant</i>	1 month to under 2 years
<i>Children</i>	2 years to under 12 years
<i>Adolescent</i>	12 years to under 16 years

From the age of 16 years, individuals are considered to be adults in the context of these guidelines.

- 6.6.6.4 The pharmacokinetic profile of each active should be established in the age groups for which the FDC is indicated.
- 6.6.6.5 If it is possible to define target plasma concentrations in both adults and the paediatric population for an FDC that has

established safety and efficacy in adults, then it may be possible to define suitable doses in the paediatric population on the basis of pharmacokinetics. The task is easier for actives that have the same target concentrations in adults and the paediatric population, such as antimicrobials that have established minimum inhibitory concentrations (MICs) and established safety at these concentrations.

- 6.6.6.6 When defining target plasma concentrations in the paediatric population, possible differences in the concentration–effect relationship should be taken into account.
- 6.6.6.7 If safe and effective use of the FDC has not been established in any age group, and extrapolation between groups is not possible based on pharmacokinetic data, then new clinical, and possibly also preclinical, safety and efficacy data should be obtained.

7. Product information (or summary of product characteristics) for fixed-dose combination finished pharmaceutical products

The product information is the information provided by the supplier of an FPP that allows prescribers and consumers to ensure the safe and effective use of drugs. If it is written especially for prescribers, it may be termed prescribing information. The summary of product characteristics (SPC) is a term used in the European Union (EU). Product information or data sheets in the EU should be based on the approved SPC.

This section of the guideline applies to all scenarios.

- 7.1 The product information should contain all of the information listed in the Appendix to WHO's Ethical criteria for medicinal drug promotion (see Table 1) in addition to the information mentioned below.
- 7.2 The product information should be an integrated evaluation of the FDC, and not a summation of the product information for each of the actives.
- 7.3 The rationale for use of the product should be presented in terms of the combination rather than in terms of the individual actives.
- 7.4 Only those indications for which each active in the FDC makes a useful contribution should be included in the product information. Each indication should be a well-recognized disease state, modification of a physiological state, dysfunctional state, syndrome or pathological entity.

- 7.5 For each indication there should be a statement as to whether the FDC is recommended for first- or second-line therapy.
- 7.6 Any pharmacokinetic and pharmacodynamic interactions between the actives should be described in qualitative and, as far as possible, in quantitative terms.
- 7.7 All clinically relevant interactions between the FDC and other drugs should be described, together with the resulting contraindications and precautions. Any deviations from expected interactions known for the single components should be highlighted.
- 7.8 When safety experience with the FDC is limited in comparison with that for the individual components, safety experience from clinical trials and postmarketing experience should be presented for both the FDC and the individual components, and should be identified as such.
- 7.9 If the safety profile for the combination is different to that for the individual actives, this should be highlighted. For example a combination of a fibrate and a statin might carry a risk of more frequent or more severe rhabdomyolysis than for either individual active.

8. Postmarketing studies and variations

- 8.1 Postmarket monitoring of safety is an important part of the role of both drug regulatory authorities and manufacturers. It is especially important when there are unresolved concerns regarding safety, and when a new product is intended for wide community use, as for example a new antimicrobial FDC-FPP for use in the treatment of tuberculosis, malaria or HIV/AIDS. See WHO's *The importance of pharmacovigilance: safety monitoring of medicinal products* (2002). Manufacturers should have (and use) written operating procedures for continuous assessment of the safety and utilization of their products following marketing authorization; SOPs can be examined during a GMP inspection. For antimicrobials, monitoring of patterns of resistance is an important component of pharmacovigilance. Note also that pharmacovigilance outcomes can differ with diet, ethnicity, comorbidity and other factors.
- 8.2 For scenarios 1 and 2, passive surveillance (spontaneous reporting) would usually be acceptable. For scenarios 3 and 4, additional active (prospective) surveillance should be considered, especially when there is an outstanding safety concern. For more information, see the draft ICH guideline *Pharmacovigilance planning* (Table 5), or later updates thereof.
- 8.3 Once the product information has been approved, any proposed changes should be validated according to principles similar to those for the initial application.

To ensure that drug regulatory authorities are aware of proposed changes to product information, it is recommended that marketing approval letters contain this statement:

“The product information may not be altered without prior approval, except for safety updates that further restrict use of the product. Any such safety-related changes should be notified to [name of regulatory authority] within five days of making the change.”

From Annex 9 of *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for a drug regulatory authority* (WHO, 1999).

- 8.4 Variations to pharmaceutical aspects of registered FDC-FPPs are subject to similar considerations to those described in Section IV and Annex 10 of *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for a drug regulatory authority* (WHO, 1999). As outlined in that text, some changes may be made without prior approval (“self-assessable” changes), and some require prior consideration by the drug regulatory authority.

To ensure that drug regulatory authorities are aware of proposed variations, it is recommended that marketing approval letters contain this statement:

“No changes may be made to the product without prior approval, except for changes of the type listed in [name of regulatory authority]’s policy on ‘Changes to pharmaceutical aspects which may be made without prior approval’. Conditions in that policy apply.”

From Annex 9 of *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for a drug regulatory authority* (WHO, 1999).

Reference

1. Haynes RB, McDonald HP, Garg AX. *Interventions for helping patients to follow prescriptions for medications*. Cochrane Library: Update software Issue #2, 2002.

Appendix 1

Guidelines for co-packaged fixed-dose combinations

A *co-packaged product* consists of two or more separate pharmaceutical products in their final dosage form that are packaged together for distribution to patients in the co-packaging.

1. Co-packaged products may fall into any of scenarios 1 to 4. The data requirements for each scenario are the same as those listed in Table 6 of this Annex.
2. A full quality data set is required for all components of copackaged pharmaceutical products, except for any component that already has marketing authorization in which case more limited requirements apply (see below).
3. If one or more of the pharmaceutical products already has marketing authorization, then the additional quality information to support co-packaging of those pharmaceutical products will typically be limited to data on stability of the products in the co-packaging. However the manufacturer of each component pharmaceutical product should provide an assurance that the product as used in copackaging will be identical in formulation and method of manufacture to the one that already has marketing authorization. This is especially important when the manufacturer of a component is not the manufacturer of the co-packaged product.
4. Submissions concerning co-packaged pharmaceutical products should take into account the Guidelines on packaging for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 9.

Appendix 2

Principles for determining whether data from the scientific literature are acceptable

Literature-based data concerning FDCs may be acceptable, subject to the principles below.

1. Bibliographical data should not replace the source data (i.e. original study reports) if they are available.
2. The overall strength of literature-based evidence will depend on its quality, quantity and consistency of outcomes.
3. Unless otherwise justified by the applicant, literature-based data concern actives that have an extensive marketing history.
4. All documents that are directly relevant to the application should be provided.
5. Literature-based submissions should include:
 - 5.1 Details of the search strategy, including a list of the databases searched and the service provider.
 - 5.2 The date on which the search was performed.
 - 5.3 The rationale for the search strategy, including an explanation of and reasons for the inclusion and exclusion criteria.
 - 5.4 An unedited search strategy and the outcome thereof.
 - 5.5 An analysis of the data collected, including both favourable and unfavourable results; this is a critical component of a submission that includes data from the scientific literature.
6. The applicant's analysis of literature-based data should:
 - 6.1 Include an appraisal of:
 - 6.1.1 The quality of the data.
 - 6.1.2 Relevance to the application being made (including a comparison of formulations and methods of manufacture of products used in clinical studies reported in the literature with those proposed for marketing).
 - 6.1.3 Consistency and compatibility of the data from the literature with any original data submitted.
 - 6.1.4 The impact of the literature-based data on the risk–benefit assessment for the FDC.
 - 6.1.5 Any contradictions between favourable and unfavourable results.

- 6.2 Include cross-references to appended copies of publications and to any original data submitted.
- 6.3 Include separate sections for clinical, preclinical and quality data.
- 6.4 Include an appraisal of the sources of information, in particular whether the data come from an independently refereed source or from other sources.
7. If a literature search and/or the analysis of data from the literature is more than 6 months old, the submission should justify using this search and analysis and should indicate why more recent publications and data have not been used. Alternatively a supplementary review of the more recent literature may be appended to the report that brings it to within 6 months of the date of submission.
8. Copies of all documents referred to in the submission or in the data analysis should be appended to the submission. If a document is not written in a language that is acceptable in the jurisdiction, a certified translation should also be attached (in addition to the original).
9. Review articles are acceptable in principle, but should be judged on their quality.
10. “Consensus” publications are acceptable in principle, but should be judged on their quality and on whether the original data and documentation are attached.
11. Searches of company or in-house databases (including postmarketing surveillance reports) are acceptable, provided that they are identified as such. If possible, these searches should be stratified according to patient groups such as age and ethnicity.
12. The relative strength of clinical publications is generally in this order:
 - 12.1 Controlled clinical trials.
 - 12.2 Cohort/case-control studies.
 - 12.3 Uncontrolled studies.
 - 12.4 Case descriptions.
 - 12.5 Expert opinion.
13. Clinical studies published according to accepted protocol guidelines (for example Consort, Cochrane and others) generally carry more weight than studies that fail to report all pertinent data (e.g. safety data). Although a good reporting format facilitates evaluation, it is not in itself a criterion for the quality of the data set.
14. Papers from peer-reviewed journals carry more weight in the regulatory decision than papers from non-peer-reviewed publications.
15. Clinical studies carry more weight if they meet current standards of design and control, including compliance with a code of good clinical practice.

16. Reports of preclinical studies carry more weight in the regulatory decision if they:
 - 16.1. Include individual animal reports.
 - 16.2. Are reported according to internationally accepted guidelines.
 - 16.3. Are in compliance with the principles of good laboratory practice (GLP). See, for example WHO's *Handbook: Good laboratory practice* (2001).

Appendix 3

Pharmaceutical development (or preformulation) studies

Pharmaceutical development studies identify, document and control those attributes of the ingredients of the formulation and critical parameters of the manufacturing process that influence final product quality. If a manufacturer fails to conduct such studies or to obtain the information from the literature, and consequently develops a poor formulation, there is a temptation to continue with that formulation and method of manufacture rather than lose time and possibly competitiveness. Consequently it is in the interests of product quality that a drug regulatory authority seek the results of preformulation studies with applications to register new products.

Consequently a section on pharmaceutical development is an integral part of an application for marketing authorization. A thorough literature search may provide some of the information and commonly this part of a submission will be a hybrid of new data and reports from the literature.

Systematic studies should be conducted on APIs, on pilot formulations of the finished product and on manufacturing processes. For each API, there should be studies of:

- physicochemical properties;
- chemical and physicochemical stability, including stability under stress conditions (see below);
- impurity profile and batch-to-batch variation thereof;
- chemical and physicochemical compatibility of the API with possible excipients under stress conditions;
- the manufacturing process, and definition and control of its critical parameters;
- dissolution rate of the API in pilot formulations; and
- stability of pilot formulations under accelerated stability testing conditions and under the maximum recommended conditions of storage.

With this information there is a greater likelihood that the finished product will:

- meet specifications, including for assay, impurities and dissolution rate;
- be of consistent quality within and between batches;
- have optimum chemical and physicochemical stability;
- be manufacturable for the minimum cost that is consistent with acceptable quality; and
- be found acceptable in stability and bioequivalence studies.

A typical set of studies of the degradation paths of an active pharmaceutical ingredient

Degradation paths for APIs are typically reactions of hydrolysis, oxidation, photolysis and/or acid–base chemistry. To force these reactions, the API is placed in solution under stress conditions such as those shown in Table A.1 below. For well-established drugs, some of this information may already be available in the literature.

The objective is not to completely degrade the API, but to cause degradation to occur to a small extent, typically 10–30% loss of active by assay when compared with non-degraded API. This target is chosen so that some degradation occurs, but not enough to generate secondary products. For this reason, the conditions and duration may need to be varied when the API is especially susceptible to a particular stress factor.

If no degradation products are detectable after 10 days under the conditions in Table A.1, the API is considered stable. If degradation is detectable, but its extent is significantly less than 10%, then the stress factors, stress conditions or duration may need to be increased to identify and monitor degradation products.

Solid-state degradation can also be considered. For APIs, exposing a solid sample to elevated temperatures such as 60–120 °C, or 5–10°C below the melting point, can generate a different degradation profile. This approach usually generates degradation products that can be used as a worst case to assess the performance of the analytical method.

Table A.1
Typical stress conditions in preformulation stability studies

Stress factor	Conditions	Concentration of API ^a	Time
Heat	60°C	1: 1 with diluent ^b	1–10 days
Humidity	75% relative humidity or greater	Solid state	1–10 days
Acid	0.1 N hydrochloric acid	2: 1 in 0.1 N hydrochloric acid	1–10 days
Base	0.1N sodium hydroxide	2: 1 in 0.1N sodium hydroxide	1–10 days
Oxidation	3% hydrogen peroxide	1:1 in 3% hydrogen peroxide	1–3 hours
Photolysis	Metal halide, mercury, xenon or ultraviolet-B fluorescent lamp	1: 1 with diluent ^b	1–10 days
Metal ions (optional)	0.05M Fe ₂ ⁺ or Cu ₂ ⁺	1:1 with solution of metal ions	1–10 days

^a When testing degradability of APIs in combination, the APIs should be in the same ratio as in the FDC-FPP.

^b In each case, the diluent is either an excipient or all excipients in the formulation in the same ratios as in the formulation. Other ratios of diluent may also be appropriate, for example the approximate ratio in which the drug and excipients will be used in a formulation.

Appendix 4

Superiority, equivalence and non-inferiority clinical trials

Definitions

Equivalence trial

A trial that has the primary objective of testing whether the difference in quantitative response to two or more treatments is clinically unimportant. This is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence margin of clinically acceptable differences.

Non-inferiority trial

A trial that has the primary objective of testing whether the response to the investigational product is clinically inferior to that of a comparator product. The comparator may be an active or a placebo control. The aim is to test whether the new product is inferior to the comparator by more than a specified small margin (the noninferiority margin).

Superiority trial

A trial that has the primary objective of testing whether the response to the investigational product is superior to that to a comparator. The comparator agent may be an active or a placebo control.

Points to note

1. Protocols should clearly state whether the demonstration of non-inferiority, equivalence or superiority is the objective of the study.
2. If superiority is demonstrated in a non-inferiority trial, the results can generally be considered to show superiority, but the analysis should be based mainly on the intention-to-treat analysis.
3. If superiority cannot be demonstrated in a superiority trial, noninferiority can generally not be claimed unless the lower margin of the confidence interval for the treatment difference is above a level that had been defined in the planning of the study. If noninferiority is an acceptable outcome, it is, therefore, prudent to specify a non-inferiority margin in the protocol before the study is conducted. A non-inferiority margin may not be specified after the trial has commenced.
4. In a non-inferiority trial, the intention-to-treat analysis and the per-protocol analysis have equal importance for interpretation of the results.

5. In therapeutic areas where there is a problem of lack of assay sensitivity (e.g. allergy or depression), a non-inferiority trial that does not also include a placebo arm is not possible.
6. If the comparator has only modest efficacy, it may not be possible to define a non-inferiority margin. Therefore, if a placebo arm is not permissible, the only other alternative for demonstrating efficacy is a superiority trial.

Further reading

See these CHMP guidelines.

- Points to consider on switching between superiority and non-inferiority. CPMP/EWP/482/99.
- DRAFT Points to consider on the choice of non-inferiority margins. EMEA, CPMP/EWP/2158/99.
- DRAFT Statistical principles for clinical trials. EMEA, CPMP/ICH/363/99.

2.3 Stability testing of active pharmaceutical ingredients and finished pharmaceutical products

Annex 10, WHO Technical Report Series, 1010, 2018

Introduction and background

The guidance on *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* was published as Annex 2 in the World Health Organization (WHO) Technical Report Series, No. 953, 2009 (1).

The aim of these regulatory guidelines is to outline the core stability data package required for registration of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs), replacing the previous WHO guidelines in this area. The guidelines cross-refer to the series of related documents published by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (2) and other WHO guidelines.

It was recommended that at the time of their publication these guidelines should also be applied to products that are already being marketed, making allowance for an appropriate transition period, for example, they could become applicable upon re-registration or upon re-evaluation.

The 2009 guidance not only followed the usual consultation process, but it was also the result of numerous discussions with the various regulatory forums, including ICH. As a result, the ICH parties withdrew one of their guidance texts (Q1F) and published the following text on their website:

“Explanatory Note on the Withdrawal of ICH Q1F for the ICH Website

ICH Q1 F Stability Data Package for Registration Applications in Climatic Zones III and IV defined storage conditions for stability testing in countries located in Climatic Zones III (hot and dry) and IV (hot and humid), i.e. countries not located in the ICH regions and not covered by ICH Q1 A (R2) Stability Testing for New Drug Substances and Drug Products. ICH Q1 F described harmonised global stability testing requirements in order to facilitate access to medicines by reducing the number of different storage conditions. In the course of the discussions which led to the development of the guideline, WHO conducted a survey amongst their member states to find consensus on 30 °C/65% [relative humidity] RH as the long-term storage conditions for hot and humid regions. As no significant objections were raised in this survey, 30 °C/65% RH was defined as the long-term storage condition for Climatic Zone III/IV countries in ICH Q1F. The document was adopted by the ICH Steering Committee in February 2003 and subsequently implemented in the ICH regions.

However, based on new calculations and discussions, some countries in Climatic Zone IV have expressed their wish to include a larger safety margin for medicinal products to be marketed in their region than foreseen in ICH Q1F. As a consequence, several countries and regions have revised their own stability testing guidelines, defining up to 30 °C/75% RH as the long-term storage conditions for hot and humid regions. Due to this divergence in global stability testing requirements, the ICH Steering Committee has decided to withdraw ICH Q1F and to leave definition of storage conditions in Climatic Zones III and IV to the respective regions and WHO.

In assessing the impact of the withdrawal of ICH Q1F on intermediate testing conditions defined in ICH Q1A (R2), the decision was reached to retain 30 °C/65%RH. However, regulatory authorities in the ICH regions have agreed that the use of more stringent humidity conditions such as 30 °C/75% RH will be acceptable should the applicant decide to use them.”¹

Based on recent developments, an analysis was commissioned to evaluate whether the existing guidelines would need to be updated.

During the joint meeting on regulatory guidance for multisource products with the Medicines Quality Assurance Group and the Prequalification of Medicines Team assessment group held in Copenhagen from 8 to 9 July 2016, this analysis was discussed in detail and feedback provided by the participants on the report as well as on the various sections of the existing guidelines. In conclusion the participants agreed that a revision of this text would be timely.

¹ http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1F/Q1F_Explanatory_Note.pdf.

1. Introduction	184
1.1 Objectives of these guidelines	184
1.2 Scope of these guidelines	184
1.3 General principles	184
2. Guidelines	185
2.1 Active pharmaceutical ingredient	185
2.1.1 General	185
2.1.2 Stress testing	185
2.1.3 Selection of batches	186
2.1.4 Container-closure system	186
2.1.5 Specification	186
2.1.6 Testing frequency	187
2.1.7 Storage conditions	187
2.1.8 Stability commitments	190
2.1.9 Evaluation	190
2.1.10 Statements and labelling	191
2.1.11 Ongoing stability studies	192
2.2 Finished pharmaceutical product	193
2.2.1 General	193
2.2.2 Stress testing	193
2.2.3 Selection of batches	193
2.2.4 Container-closure system	194
2.2.5 Specification	194
2.2.6 Testing frequency	195
2.2.7 Storage conditions	195
2.2.8 Stability commitments	201
2.2.9 Evaluation	201
2.2.10 Statements and labelling	202
2.2.11 In-use and hold time stability	203
2.2.12 Variations	204
2.2.13 Ongoing stability studies	204
3. Glossary	206
References	211
Appendix 1 Examples of testing parameters	213
Appendix 2 Recommended labelling statements	217
Appendix 3 Interpretation of storage statements for products approved in climatic zone II when the products are to be distributed in zone IV	220

1. Introduction

1.1 Objectives of these guidelines

The aim of these guidelines is to outline the core stability data package required for registration of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs), replacing the previous WHO guidelines in this area (1). However, alternative approaches can be used when they are scientifically justified. Further guidance can be found in guidelines published by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (2), in the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part* (3), WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part* (4) and WHO *guidelines on the active pharmaceutical ingredient master file procedure* (5).

It is recommended that these guidelines should also be applied to products that are already being marketed, for example, upon re-registration or upon re-evaluation.

1.2 Scope of these guidelines

These guidelines apply to new and existing APIs and address information to be submitted in original and subsequent applications for marketing authorization of their related FPP for human use. These guidelines may generally apply to stability testing for biologicals; however, there are additional requirements specific to such products and further guidance can be found in ICH guideline Q5C (2).

1.3 General principles

The purpose of stability testing is to provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability testing programme also includes the study of product-related factors that influence its quality, for example, interaction of the API with excipients, container-closure systems and packaging materials. In fixed-dose combination FPPs (fixed-dose combinations (FDCs)) the interaction between two or more APIs also has to be considered.

As a result of stability testing, a retest period for the API (in exceptional cases, for example, for unstable APIs, a shelf life is given) or a shelf life for the FPP can be established and storage conditions can be recommended. An API can be considered unstable (under the conditions studied, in a particular type of packaging, etc.) when a significant change is observed.

Various analyses have been done to identify suitable testing conditions for WHO Member States based on climatic data, to enable each Member State to decide on long-term (real-time) stability testing conditions. Those Member States that have

notified WHO of the long-term stability testing conditions they require when requesting a marketing authorization are listed in “Long-term stability testing conditions as identified by WHO Member States”.²

2. Guidelines

2.1 Active pharmaceutical ingredient

2.1.1 General

Information on the stability of the API is an integral part of the systematic approach to stability evaluation. Potential attributes to be studied during stability testing of an API are listed in the examples of testing parameters (Appendix 1). **The selection of potential attributes and time points to be tested should be justified.**

The retest period or shelf life assigned to the API by the API manufacturer should be derived from stability testing data.

2.1.2 Stress testing

Stress testing of the API can help identify the likely degradation products, which in turn can help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability-indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual API and the type of FPP involved.

For an API the following approaches may be used:

- when available, it is acceptable to provide the relevant data published in the scientific literature to support the identified degradation products and pathways;
- when no published data are available, stress testing should be performed.

Stress testing may be carried out on a single batch of the API. It should include the effect of temperature (in 10 °C increments (for example, at 50 °C, 60 °C) above the temperature used for accelerated testing), humidity (for example, 75% relative humidity (RH) or greater) and, where appropriate, oxidation and photolysis of the API. The testing should also evaluate the susceptibility of the API to hydrolysis across a justified range of pH values when in solution or suspension (6).

Assessing the necessity for photostability testing should be an integral part of a stress testing strategy. More details can be found in other guidelines (2).

The objective of stress testing is to identify primary degradation products and not to completely degrade the API. The conditions studied should cause degradation

² http://www.who.int/medicines/areas/quality_safety/quality_assurance/StabilityConditionsTable2UpdatedMarch2015.pdf?ua=1, accessed 1 March 2017.

to occur to a small extent, typically 10–30% loss of API as determined by assay when compared with non-degraded API. The target should be chosen so that some degradation occurs, but not enough to generate secondary products. For this reason, the conditions and duration may need to be varied when the API is especially susceptible to a particular stress factor. In the total absence of degradation products after 10 days the API is considered stable under the particular stress condition. However, in this case the stress conditions employed should be justified.

Although examining degradation products under stress conditions is useful in establishing degradation pathways and developing and validating suitable analytical procedures, it may not be necessary to examine specifically for certain degradation products if it has been demonstrated that they are not formed under accelerated or long-term storage conditions.

Results from these studies will form an integral part of the information provided to regulatory authorities.

2.1.3 Selection of batches

The requirements that follow are not intended to apply to variations; these are covered in section 2.2.12 Variations.

Data from stability studies on at least three primary batches of the API should normally be provided. The batches should be manufactured at a minimum of pilot scale by the same synthesis route as production batches, and using a method of manufacture and a procedure that simulates the final process to be used for production batches. The overall quality of the batches of API placed on stability studies should be representative of the quality of the material to be made on a production scale.

Other supporting data can be provided.

2.1.4 Container-closure system

The stability studies should be conducted on the API packaged in a container-closure system that is the same as, or simulates, the packaging proposed for storage and distribution.

2.1.5 Specification

Stability studies should include testing of stability-indicating attributes of the API, i.e. those that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes. A guide to the potential attributes to be tested in the stability studies is provided in Appendix 1.

Validated stability-indicating analytical procedures should be applied. Whether and to what extent replication should be performed will depend on the results from validation studies (7, 8).

2.1.6 Testing frequency

For long-term studies, the frequency of testing should be sufficient to establish the stability profile of the API.

For APIs with a proposed retest period or shelf life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every three months over the first year, every six months over the second year, and annually thereafter throughout the proposed retest period or shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a six-month study is recommended. Where it is expected (based on development experience) that results from accelerated studies are likely to approach significant change criteria, additional testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design. When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g. 0, 6, 9 and 12 months), from a 12-month study is recommended.

2.1.7 Storage conditions

In general, an API should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage and shipment.

Storage condition tolerances are defined as the acceptable variations in temperature and RH of storage facilities for stability studies. The equipment used should be capable of controlling the storage conditions within the ranges defined in these guidelines. The storage conditions should be monitored and recorded. Short-term environmental changes due to opening the doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be assessed, addressed and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effects assessed.

The following requirements for data at the time of submission are not generally intended to apply to variations; instead see section 2.2.12 Variations. For new APIs, the long-term testing should normally have taken place over a minimum of 12 months for the number of batches specified in section 2.1.3 at the time of submission, and should be continued for a period of time sufficient to cover the proposed retest period or shelf life. For existing APIs, data covering a minimum of six months may be submitted. Additional data accumulated during the period while the registration application is being assessed should be submitted to the authorities when submitting data in response to outstanding questions. Data from the accelerated storage condition and, if appropriate, from

the intermediate storage condition, can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated and, where appropriate, intermediate storage conditions for APIs are detailed in sections 2.1.7.1–2.1.7.3. The general case applies if the API is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

If long-term studies are conducted at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$ and “significant change” occurs at any time during six months’ testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. In this case, testing at the intermediate storage condition should include all long-term tests, unless otherwise justified, and the initial application should include a minimum of six months’ data from a 12-month study at the intermediate storage condition.

“Significant change” for an API is defined as failure to meet its specification.

2.1.7.1 *General case*

Study	Storage condition	Minimum time period covered by data at submission
Long-term ^a	$25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$	12 months or 6 months as described in point 2.1.7
Intermediate ^b	$30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$	6 months
Accelerated	$40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$	6 months

^a Whether long-term stability studies are performed at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$ is determined by the climatic condition under which the API is intended to be stored (see “Long-term stability testing conditions as identified by WHO Member States”). Testing at a more severe long-term condition can be an alternative to testing condition, i.e. $25^{\circ}\text{C}/60\% \text{ RH}$ or $30^{\circ}\text{C}/65\% \text{ RH}$ for zone II.

^b If $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$ is the long-term condition there is no intermediate condition.

2.1.7.2 *Active pharmaceutical ingredients intended for storage in a refrigerator*

Study	Storage condition	Minimum time period covered by data at submission
Long-term	$5^{\circ}\text{C} \pm 3^{\circ}\text{C}$	12 months or 6 months as referred to in section 2.1.7

Table continued

Study	Storage condition	Minimum time period covered by data at submission
Accelerated ^a	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	6 months

^a Whether accelerated stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe accelerated condition can be an alternative to storage testing at 25 °C/60% RH or 30 °C/65% RH.

Data on refrigerated storage should be assessed according to the evaluation section of these guidelines, except where explicitly noted below.

If significant change occurs between three and six months' testing at the accelerated storage condition, the proposed retest period should be based on the data available at the long-term storage condition.

If significant change occurs within the first three months' testing at the accelerated storage condition a discussion should be provided addressing the effect of short-term excursions outside the label storage condition, e.g. during shipping or handling. This discussion can be supported, if appropriate, by further testing on a single batch of the API for a period shorter than three months but with more frequent testing than usual. It is considered unnecessary to continue to test an API for the whole six months when a significant change has occurred within the first three months.

2.1.7.3 Active pharmaceutical ingredients intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long-term	–20 °C ± 5 °C	12 months or 6 months as referred to in section 2.1.7

In the rare case of any API of nonbiological origin being intended for storage in a freezer, the retest period or shelf life should be based on the long-term data obtained at the long-term storage condition. In the absence of an accelerated storage condition for APIs intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. 5 °C ± 3 °C or 25 °C ± 2 °C or 30 °C ± 2 °C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition, e.g. during shipping or handling.

2.1.7.4 *Active pharmaceutical ingredients intended for storage below –20 °C*

APIs intended for storage below –20 °C should be treated on a case-by-case basis.

2.1.8 **Stability commitments**

When the available long-term stability data on primary batches do not cover the proposed retest period or shelf life granted at the time of approval, a commitment should be made to continue the stability studies post-approval in order to firmly establish the retest period or shelf life.

Where the submission includes long-term stability data on three production batches covering the proposed retest period or shelf life, a post-approval commitment is considered unnecessary. Otherwise one of the following commitments should be made:

- if the submission includes data from stability studies on three production batches, a commitment should be made to continue these studies through the proposed retest period or shelf life;
- if the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue these studies through the proposed retest period and to place additional production batches, up to a total of at least three, in long-term stability studies through the proposed retest period or shelf life;
- if the submission does not include stability data on production batches, a commitment should be made to place the first three production batches (see section 2.1.3) on long-term stability studies through the proposed retest period or shelf life.

The stability protocol used for long-term studies for the stability commitment should be the same as that for the primary batches, unless otherwise scientifically justified.

See also 2.1.11 Ongoing stability studies.

2.1.9 **Evaluation**

The primary stability programme should be described in a written protocol and the results presented in a formal report as outlined in 2.1.11.

The purpose of the stability study is to establish – based on testing a minimum of three batches of the API, unless otherwise justified, and evaluating the stability information (including, as appropriate, results of the physical, chemical, biological and microbiological tests) – a retest period or shelf life applicable to all future batches of the API manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned retest period or shelf life.

The data may show so little degradation and so little variability that it is apparent from looking at them that the requested retest period or shelf life will be granted. Under these circumstances it is normally unnecessary to go through the statistical analysis.

One approach for analysing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g. P values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall retest period or shelf life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic or cubic function on an arithmetic or logarithmic scale. As far as possible the choice of model should be justified by a physical and/or chemical rationale and should also take into account the amount of available data (parsimony principle to ensure a robust prediction). Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the long-term data from the long-term storage condition beyond the observed range to extend the retest period or shelf life can be undertaken if justified. This justification should be based on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size and existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data (please refer to ICH Q1E).

Any evaluation should cover not only the assay but also the levels of degradation products and other stability-indicating attributes.

2.1.10 Statements and labelling

A storage statement should be established for display on the label based on the stability evaluation of the API. Where applicable, specific instructions should be provided, particularly for APIs that cannot tolerate freezing or excursions in temperature. Terms such as “ambient conditions” or “room temperature” should be avoided.

The recommended labelling statements for use when supported by the stability studies are provided in Appendix 2.

A retest period should be derived from the stability information, and a retest date should be displayed on the container label if appropriate.

After this retest period a batch of API destined for use in the manufacture of an FPP could be retested and then, if in compliance with the specification, could be used

immediately (e.g. within 30 days). If retested and found compliant, the batch does not receive an additional period corresponding to the time established for the retest period. However, an API batch can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For APIs known to be labile (e.g. certain antibiotics) it is more appropriate to establish a shelf life than a retest period.

2.1.11 Ongoing stability studies

The stability of the API should be monitored according to a continuous and appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of degradation products). The purpose of the ongoing stability programme is to monitor the API and to determine that the API remains, and can be expected to remain, within specifications under the storage conditions indicated on the label, within the retest period or shelf life in all future batches.

The ongoing stability programme should be described in a written protocol and the results presented in a formal report that should be available on site.

The protocol for an ongoing stability programme should extend to the end of the retest period or shelf life and should include, but not be limited to, the following parameters:

- number of batch(es) and different batch sizes, if applicable;
- relevant physical, chemical, microbiological and biological test parameters with acceptance criteria or reference to the attached specifications;
- reference to test methods;
- description of the container-closure system(s);
- testing frequency;
- description of the conditions of storage (standardized conditions for long-term testing as described in these guidelines, and consistent with the API labelling, should be used);
- other applicable parameters specific to the API.

At least one production batch per year of API (unless none is produced during that year) should be added to the stability monitoring programme and generally should be tested at least every 6 months in the first year and then annually to confirm the stability (7).

In certain situations additional batches should be included in the stability programme and may require more frequent testing. For example, a stability study should be initiated after any significant change or significant deviation of the synthetic route, process or container-closure system that may have an impact upon the stability of the API (refer to section 2.2.12 Variations).

Out-of-specification (OOS) results or significant atypical trends should be investigated. Any confirmed significant change or OOS result should be reported immediately to the relevant finished product manufacturer. The possible impact on batches on the market should be considered in consultation with the relevant finished product manufacturers and the competent authorities.

A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained and should be available on site. This summary should be subjected to periodic review.

2.2 Finished pharmaceutical product

2.2.1 General

The design of the stability studies for the FPP should be based on knowledge of the behaviour and properties of the API, information from stability studies on the API and on experience gained from preformulation studies, similar marketed formulations and investigational FPPs. The likely changes during storage and the rationale for the selection of attributes to be tested in the stability studies should be stated.

2.2.2 Stress testing

Photostability testing, which is an integral part of stress testing, should be conducted on at least one primary batch of the FPP if appropriate. More details can be found in other guidelines (2).

Additional stress testing of specific types of dosage forms may be appropriate, e.g. cyclic studies for semi-solid products or freeze–thaw studies for liquid products.

2.2.3 Selection of batches

The requirements that follow are not generally intended to apply to variations, which are covered in section 2.2.12 Variations.

For FPPs containing new APIs, data from stability studies should be provided on at least three primary batches of each proposed strength of the FPP. Two of the three batches should be at least pilot-scale batches and the third batch can be smaller, if justified (see example below).

For FPPs containing existing APIs (e.g. generics), data should be provided on not less than two batches of at least pilot scale, or in the case of an uncomplicated³ FPP (e.g. immediate-release solid FPPs (with noted exceptions) or non-sterile solutions), at least one batch of at least pilot scale and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules) of each proposed strength of the FPP.

³ The term “complicated FPP” includes sterile products, metered dose inhaler products, dry powder inhaler products and transdermal delivery systems. Solid oral products considered “complicated” include modified-release FPPs, products containing problematical APIs such as ritonavir and FDCs containing APIs such as rifampicin or an artemisinin.

The primary batches should be of the same formulation and packaged in the same container-closure system as that proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing.

When a batch size smaller than pilot scale is used as a primary batch, data or a discussion is required to confirm that the smaller batch is representative of the intended production size, including its formulation and method of manufacture.

Where possible, batches of the FPP should be manufactured using different batches of the API(s).

Stability studies should be performed on each individual strength, dosage form and container type and size of the FPP unless bracketing or matrixing is applied (refer to ICH Q1D).

2.2.4 Container-closure system

Stability testing should be conducted on the dosage form packaged in the primary container-closure systems proposed for marketing. If the secondary container-closure system has protective properties, and labelling clearly indicates that the product is to be stored in the primary and secondary packaging (e.g. “store tablets in blisters in the provided cartons”), or if the product is packaged in a semi-permeable container where components from the secondary packaging can migrate into the product, the secondary packaging may also form part of the packaging system for stability samples. Any available studies carried out on the FPP outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

2.2.5 Specification

Stability studies should include testing of stability-indicating attributes of the FPP, i.e. those that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes, preservative content (e.g. antioxidant or antimicrobial preservatives) and functionality tests (e.g. for a dose delivery system). Examples of testing parameters in the stability studies are listed in Appendix 1. Analytical procedures should be fully validated and stability-indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.

Shelf-life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf-life and release acceptance criteria based on the stability evaluation and the changes observed on storage. Any differences between the release and shelf-life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated

during development of the pharmaceutical product with the product in its final formulation (except for preservative concentration) intended for marketing. A single primary stability batch of the FPP should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

2.2.6 Testing frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the FPP.

For products with a proposed shelf life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every three months over the first year, every six months over the second year and annually thereafter throughout the proposed shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a six-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, testing should be increased either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g. 0, 6, 9 and 12 months), from a 12-month study is recommended.

The initial date of storage should be considered t_0 and stability time points should be defined as a date with respect to t_0 . For example, if t_0 is 1 January 2020 then the one-month time point corresponds to either 1 February or 31 January 2020. For each time point, samples should be withdrawn and tested as per the protocol. Testing should be completed as soon as possible. Deviations from the protocol should be recorded and justified.

Reduced designs, i.e. matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied if justified (refer to ICH Q1D).

2.2.7 Storage conditions

Stability data must demonstrate stability of the medicinal product throughout its intended shelf life under the climatic conditions prevalent in the target countries. Merely applying the same requirements appropriate to other markets could potentially lead to substandard products if stability studies are conducted at the storage conditions for countries in Climatic Zone I/II when the products are supplied in countries in Climatic Zones III and IV.

In general an FPP should be evaluated under storage conditions with specified tolerances that test its thermal stability and, if applicable, its sensitivity to moisture

or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment and subsequent use with due regard to the climatic conditions in which the product is intended to be marketed.

The orientation of the product during storage, i.e. upright, on the side or inverted, as well as the rationale for the orientation, may need to be included in a protocol where contact of the product with the closure system may be expected to affect the stability of the products contained (e.g. liquids and semisolids), or where there has been a change in the container-closure system.

Storage condition tolerances are usually defined as the acceptable variations in temperature and RH of storage facilities for stability studies. The equipment used should be capable of controlling the storage conditions within the ranges defined in these guidelines. The storage conditions should be monitored and recorded. Short-term environmental changes due to opening of the doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be assessed, addressed and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effects assessed.

The following requirements for data at the time of submission are not generally intended to apply to variations; instead refer to section 2.2.12 Variations. At the time of submission, the long-term testing should cover a minimum of six months for FPPs containing existing APIs or 12 months for FPPs containing new APIs and should be continued for a period of time sufficient to cover the proposed shelf life. The period of data collection required at the time of submission may be shortened in some circumstances, for example, to address shortages of medicines.

Additional data accumulated during the assessment period of the registration application should be submitted to the authorities when submitting data in response to outstanding questions. Data from the accelerated storage condition and from the intermediate conditions, where appropriate, can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated and, where appropriate, intermediate storage conditions for FPPs are detailed in the sections below. The general case applies if the FPP is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

2.2.7.1 *General case*

Study	Storage condition	Minimum time period covered by data at submission
Long-term ^a	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	12 months or 6 months as described in point 2.2.7

Table *continued*

Study	Storage condition	Minimum time period covered by data at submission
Intermediate ^b	30 °C ± 2 °C/65% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

^a Whether long-term stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is determined by the climatic zone in which the FPP is intended to be marketed. Testing at a more severe long-term condition can be an alternative to storage at 25 °C/60% RH or 30 °C/65% RH.

^b If 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25 °C ± 2 °C/60% RH ± 5% RH and “significant change” occurs at any time during 6 months’ testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. In this case the initial application should include a minimum of six months’ data from a 12-month study at the intermediate storage condition.

In general, “significant change” for an FPP is defined as:

- a change from the initial content of API(s) of 5% or more detected by assay, or failure to meet the acceptance criteria for potency when using biological or immunological procedures;
- any degradation product exceeding its acceptance criterion;
- failure to meet the acceptance criteria for appearance, physical attributes and functionality test (e.g. colour, phase separation, resuspendability, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g. softening of suppositories, melting of creams, partial loss of adhesion for transdermal products) may be expected under accelerated conditions.

Also, as appropriate for the dosage form:

- failure to meet the acceptance criterion for pH; or
- failure to meet the acceptance criteria for dissolution for 12 dosage units.

2.2.7.2 FPPs packaged in impermeable containers

Parameters required to classify the packaging materials as permeable or impermeable depend on the characteristics of the packaging material, such as sealing, thickness and permeability coefficient. The suitability of the packaging material used for a particular

product is determined by its product characteristics. Containers generally considered to be moisture-impermeable include glass ampoules.

Sensitivity to moisture or potential for solvent loss is not a concern for FPPs packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus stability studies for products stored in impermeable containers can be conducted under any controlled or ambient RH condition.

2.2.7.3 FPPs packaged in semi-permeable containers

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological and microbiological stability. This evaluation can be carried out under conditions of low RH, as discussed below. Ultimately it should be demonstrated that aqueous-based FPPs stored in semi-permeable containers could withstand environments with low RH.

Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

Study	Storage condition	Minimum time period covered by data at submission
Long-term ^a	25 °C ± 2 °C/40% RH ± 5% RH or 30 °C ± 2 °C/35% RH ± 5% RH	12 months or 6 months as described in point 2.2.7
Intermediate ^b	30 °C ± 2 °C/35% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/not more than (NMT) 25% RH	6 months

^a Whether long-term stability studies are performed at 25 °C ± 2 °C/40% RH ± 5% RH or 30 °C ± 2 °C/35% RH ± 5% RH is determined by the climatic condition under which the FPP is intended to be marketed. Testing at 30 °C/35% RH can be an alternative to the storage condition at 25 °C/40% RH.

^b If 30 °C ± 2 °C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition.

Products meeting the specifications when stored under the accelerated conditions and the long-term storage conditions appropriate to the intended market, as specified in the table above, have demonstrated the integrity of the packaging in semi-permeable containers. A significant change in water loss alone at the accelerated storage condition does not necessitate testing at the intermediate storage condition. However, data should be provided to demonstrate that the pharmaceutical product would not have significant water loss throughout the proposed shelf life if stored at 25 °C/40% RH or 30 °C/35% RH.

For long-term studies conducted at 25 °C ± 2 °C/40% RH ± 5% RH, that fail the accelerated testing with regard to water loss and show significant change with respect to any other parameters, additional testing at the “intermediate” storage condition should be performed as described under the general case to evaluate the temperature effect at 30 °C.

A 5% loss in water from its initial value is considered a significant change for a product packaged in a semi-permeable container after an equivalent of three months' storage at 40 °C and not more than (NMT) 25% RH. However, for small containers (1 mL or less) or unit-dose products, a water loss of 5% or more after an equivalent of three months' storage at 40 °C/NMT 25% RH may be appropriate, if justified.

An alternative approach to studies at the low RH as recommended in the table above (for either long-term or accelerated testing) is to perform the stability studies under higher RH and to derive the water loss at the low RH through calculation. This can be achieved by experimentally determining the permeation coefficient for the container-closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for a container-closure system can be experimentally determined by using the worst-case scenario (e.g. the most diluted of a series of concentrations) for the proposed FPP.

Example of an approach for determining water loss

For a product in a given container-closure system, container size and fill, an appropriate approach for deriving the rate of water loss at the low RH is to multiply the rate of water loss measured at an alternative RH at the same temperature, by a water loss rate ratio shown in the table below. A linear water loss rate at the alternative RH over the storage period should be demonstrated.

For example, at a given temperature, e.g. 40 °C, the calculated rate of water loss during storage at NMT 25% RH is the rate of water loss measured at 75% RH multiplied by 3.0, the corresponding water loss rate ratio.

Low-humidity testing conditions	Alternative testing condition	Ratio of water loss rates	Calculation
25 °C/40% RH	25 °C/60% RH	1.5	$(100-40)/(100-60)$
30 °C/35% RH	30 °C/65% RH	1.9	$(100-35)/(100-65)$
30 °C/35% RH	30 °C/75% RH	2.6	$(100-35)/(100-75)$
40 °C/NMT 25% RH	40 °C/75% RH	3.0	$(100-25)/(100-75)$

Valid water loss rate ratios at RH conditions other than those shown in the table above can also be used.

2.2.7.4 FPPs intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5 °C ± 3 °C	12 months or 6 months as referred to in section 2.2.7
Accelerated ^a	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	6 months

^a Whether accelerated stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe accelerated condition can be an alternative to the storage condition at 25 °C/60% RH or 30 °C/65% RH.

If the FPP is packaged in a semi-permeable container, appropriate information should be provided to assess the extent of water loss.

Data from refrigerated storage should be assessed according to the evaluation section of these guidelines, except where explicitly noted below.

If significant change occurs between three and six months' testing at the accelerated storage condition, the proposed shelf life should be based on the data available from the long-term storage condition.

If significant change occurs within the first three months' testing at the accelerated storage condition, a discussion should be provided addressing the effect of short-term excursions outside the label storage condition, e.g. during shipment and handling. This discussion can be supported, if appropriate, by further testing on a single batch of the FPP for a period shorter than three months but with more frequent testing than usual. It is considered unnecessary to continue to test a product throughout six months when a significant change has occurred within the first three months of accelerated studies at the specific condition chosen in accordance with the risk analysis.

2.2.7.5 FPPs intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long-term	-20 °C ± 5 °C	12 months or 6 months as referred to in section 2.2.7

For FPPs intended for storage in a freezer, the shelf life should be based on the long-term data obtained at the long-term storage condition. In the absence of an

accelerated storage condition for FPPs intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. $5\text{ }^{\circ}\text{C} \pm 3\text{ }^{\circ}\text{C}$ or $25\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ or $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition.

2.2.7.6 FPPs intended for storage below $-20\text{ }^{\circ}\text{C}$

FPPs intended for storage at temperatures below $-20\text{ }^{\circ}\text{C}$ should be treated on a case-by-case basis.

2.2.8 Stability commitments

One or more of the following commitments should be made.

- When the available long-term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies post-approval throughout the proposed shelf life. This is the primary batch stability commitment.
- If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to place the next production batches, up to a total of at least three, on long-term stability studies throughout the proposed shelf life and on accelerated studies for six months. This is the production batch stability commitment.
- For each product, an ongoing stability programme is required to monitor the product over its shelf life and to determine that the product remains and can be expected to remain within specifications under the storage conditions on the label. See 2.2.13. This is the ongoing stability commitment.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

2.2.9 Evaluation

The primary stability programme should be described in a written protocol and the results presented in a formal report as outlined in 2.2.13.

A systematic approach should be adopted to the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological and microbiological tests, including particular attributes of the dosage form (e.g. dissolution rate for solid oral dosage forms). *Where appropriate, a summary of additional knowledge and an understanding of stability gained from supporting studies, modelling, predictive tools, etc., may be incorporated to support knowledge gained from the primary stability programme.*

The purpose of the stability study is to establish, based on testing a minimum number of batches of the FPP as specified in section 2.2.3, a shelf life and label storage instructions applicable to all future batches of the FPP manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the statistical analysis.

One approach for analysing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g. P values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic or cubic function on an arithmetic or logarithmic scale. As far as possible, the choice of model should be justified by a physical and/or chemical rationale and should also take into account the amount of available data (parsimony principle to ensure a robust prediction).

Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the long-term data from the long-term storage condition beyond the observed range to extend the shelf life can be undertaken, if justified. This justification should be based on what is known about the mechanisms of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size and the existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data (refer to ICH Q1E).

Any evaluation should consider not only the assay but also the degradation products and other appropriate attributes.

2.2.10 Statements and labelling

A storage statement should be established for the label based on the stability evaluation of the FPP. Where applicable, specific instructions should be provided, particularly for FPPs that cannot tolerate freezing. Terms such as “ambient conditions” or “room temperature” should be avoided.

There should be a direct link between the storage statement on the label and the demonstrated stability of the FPP. An expiry date should be displayed on the container label.

The labelling statements recommended for use, if supported by the stability studies, are provided in Appendix 2. Information on the interpretation and conversion of storage statements for products approved in zone II when the products are to be distributed in zone IV is provided in Appendix 3.

In principle, FPPs should be packed in containers that ensure stability and protect the FPP from deterioration. A storage statement should not be used to compensate for inadequate or inferior packaging. Additional labelling statements could be used in cases where the results of the stability testing demonstrate limiting factors (see Appendix 2).

2.2.11 In-use and hold time stability

The purpose of in-use stability testing is to provide information for the labelling on the preparation, storage conditions and utilization period of multidose products after opening, reconstitution or dilution of a solution. Examples include an antibiotic injection supplied as a powder for reconstitution, or a moisture-sensitive or hygroscopic solid oral FPP in a large format multidose container (e.g. high density polyethylene (HDPE) bottle of 500 tablets). In general, a 30-day in-use period is normally considered acceptable without further supporting data.

As far as possible the test should be designed to simulate the use of the FPP in practice, taking into consideration the filling volume of the container and any dilution or reconstitution before use. At intervals comparable to those that occur in practice, appropriate quantities should be removed by the withdrawal methods normally used and described in the product literature.

The physical, chemical and microbial properties of the FPP that are susceptible to change during storage should be determined over the period of the proposed in-use shelf life. If possible, testing should be performed at intermediate time points and at the end of the proposed in-use shelf life on the final amount of the FPP remaining in the container. Specific parameters, e.g. for liquids and semisolids: the content and effectiveness of preservatives need to be studied.

A minimum of two batches, at least pilot-scale (with the exceptions outlined in 2.2.3), should be subjected to the test. At least one of these batches should be chosen towards the end of its shelf life. If such results are not available, one batch should be tested at the final point of the submitted stability studies.

This testing should be performed on primary batches of the reconstituted or diluted FPP or the solid oral FPP (as above), throughout the proposed in-use period as part of the stability studies at the initial and final time points and, if long-term data covering the shelf life are not available at the time of submission, at 12 months or the last time point at which data will be available.

In general this testing need not be repeated on commitment batches (see 2.2.8).

Consideration should also be given to hold-time studies of bulk products, e.g. coated tablets prior to final packaging. For example, when the bulk product may be stored for a period exceeding 30 days before being packaged and/or shipped from a manufacturing site to a packaging site, the stability of the bulk product in the intended bulk container should be evaluated and studied. Similar considerations should apply to intermediates that are stored and used for periods exceeding 30 days. Further guidance can be found in the WHO *General guidance on hold-time studies* (9).

2.2.12 Variations

Once the FPP has been registered, additional stability studies are required whenever variations are made that may affect the stability of the API or FPP. The applicant should investigate whether or not the intended change will have an impact on the quality characteristics of APIs and/or FPPs and consequently on their stability. The scope and design of the stability studies for variations are based on the knowledge and experience acquired on APIs and FPPs.

The available variation guidelines should be consulted for guidance on the expectations regarding stability requirements to support changes to the API and FPP. Note that the requirements of the guidelines of the specific regulatory authority or region prevail for a given region; however, in the absence of such guidelines, the WHO Prequalification Team: Medicines guidelines can be applied (10). Depending on the variation, either the results of a stability study or a commitment to conduct such a study is required. Variation guidelines are specific detailed guidelines, therefore the following are general categories and the guidelines should be referred to for the exact circumstances and requirements. In the aforementioned guidance document (10), changes requiring supporting data include certain changes to the API retest period or storage conditions, and to the FPP formulation, manufacturing process, container-closure system, shelf life, in-use period and storage conditions. Other changes, such as certain changes to the API certificate of suitability, certificate of prequalification, manufacturing site or manufacturing process, or certain changes to the FPP manufacturing site, batch size or container-closure system, require a commitment for stability studies to support the variations.

The results of these stability studies should be communicated to the regulatory authorities concerned, following the applicable requirements stipulated in the variation guidelines for the region.

2.2.13 Ongoing stability studies

After a marketing authorization has been granted, the stability of the FPP should be appropriately monitored according to a continuous programme that will permit the detection of any stability issue (e.g. changes in levels of degradation products or dissolution profile) associated with the formulation in the container-closure system in

which it is marketed. The purpose of the ongoing stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the storage conditions on the label. The ongoing stability programme should be described in a written protocol and results formalized as a report.

The protocol for an ongoing stability programme should extend to the end of the shelf-life period and should include, but not be limited to, the following parameters:

- number of batch(es) per strength and different batch sizes, if applicable.
The batch size should be recorded, if batch sizes differ;
- relevant physical, chemical, microbiological and biological test parameters with acceptance criteria or reference to the attached specifications;
- reference to test methods;
- description of the container-closure system(s);
- testing frequency (generally at 6 months and annual time points is sufficient for ongoing studies);
- description of the conditions of storage (standardized conditions for long-term testing as described in these guidelines, and consistent with the product labelling, should be used); and
- other applicable parameters specific to the FPP.

The protocol for the ongoing stability programme can be different from that of the initial long-term stability study as submitted in the marketing authorization dossier provided that this is justified and documented in the protocol (for example, the frequency of testing as above, or when updating to meet revised recommendations).

The number of batches and frequency of testing should provide sufficient data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none is produced during that year). The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol (refer to ICH Q1D).

In certain situations additional batches should be included in the ongoing stability programme. For example, an ongoing stability study should be conducted after any significant change or significant deviation to the process or container-closure system. Any reworking, reprocessing or recovery operation should also be considered for inclusion. Refer to section 2.2.12 for further details.

OOS results or significant atypical trends should be investigated. Any confirmed significant change or OOS result should be reported immediately to the relevant competent authorities. The possible impact on batches on the market should be considered in consultation with the relevant competent authorities.

A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

3. Glossary

The definitions provided below apply to the words and phrases used in these guidelines. Although an effort has been made to use standard definitions as far as possible, they may have different meanings in other contexts and documents. The following definitions are provided to facilitate interpretation of the guidelines. The definitions are consistent with those published in other WHO quality assurance guidelines. The Quality Assurance of Medicines Terminology Database was established in August 2005 and includes the definitions of terms related to quality assurance of medicines. This database is intended to help harmonize terminology and to avoid misunderstandings that may result from the different terms and their interpretations used in various WHO publications. The main publications used as a source of information to create the Quality Assurance of Medicines Terminology Database are the quality assurance guidelines included in the thirty-sixth and subsequent reports of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

accelerated testing. Studies designed to increase the rate of chemical degradation and physical change of an active pharmaceutical ingredient or finished pharmaceutical product by using exaggerated storage conditions as part of the stability testing programme. The data thus obtained, in addition to those derived from long-term stability studies, may be used to assess longer-term chemical effects under non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions, as might occur during shipping. The results of accelerated testing studies are not always predictive of physical changes.

active pharmaceutical ingredient. Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

batch. A defined quantity of starting material, packaging material or finished pharmaceutical product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

bracketing. The design of a stability schedule such that only samples at the extremes of certain design factors, e.g. strength and package size, are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g. for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container-closure system (refer to ICH Q1D).

climatic zone. The zones into which the world is divided based on the prevailing annual climatic conditions (see reference to the living document “Long-term stability testing conditions as identified by WHO Member States”⁴).

commitment batches. Production batches of an active pharmaceutical ingredient or finished pharmaceutical product for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application.

container-closure system. The sum of packaging components that together contains and protects the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the finished pharmaceutical product. A packaging system is equivalent to a container-closure system.

dosage form. The form of the finished pharmaceutical product, e.g. tablet, capsule, elixir or suppository.

excipient. A substance or compound, other than the active pharmaceutical ingredient and packaging materials, that is intended or designated to be used in the manufacture of a finished pharmaceutical product.

existing active pharmaceutical ingredient. An active pharmaceutical ingredient that is not considered a new active substance, which has been previously approved through a finished product by a stringent regulatory authority or by the World Health Organization, but requires the filing of a dossier. This would include, for example, new product dossiers and variations to multisource products.

expiry date. The date given on the individual container (usually on the label) of a product up to and including which the active pharmaceutical ingredient and finished pharmaceutical product are expected to remain within specifications if stored under the long-term conditions at which stability was established. It is set for each batch by adding the shelf life to the date of manufacture.

finished pharmaceutical product. A product that has undergone all stages of production, including packaging in its final container and labelling. A finished pharmaceutical product may contain one or more active pharmaceutical ingredients.

⁴ http://www.who.int/medicines/areas/quality_safety/quality_assurance/StabilityConditionsTable2UpdatedMarch2015.pdf?ua=1, accessed 1 March 2017.

impermeable containers. Containers that provide a permanent barrier to the passage of gases or solvents, e.g. sealed aluminium tubes for semisolids, sealed glass ampoules for solutions and aluminium/aluminium blisters for solid dosage forms (refer to 2.2.7.2).

in-use period. A period of time during which a reconstituted preparation of the finished dosage form in a multidose container, or a moisture-sensitive product in a large-format final container (e.g. high-density polyethylene (HDPE) bottles of 500) can be used after opening.

long-term stability studies. Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of an active pharmaceutical ingredient or finished pharmaceutical product, during and beyond the expected shelf life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the retest period or the shelf life, to confirm the projected retest period and shelf life, and to recommend storage conditions.

matrixing. The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same finished pharmaceutical product should be identified as, for example, covering different batches, different strengths, different sizes of the same container-closure system, and, possibly in some cases, different container-closure systems (refer to ICH Q1D).

new active pharmaceutical ingredient. Active pharmaceutical ingredient that has not been previously authorized as a medicine for use in humans in the country in question.

ongoing stability study. The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected retest period (or shelf life) of the active pharmaceutical ingredient, or confirm or extend the shelf life of the finished pharmaceutical product.

pilot-scale batch. A batch of an active pharmaceutical ingredient or finished pharmaceutical product manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger, unless otherwise adequately justified.

primary batch. A batch of an active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP) used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf life, as the case may be. Primary batch requirements are outlined in 2.1.3 and 2.2.3 for the API and FPP, respectively.

production batch. A batch of an active pharmaceutical ingredient or finished pharmaceutical product manufactured at production scale by using production equipment in a production facility as specified in the application.

provisional shelf life. A provisional expiry date that is based on acceptable accelerated and available long-term data for the finished pharmaceutical product to be marketed in the proposed container-closure system.

release specification. The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of an active pharmaceutical ingredient or finished pharmaceutical product at the time of its release.

retest date. The date after which an active pharmaceutical ingredient should be re-examined to ensure that the material is still in compliance with the specification and thus is still suitable for use in the manufacture of a finished pharmaceutical product.

retest period. The period of time during which the active pharmaceutical ingredient (API) is expected to remain within its specification and, therefore, can be used in the manufacture of a given finished pharmaceutical product (FPP), provided that the API has been stored under the defined conditions. After this period, a batch of API destined for use in the manufacture of an FPP should be retested for compliance with the specification and then used immediately. A batch of API can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For most substances known to be labile, it is more appropriate to establish a shelf life than a retest period. The same may be true for certain antibiotics.

semi-permeable containers. Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by adsorption onto one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial-pressure gradient. Examples of semi-permeable containers include plastic bags and semi-rigid, low-density polyethylene (LDPE) pouches for large-volume parenterals and LDPE and high-density polyethylene (HDPE) ampoules, bottles and vials.

shelf life. The period of time during which an active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP), if stored under the conditions in which stability was established, is expected to comply with the specification as determined by stability studies on a number of batches of the API or FPP. The shelf life is used to establish the expiry date of each batch.

shelf-life specification. The combination of physical, chemical, biological and microbiological tests and acceptance criteria that an active pharmaceutical ingredient or finished pharmaceutical product should meet throughout its retest period or shelf life.

significant change. (See sections 2.1.7 and 2.2.7.)

“Significant change” for an active pharmaceutical ingredient (API) is defined as failure to meet its specification. In general “significant change” for a finished

pharmaceutical product is defined as: a 5% or more change in assay from its initial content of API(s), or failure to meet the acceptance criteria for potency when using biological or immunological procedures.

Any degradation product exceeding its acceptance criterion.

1. Failure to meet the acceptance criteria for appearance, physical attributes and functionality test (e.g. colour, phase separation, resuspendability, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g. softening of suppositories, melting of creams or partial loss of adhesion for transdermal products) may be expected under accelerated conditions.

Also, as appropriate for the dosage form:

2. failure to meet the acceptance criterion for pH; or
3. failure to meet the acceptance criteria for dissolution for 12 dosage units.

specification. A list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges or other criteria for the tests described. It establishes the set of criteria to which an active pharmaceutical ingredient or finished pharmaceutical product should conform to be considered acceptable for its intended use. See *Release specification* and *Shelf-life specification*.

stability-indicating methods. Validated analytical procedures that can detect the changes with time in the chemical, physical or microbiological properties of the active pharmaceutical ingredient (API) or finished pharmaceutical product, and that are specific so that the content of the API, degradation products and other components of interest can be accurately measured without interference.

stability studies (stability testing). Long-term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the retest period (or shelf life) of an active pharmaceutical ingredient or the shelf life of a finished pharmaceutical product.

stress testing (of the active pharmaceutical ingredient (API)). Studies undertaken to elucidate the intrinsic stability of an API. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

stress testing (of the finished pharmaceutical product (FPP)). Studies undertaken to assess the effect of severe conditions on the FPP. Such studies include photostability testing and specific testing on certain products (e.g. metered-dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

supporting stability data. Supplementary data, such as stability data on small-scale batches, related formulations, and products presented in containers not necessarily the same as those proposed for marketing, and scientific rationales that support the analytical procedures, the proposed retest period or the shelf life and storage conditions.

utilization period. See in-use period.

variations. A change to any aspect of a pharmaceutical product, including but not limited to, the change of use of a starting material, a change to formulation, method or site of manufacture, specifications for the finished product and ingredients, container and container labelling and product information.

References

1. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-third report. Geneva: World Health Organization; 2009: Annex 2 (WHO Technical Report Series, No. 953).
2. The following International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines (<http://www.ich.org>) may be consulted in the context of stability testing:
 - ICH Q1A (R2): Stability testing of new drug substances and products.
 - ICH Q1B: Photostability testing of new drug substances and products.
 - ICH Q1C: Stability testing of new dosage forms.
 - ICH Q1D: Bracketing and matrixing designs for stability testing of new drug substances and products.
 - ICH Q1E: Evaluation for stability data.
 - ICH Q2R1): Validation of analytical procedures: text and methodology.
 - ICH Q3A: Impurities in new drug substances.
 - ICH Q3B: Impurities in new drug products.
 - ICH Q5C: Quality of biotechnological products: stability testing of biotechnological/biological products.
 - ICH Q6A: Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances.
 - ICH Q7: Good manufacturing practice guide for active pharmaceutical ingredients.
 - ICH Q8: Pharmaceutical development.
 - ICH Q9: Quality risk management.
 - ICH Q11: Development and manufacture of drug substances (chemical entities and biotechnological/biological entities).
3. Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 6 (WHO Technical Report Series, No. 986).
4. Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-sixth report. Geneva: World Health Organization; 2012: Annex 4 (WHO Technical Report Series, No. 970).
5. Guidelines on active pharmaceutical ingredient master file procedure. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-second report. Geneva: World Health Organization; 2008: Annex 4 (WHO Technical Report Series, No. 948).

6. Guidelines for registration of fixed-dose combination medicinal products. Appendix 3: Pharmaceutical development (or preformulation) studies. Table A1: Typical stress conditions in preformulation stability studies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-ninth report. Geneva: World Health Organization; 2005: Annex 5 (WHO Technical Report Series, No. 929).
7. Supplementary guidelines on good manufacturing practices: validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fortieth report. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937) and forty-ninth report. Geneva: World Health Organization; 2015: Annex 3 (WHO Technical Report Series, No. 992).
8. WHO good manufacturing practices: main principles for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986).
9. General guidance on hold time studies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2015: Annex 4 (WHO Technical Report Series, No. 992).
10. Prequalification Programme – Priority Essential Medicines. A United Nations Programme managed by WHO. Information for applicants (<https://extranet.who.int/prequal/medicines/welcome-medicines-prequalification>).

Appendix 1

Examples of testing parameters

Section I for active pharmaceutical ingredients

In general, appearance, assay and degradation products should be evaluated for all active pharmaceutical ingredients (APIs). Since some related substances might only be identified as degradation products in the outcome of the stability studies, all specified related substances should be monitored as part of API stability studies. Other API parameters that may be susceptible to change should also be studied where applicable (e.g. particle size and/or polymorphism when relevant for low-solubility APIs).

Section II for finished pharmaceutical products

The following list of parameters for each dosage form is presented as a guide to the types of tests to be included in a stability study. In general, appearance, assay and degradation products should be evaluated for all dosage forms, as well as the preservative and antioxidant content if applicable.

The microbial quality of multiple-dose sterile and non-sterile dosage forms should be controlled. Challenge tests should be carried out at least at the beginning and at the end of the shelf life. Such tests would normally be performed as part of the development programme, for example, within primary stability studies. They need not be repeated for subsequent stability studies unless a change has been made which has a potential impact on microbiological status.

It is not expected that every test listed be performed at each time point. This can also apply to sterility testing, which may be conducted for most sterile products at least at the beginning and at the end of the stability test period. A validated container-closure integrity test may be used in lieu of sterility testing. Tests for pyrogens and bacterial endotoxins may be limited to the time of release. Sterile dosage forms containing dry materials (powder-filled or lyophilized products) and solutions packaged in sealed glass ampoules may need no additional microbiological testing beyond the initial time point. The level of microbiological contamination in liquids packed in glass containers with flexible seals or in plastic containers should be tested at least at the beginning and at the end of the stability test period; if the long-term data provided to the regulatory authorities for marketing authorization registration do not cover the full shelf-life period, the level of microbial contamination at the last time point should also be provided. Weight loss from plastic containers should be reported over the shelf life.

The list of tests presented for each dosage form is not intended to be exhaustive, nor is it expected that every test listed be included in the design of a stability protocol for a particular finished pharmaceutical product (FPP) (for example, a test for odour should be performed only when necessary and with due consideration for the analyst's safety).

The storage orientation of the product, i.e. upright versus inverted, may need to be included in a protocol when contact of the product with the closure system may be expected to affect the stability of the products contained (e.g. liquids or semisolids), or where there has been a change in the container-closure system.

Tablets

Dissolution, disintegration, water content and hardness/friability. Dispersible tablets should additionally be tested for disintegration (with a limit of not more than 3 minutes) and fineness of dispersion.

Capsules

- hard gelatin capsules: brittleness, dissolution, disintegration, water content and level of microbial contamination;
- soft gelatin capsules: dissolution, disintegration, level of microbial contamination, pH, leakage and pellicle formation.

Oral solutions, suspensions and emulsions

Formation of precipitate, clarity (for solutions), pH, viscosity, extractables, level of microbial contamination.

- Additionally for suspensions, dispersibility, rheological properties, mean size and distribution of particles should be considered. Also polymorphic conversion may be examined, if applicable.
- Additionally for emulsions, phase separation, mean size and distribution of dispersed globules should be evaluated.

Powders and granules for oral solution or suspension

Water content and reconstitution time.

Reconstituted products (solutions and suspensions) should be evaluated as described above under “Oral solutions suspensions and emulsions” after preparation according to the recommended labelling, through the maximum intended use period.

Metered-dose inhalers and nasal aerosols

Some parameters listed may be assessed during development and not be required subsequently in stability studies. Dose content uniformity, labelled number of medication actuations per container meeting dose content uniformity, aerodynamic particle size distribution, microscopic evaluation, water content, leak rate, level of microbial contamination, valve delivery (shot weight), extractables/leachables from plastic and elastomeric components, weight loss, pump delivery, foreign particulate

matter and extractables/leachables from plastic and elastomeric components of the container, closure and pump. Samples should be stored in upright and inverted/on-the-side orientations.

For suspension-type aerosols, microscopic examination of appearance of the valve components and the container's contents for large particles, changes in morphology of the API particles, extent of agglomerates, crystal growth, foreign particulate matter, corrosion of the inside of the container or deterioration of the gaskets.

Nasal sprays: solutions and suspensions

Clarity (for solution), level of microbial contamination, pH, particulate matter, unit spray medication content uniformity, number of actuations meeting unit spray content uniformity per container, droplet and/or particle size distribution, weight loss, pump delivery, microscopic evaluation (for suspensions), foreign particulate matter and extractables/leachables from plastic and elastomeric components of the container, closure and pump.

Topical, ophthalmic and otic preparations

Included in this broad category are ointments, creams, lotions, pastes, gels, solutions, eye drops and cutaneous sprays.

- Topical preparations should be evaluated for clarity, homogeneity, pH, suspendability (for lotions), consistency, viscosity, particle size distribution (for suspensions, when feasible), level of microbial contamination/sterility and weight loss (when appropriate).
- Evaluation of ophthalmic or otic products (e.g. creams, ointments, solutions and suspensions) should include the following additional attributes: sterility, particulate matter and extractable volume.
- Evaluation of cutaneous sprays should include: pressure, weight loss, net weight dispensed, delivery rate, level of microbial contamination, spray pattern, water content and particle size distribution (for suspensions).

Suppositories

Disintegration and dissolution (at 37 °C) and as appropriate for the type, net filled content, rupture time, melting and solidification, liquefaction/softening time, leakage, pellicles and pH.

Small volume parenterals (SVPs)

Colour, clarity (for solutions), particulate matter, pH, sterility, endotoxins.

Stability studies for powders for injection solution should include monitoring for colour, reconstitution time and water content. Specific parameters to be examined at

appropriate intervals throughout the maximum intended use period of the reconstituted drug product, stored under condition(s) recommended on the label, should include clarity, colour, pH, sterility, pyrogen/endotoxin and particulate matter. It may be appropriate to consider monitoring of sterility after reconstitution into a product, e.g. dual-chamber syringe, where it is claimed that reconstitution can be performed without compromising sterility.

- The stability studies for suspension for injection should include, in addition, particle size distribution, dispersibility, specific gravity, resuspendability, rheological properties and dissolution (when applicable). Content uniformity may be considered a stability-indicating parameter for the primary stability studies of a depot injection such as depomedroxyprogesterone acetate (DMPA) (refer to the WHO Prequalification Team-medicines (PQTm) DMPA guidance document published on the PQTm website: who.int/prequal/).¹
- The stability studies for emulsion for injection should include, in addition, phase separation, viscosity, mean size and distribution of dispersed phase globules.

Large volume parenterals (LVPs)

Colour, clarity, particulate matter, pH, sterility, pyrogen/endotoxin and volume.

Transdermal patches

In vitro release rates, leakage, level of microbial contamination/sterility, peel and adhesive forces.

¹ https://extranet.who.int/prequal/sites/default/files/documents/46%20DMPA_Aug2015_0.pdf.

Appendix 2

Recommended labelling statements

1. Active pharmaceutical ingredients

The statements that should be used if supported by the stability studies for active pharmaceutical ingredients (APIs) are listed in Table A10.1.

Table A10.1

Recommended labelling statements for active pharmaceutical ingredients

Testing condition under which the stability of the API has been demonstrated	Recommended labelling statement ^a
25 °C/60% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 25 °C"
25 °C/60% RH (long-term) 30 °C/65% RH (intermediate, failure during accelerated stability studies)	"Do not store above 25 °C" ^b
30 °C/65% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C" ^b
30 °C/75% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"
5 °C ± 3 °C	"Store in a refrigerator (2 °C to 8 °C)"
–20 °C ± 5 °C	"Store in freezer"

^a During storage, shipment and distribution of the API, the current *Good trade and distribution practices (GTDP)* for *pharmaceutical starting materials* are to be observed (1). Details on storage and labelling requirements can be found in *WHO guide to good storage practices for pharmaceuticals* (2).

^b "Protect from moisture" should be added as applicable.

2. Finished pharmaceutical products

The statements that should be used if supported by the stability studies for finished pharmaceutical products (FPPs) are listed in Table A10.2.

Table A10.2

Recommended labelling statements for finished pharmaceutical products

Testing condition under which the stability of the FPP has been demonstrated	Recommended labelling statement ^a
25 °C/60% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 25 °C"
25 °C/60% RH (long-term) 30 °C/65% RH (intermediate, failure during accelerated stability studies)	"Do not store above 25 °C" ^b
30 °C/65% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C" ^b
30 °C/75% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"
5 °C ± 3 °C	"Store in a refrigerator (2 °C to 8 °C)"
–20 °C ± 5 °C	"Store in freezer"

^a During storage, shipment and distribution of the FPP, the current *good distribution practices (GDP) for pharmaceutical products* are to be observed (3). Details on storage and labelling requirements can be found in *WHO guide to good storage practices for pharmaceuticals* (2).

^b "Protect from moisture" should be added as applicable.

In principle, FPPs should be packed in containers that ensure stability and protect the FPP from deterioration. A storage statement should not be used to compensate for inadequate or inferior packaging. Additional labelling statements that could be used in cases where the result of the stability testing demonstrates limiting factors are listed in Table A10.3.

Table A10.3

Additional labelling statements for use where the result of the stability testing demonstrates limiting factors

Limiting factors	Additional labelling statement, where relevant
Finished pharmaceutical products (FPPs) that cannot tolerate refrigeration	"Do not refrigerate or freeze" ^a
FPPs that cannot tolerate freezing	"Do not freeze" ^a
Light-sensitive FPPs	"Protect from light"

Table A10.3 *continued*

Limiting factors	Additional labelling statement, where relevant
FPPs that cannot tolerate excessive heat, e.g. suppositories	"Store and transport not above 30 °C"
Hygroscopic FPPs	"Store in dry condition"
Packaging (with the packaging format specified in the statement, e.g. bottle, blister)	"Store in the original package" "Keep the container in the outer carton" "Keep the container tightly closed in order to protect from light and moisture"

^a Depending on the pharmaceutical form and the properties of the FPP, there may be a risk of deterioration due to physical changes if subjected to low temperatures, e.g. liquids and semisolids. Low temperatures may also have an effect on the packaging in certain cases. An additional statement may be necessary to take account of this possibility.

References

1. Good trade and distribution practices for pharmaceutical starting materials. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 6 (WHO Technical Report Series, No. 996).
2. Guide to good storage practices for pharmaceuticals. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-seventh report. Geneva: World Health Organization; 2003: Annex 9 (WHO Technical Report Series, No. 908).
3. Good distribution practices for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fortieth-fourth report. Geneva: World Health Organization; 2010: Annex 5 (WHO Technical Report Series, No. 957).

Appendix 3

Interpretation of storage statements for products approved in climatic zone II when the products are to be distributed in zone IV

In order to ensure the safe use of medicines in recipient countries, the wording on labelling storage statements must be considered in the context of both the region in and for which the stability studies were conducted and the region(s) in which the products are intended to be distributed.

For example, for products approved in a zone II region the stability testing has usually been conducted at accelerated conditions and at zone II long-term conditions. Demonstrated stability at zone II conditions may result in a label storage statement of “Store between 15 and 30 °C” in line with the convention of some zone II regions. A product with such a statement, received in a zone IV country, would be expected to have demonstrated stability at zone IVa or IVb long-term stability conditions. However, when the stability was demonstrated at zone II long-term conditions, the appropriate statement for distribution in a zone IV region would be “Do not store above 25 °C”.

Typical examples of the storage statements for products approved in zone II, with examples of the stability data on which the statements are based and the corresponding WHO-recommended storage statement for distribution in zone IV are provided in Table A10.4.

Table A10.4

Examples of stability data and storage statements for products approved in climatic zone II and WHO-recommended storage statements (for zone IV) based on the same data

Storage statement for products approved in zone II	Examples of stability data on which the statements are based	WHO-recommended storage statement for products to be distributed in zone IVa
This medicinal product does not require any special storage conditions (or similar, i.e. no temperature mentioned) (EU)	Zone II + accelerated (finished pharmaceutical product (FPP) is stable at long-term conditions, with no significant change at accelerated conditions)	“Do not store above 25 °C. Protect from moisture”

Table A10.4 *continued*

Storage statement for products approved in zone II	Examples of stability data on which the statements are based	WHO-recommended storage statement for products to be distributed in zone IVa
This medicinal product does not require any special storage conditions (EU)	Zone II + Zone IVb + accelerated (FPP is stable at long-term conditions (zones II and IVb), with no significant change at accelerated conditions)	"Do not store above 30 °C"
Do not store above 30 °C (EU)	Zone IVa + accelerated (FPP is stable at long-term conditions, with significant change at accelerated conditions)	"Do not store above 30 °C, avoid excursions. Protect from moisture"
Store at 15 °C to 30 °C (USA, Canada) OR Store at 25 °C; excursions permitted to 15 °C to 30 °C (USA) OR Store at controlled room temperature (15–30 °C). (Canada)	Zone II + accelerated (FPP is stable at long-term conditions, with no significant change at accelerated conditions)	"Do not store above 25 °C. Protect from moisture"

Note: Zone II is 25 °C/60% RH, zone IVa is 30 °C/65% RH and zone IVb is 30 °C/75% RH.

Note: IVa may be acceptable in lieu of IVb when humidity is not an issue, for example, for storage in glass containers (see 2.2.7.2 of the main text of the Annex).

2.4 Guidelines on packaging for pharmaceutical products

Annex 9, WHO Technical Report Series, 902, 2002

Introductory note	224
Glossary	225
1. Aspects of packaging	228
1.1 General considerations	228
1.2 Functions of packaging	230
1.2.1 Containment	230
1.2.2 Protection	231
1.3 Presentation and information	232
1.3.1 Labels	233
1.3.2 Repacking, relabelling and dispensing	234
1.3.3 Package inserts for patients (patient information leaflets)	234
1.4 Compliance	234
1.5 Protection of patients	234
1.6 Detection of counterfeiting	235
2. Packaging materials and closures	235
2.1 Types of material	235
2.1.1 Glass	235
2.1.2 Plastics	236
2.1.3 Metal	236
2.2 Closures	236
2.2.1 Rubber closures	237
2.2.2 Caps or overseals	237
2.2.3 Special types of closure	238
3. Quality assurance aspects of packaging	239
3.1 General considerations	239
3.2 Quality control	240
3.2.1 Sampling	241
3.2.2 Testing programme	241
3.3 Inspection and audit	242
3.3.1 Rules	242
3.3.2 Audits of suppliers	242

4. Protection of the environment	242
4.1 Packaging waste	242
4.2 Waste policies	243
5. Quality specifications	244
5.1 Requirements in The international pharmacopoeia	244
5.1.1 Packaging materials	244
5.1.2 Requirements for dosage form containers	245
5.2 Pharmacopoeial requirements for containers in Europe, Japan and the United States	246
5.2.1 Glass containers	246
5.2.2 Plastic containers	246
5.2.3 Rubber closures	246
5.3 International Standards	247
References	247
Bibliography	249
Appendix 1 Storage areas	252
Appendix 2 Labels	253
Appendix 3 Self-inspection and quality audits	254
Appendix 4 International standards on packaging	256

Introductory note

This review of the various elements of the packaging of a pharmaceutical product is aimed at ensuring that medicines arrive safely in the hands of the patients for whom they are prescribed.

In the manufacture of pharmaceutical products, quality assurance is defined as “the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use” (1).

In addition, the system of quality assurance for the manufacture of pharmaceutical products should ensure that “arrangements are made for the manufacture, supply and use of the correct starting and packaging materials” (1).

Public opinion sometimes considers packaging to be superfluous. However, it must be emphasized that packaging preserves the stability and quality of medicinal products and protects them against all forms of spoilage and tampering.

All medicinal products need to be protected and “consequently need to be packaged in containers that conform to prescribed standards, particularly with respect to the exclusion of moisture and light and the prevention of leaching of extractable substances into the contents and of chemical interaction with the contents. However, the limits of acceptability in these various respects depend, at least in part, on climatic variables. Recommendations in *The international pharmacopoeia* can only be advisory; precise quantitative standards will have to be locally determined” (2).

The complexity of packaging materials and the highly technological nature of medicinal products is such that manufacturers are confronted with significant problems. Interaction between packaging and such products is possible due to the combination of a multiplicity of container components and active pharmaceutical ingredients, excipients and solvents used in a variety of dosage forms.

The quality of the packaging of pharmaceutical products plays a very important role in the quality of such products. It must:

- protect against all adverse external influences that can alter the properties of the product, e.g. moisture, light, oxygen and temperature variations;
- protect against biological contamination;
- protect against physical damage;
- carry the correct information and identification of the product.

The kind of packaging and the materials used must be chosen in such a way that:

- the packaging itself does not have an adverse effect on the product (e.g. through chemical reactions, leaching of packaging materials or absorption);
- the product does not have an adverse effect on the packaging, changing its properties or affecting its protective function.

The resulting requirements must be met throughout the whole of the intended shelf-life of the product. Given the link between the quality of a pharmaceutical product and the quality of its packaging, pharmaceutical packaging materials and systems must be subject, in principle, to the same quality assurance requirements as pharmaceutical products.

The appropriate system of quality assurance for the manufacture of pharmaceutical products should therefore follow the WHO guidelines for good manufacturing practices (GMP) (1).

The requirements to be met by pharmaceutical packaging and packaging materials as described in compendia (pharmacopoeias) and standards (e.g. those of the International Organization for Standardization (ISO)) must be considered only as general in character. The suitability of packaging or packaging material for any particular requirements and conditions can only be ascertained through detailed packaging and stability studies on the product concerned.

Glossary

The definitions given below apply specifically to the terms used in these guidelines. They may have different meanings in other contexts.

General

bulk product

Any product that has completed all the processing stages up to, but not including, final packaging (1).

containers

A container for pharmaceutical use is an article which holds or is intended to contain and protect a drug and is or may be in direct contact with it. The closure is a part of the container. The container and its closure must not interact physically or chemically with the substance within in any way that would alter its quality. The following terms include general requirements for the permeability of containers (3):

- *Well-closed containers* must protect the contents from extraneous matter or from loss of the substance under normal conditions of handling, shipment or storage.
- *Tightly closed containers* must protect the contents from extraneous matter, from loss of the substance, and from efflorescence, deliquescence or evaporation under normal conditions of handling, shipment or storage. If the container is intended to be opened on several occasions, it must be designed to be airtight after reclosure.

- *Hermetically closed containers* must protect the contents from extraneous matter and from loss of the substance, and be impervious to air or any other gas under normal conditions of handling, shipment or storage.

Substances and dosage forms requiring protection from light should be maintained in a *light-resistant container* that — either by reason of the inherent properties of the material of which it is composed, or because a special coating has been applied to it — shields the contents from the effects of light. Alternatively, the container may be placed inside a suitable light-resistant (opaque) covering and/or stored in a dark place (3).

labels

All finished drug products should be identified by labelling, as required by the national legislation, bearing at least the following information:

- (a) the name of the drug product;
- (b) a list of the active ingredients (if applicable, with the International Nonproprietary Names (INNs)), showing the amount of each present, and a statement of the net contents, e.g. number of dosage units, mass or volume;
- (c) the batch number assigned by the manufacturer;
- (d) the expiry date in an uncoded form;
- (e) any special storage conditions or handling precautions that may be necessary;
- (f) the directions for use, and any warnings and precautions that may be necessary;
- (g) the name and address of the manufacturer or the company or person responsible for placing the product on the market.

marketing authorization (product licence, registration certificate)

A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, information given on the label, product information and shelf-life (1).

materials

A term used to denote starting materials, process aids, intermediates, active pharmaceutical ingredients, packaging and labelling materials.

packaging material

Any material, including printed material, employed in the packaging of a pharmaceutical product, excluding any outer packaging used for transportation or shipment. Primary packaging materials are those that are in direct contact with the product (1).

packaging process

All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product (1).

production

All operations involved in the preparation of a pharmaceutical product, from receipt of the starting materials, through processing and packaging, to completion of the finished product (1).

quarantine

The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing (1).

Containers for pharmaceuticals¹***ampoule***

A container sealed by fusion and to be opened exclusively by breaking. The contents are intended for use on one occasion only.

bag

A container consisting of surfaces, whether or not with a flat bottom, made of flexible material, closed at the bottom and at the sides by sealing; the top may be closed by fusion of the material, depending on the intended use.

blister

A multi-dose container consisting of two layers, of which one is shaped to contain the individual doses. Strips are excluded.

bottle

A container with a more or less pronounced neck and usually a flat bottom.

cartridge

A container, usually cylindrical, suitable for liquid or solid pharmaceutical dosage forms; generally for use in a specially designed apparatus (e.g. a prefilled syringe).

gas cylinder

A container, usually cylindrical, suitable for compressed, liquefied or dissolved gas, fitted with a device to regulate the spontaneous outflow of gas at atmospheric pressure and room temperature.

¹ Based on a list of terms drawn up in response to a request from the European Commission to revise and replace the guidelines of the Committee for Proprietary Medicinal Preparations (III/3593/91).

injection needle

A hollow needle with a locking device intended for the administration of liquid pharmaceutical dosage forms.

injection syringe

A cylindrical device with a cannula-like nozzle, with or without a fixed needle and a movable piston, used for the administration, usually parenteral, of an accurately measured quantity of a liquid pharmaceutical form. The syringe may be prefilled, and can be for single-dose or multi-dose use.

pressurized container

A container suitable for compressed, liquefied or dissolved gas fitted with a device that, after its actuation, produces a controlled spontaneous release of the contents at atmospheric pressure and room temperature.

single-dose container

A container for single doses of solid, semi-solid or liquid preparations.

strip

A multi-dose container consisting of two layers, usually provided with perforations, suitable for containing single doses of solid or semi-solid preparations. Blisters are excluded.

tube

A container for multi-dose semi-solid pharmaceutical forms consisting of collapsible material; the contents are released via a nozzle by squeezing the package.

vial

A small container for parenteral medicinal products, with a stopper and overseal; the contents are removed after piercing the stopper. Both single-dose and multi-dose types exist.

1. Aspects of packaging

1.1 General considerations

Packaging may be defined as the collection of different components (e.g. bottle, vial, closure, cap, ampoule, blister) which surround the pharmaceutical product from the time of production until its use.

The aspects of packaging to be considered (4) include:

- the functions of packaging;
- the selection of a packaging material;
- the testing of the material selected;
- filling and assembling;

- sterilization;
- storage and stability.

Packaging materials (see section 2) include printed material employed in the packaging of a pharmaceutical product, but not any outer packaging used for transportation or shipment. Examples of the types of materials used are shown in Table 1.

A distinction must be made between primary and secondary packaging components. The primary packaging components (e.g. bottles, vials, closures, blisters) are in direct physical contact with the product, whereas the secondary components are not (e.g. aluminium caps, cardboard boxes). The choice of primary and/or secondary packaging materials will depend on the degree of protection required, compatibility with the contents, the filling method and cost, but also the presentation for over-the-counter (OTC) drugs and the convenience of the packaging for the user (e.g. size, weight, method of opening/ reclosing (if appropriate), legibility of printing).

Table 1
Types of raw materials used in packaging

Types of materials	Uses
Cardboard	Boxes Display units
Paper	Labels Leaflets
Glass	Ampoules Bottles Vials Syringes Cartridges
Plastic	Closures Bottles Bags Tubes Laminates with paper or foil
Metal, e.g. aluminium	Collapsible tubes Rigid cans Foil Needles Gas cylinders Pressurized containers
Rubber	Closures, including plungers

Containers may be referred to as primary or secondary, depending on whether they are for immediate use after production of the finished product or not. Both single-dose and multi-dose containers exist. Containers may be well-closed, tightly closed, hermetically closed or light-resistant, as defined in the glossary (3).

The packaging process, as defined in the glossary, is the process that a bulk material must undergo to become a finished product. The properties and attributes of the product should be as specified by the manufacturer and required by the user. The packaging process consists of the following stages:

- filling and assembling;
- sterilization in the final container, if applicable;
- placing labels on the container;
- storage at the manufacturing and shipping sites.

Packaging documentation (1) includes aspects related to:

- specifications and quality control, including batch records;
- labels, inks and adhesive materials (e.g. glue);
- package inserts for patients.

Apart from primary and secondary packaging, two types of special packaging are currently in use, as follows:

- *Unit-dose packaging.* This packaging guarantees safer medication by reducing medication errors; it is also more practical for the patient. It may be very useful in improving compliance with treatment and may also be useful for less stable products.
- *“Device” packaging.* Packaging with the aid of an administration device is user-friendly and also improves compliance. This type of packaging permits easier administration by means of devices such as prefilled syringes, droppers, transdermal delivery systems, pumps and aerosol sprays. Such devices ensure that the medicinal product is administered correctly and in the right amount.

1.2 Functions of packaging

1.2.1 Containment

The containment of the product is the most fundamental function of packaging for medicinal products. The design of high-quality packaging must take into account both the needs of the product and of the manufacturing and distribution system. This requires the packaging:

- not to leak, nor allow diffusion and permeation of the product;
- to be strong enough to hold the contents when subjected to normal handling;
- not to be altered by the ingredients of the formulation in its final dosage form.

1.2.2 Protection

The packaging must protect the product against all adverse external influences that may affect its quality or potency, such as:

- light
- moisture
- oxygen
- biological contamination
- mechanical damage.

The compatibility of the packaging with the active pharmaceutical ingredients is very important in maintaining the integrity of the product.

Stability. Information on stability is given in the guidelines for stability testing of pharmaceutical products containing well-established drug substances in conventional dosage forms (4).

For primary packaging, it is necessary to know the possible interactions between the container and the contents. Normally, product/ component stability and compatibility are confirmed during the primary research and development stage.

While excluding the effect of external factors on the product, the packaging itself should not interact with it so as to introduce unacceptable changes. There are numerous possibilities of interactions between (primary) packaging materials and pharmaceutical products, such as:

- the release of chemicals from components of the packaging materials;
- the release of visible and/or subvisible particles;
- the absorption or adsorption of pharmaceutical components by the packaging materials;
- chemical reactions between the pharmaceutical product and the packaging materials;
- the degradation of packaging components in contact with the pharmaceutical products;
- the influence of the manufacturing process (e.g. sterilization) on the container.

The active pharmaceutical ingredients should remain within their specification limits over the shelf-life of the pharmaceutical product. The question of whether a packaging will provide the required protection for the pharmaceutical product and the required stability over a certain time period can only be answered by means of real-time stability studies. Such studies must evaluate the changes in the quality of the product, in contact with its packaging, during a period equivalent to its intended shelf-life.

In addition, packaging must meet the following requirements:

- it must preserve the physical properties of all dosage forms and protect them against damage or breakage;
- it must not alter the identity of the product;
- it must preserve the characteristic properties of the product, so that the latter complies with its specifications;
- it must protect the product against undesirable or adulterating chemical, biological or physical entities.

Storage. Packaging materials should be stored in accordance with GMP for storage areas (1; see Appendix 1). The characteristics of the active pharmaceutical ingredients will determine whether different packaging will be needed. For example, the packaging requirements of medicinal products kept at temperatures between 2 and 8 °C may differ from those of products intended for tropical countries or light-sensitive products. If the contents are sterile, sterility must be maintained, including that of any unused remaining product.

The shelf-life and utilization period are always determined in relation to storage conditions and the stability of the active pharmaceutical ingredient.

Normal storage conditions are defined as “storage in dry, well-ventilated premises at temperatures of 15–25 °C or, depending on climatic conditions, up to 30 °C. Extraneous odours, other indications of contamination, and intense light have to be excluded” (5).

1.3 Presentation and information

Packaging is also an essential source of information on medicinal products. Such information is provided by labels and package inserts for patients.

The information provided to the patient may include the following:

- the name of the patient;
- the identification number for dispensing records;
- the name, strength, quantity and physical description or identification of the medicinal product;
- directions for use and cautionary statements, if applicable;
- the storage instructions;

- the date of dispensing and period of use (related to the expiry date);
- the name and address of the dispenser.

1.3.1 Labels

Throughout manufacturing, a succession of specific outer labels are applied to the container of the medicinal product. The level of processing is indicated by the following words:

- quarantine
- storage
- distribution.

Specifications for labels for finished drug products are defined in the WHO guidelines on GMP for pharmaceutical products (1; see Appendix 2).

Written labels on the packaging:

- Permit the identification of each active ingredient by means of its INN, and also give the dosage form and the trade name/trademark. All information concerning the medicinal product, as required by national legislation, must be stated on the packaging.
- Preserve the stability of the medicinal product by giving advice on its storage (4):

After the stability of the product has been evaluated, one of the following recommendations as to storage conditions can be prominently indicated on the label:

- store under normal storage conditions;
 - store between 2 and 8 °C (under refrigeration, no freezing);
 - store below 8 °C (under refrigeration);
 - store between -5 and -20 °C (in a freezer);
 - store below -18 °C (in a deep freezer).
- Permit the follow-up of a specific medicinal product by means of the batch number on the labels. It must be possible to follow the route of distribution of a product from the manufacturing process to its administration to the patient with the aim of locating and identifying products that are of potential risk (e.g. blood products, blood-derived products).
 - Mask the real identity of the medicinal product in clinical studies. This is extremely important in clinical trials in determining the real efficacy of a medicinal product in blinded studies. If the identity is masked by a code, it must be possible to disclose it at any time in a medical emergency.

National legislation must be followed with regard to the information provided to the patient, as well as the record-keeping and packaging instructions.

1.3.2 Repacking, relabelling and dispensing

In some countries, it is common practice not to dispense drugs in the original packaging, but rather in a personalized manner to each patient. This applies especially to solid oral dosage forms, and involves the “repacking” and “relabelling” of drugs in small quantities. Different drugs may even be included in “customized” medication packages, also referred to as “patient med packs”. The quantities of drugs supplied in this way are usually enough only for a short period of time, i.e. to provide drugs for immediate use. It should be remembered, however, that data obtained in stability studies undertaken by the manufacturer are no longer valid for drugs removed from the original package.

Where repacking and relabelling are necessary, the WHO guidelines on GMP for pharmaceutical products (1) should be followed to avoid any mix-up or contamination of the product, which could place the patients’ safety at risk.

1.3.3 Package inserts for patients (patient information leaflets)

Product information must help patients and other users to understand the medication. The patient package insert, together with the label, provides the patient with key information concerning the proper use of the product, potential adverse drug reactions and interactions, storage conditions and the expiry date.

In OTC medicinal products, the package insert, together with the label, may constitute the only pharmaceutical advice that the patient receives.

1.4 Compliance

Packaging and labelling may help to reinforce the instructions given by the physician or the pharmacist, and improve compliance with drug therapy. In this respect, packaging becomes a compliance aid.

The design of pharmaceutical packaging should be such that the product can easily be administered in a safe manner to the patient. If the patient feels at ease with the packaging and route of administration, the design of the packaging may become a key factor in increasing compliance. This is also an important factor in clinical trials.

1.5 Protection of patients

Packaging must not only increase compliance through its design, but must also protect the patient and indicate the integrity of the product. Packaging equipped with a tamper-evident device protects against incidental and accidental poisoning. To protect children, several child-resistant closures have been developed (see section 2.2.3).

1.6 Detection of counterfeiting

The Forty-first World Health Assembly, after reviewing the report of the Executive Board on the implementation of WHO's revised drug strategy, requested: "... governments and pharmaceutical manufacturers to cooperate in the detection and prevention of the increasing incidence of the export or smuggling of falsely labelled, spurious, counterfeited or substandard pharmaceutical preparations" (6).

Several documents (2, 6–9) show that counterfeit pharmaceutical products are in wide circulation. In November 1985, during the WHO Conference of Experts on the Rational Use of Drugs in Nairobi, Kenya, concern was expressed regarding the extent to which counterfeit pharmaceutical products were in circulation in developing countries (10). In view of the importance of this issue, a text has been drafted to provide model provisions to deal with counterfeit drugs (11).

The design of the packaging must therefore contribute to preventing tampering with, or the counterfeiting of, certain medicinal products. Such tamper-evident containers can allow the visual inspection of the medicinal product before use, and this may serve as a first stage in detecting counterfeit drugs.

2. Packaging materials and closures

In accordance with the methods of use and administration of medicinal products, packaging materials, closures and containers vary a great deal and have to meet a wide variety of different requirements. All the routes used for systemic access have demanding requirements, which often can only be met by complex structured and formulated medicinal products. This is particularly true of the new medicinal products that are now appearing, such as those administered via transdermal delivery systems.

To ensure the efficacy of a product during its total shelf-life, pharmaceuticals must be regarded as a combination of the medicinal product itself and the packaging.

2.1 Types of material

Only the most commonly used packaging materials and containers are described here.

2.1.1 Glass

For a large number of pharmaceuticals, including medicinal products for oral and local administration, glass containers are usually the first choice (e.g. bottles for tablets, injection syringes for unit- or multi-dose administration). Different types of glass may be necessary, depending on the characteristics and the intended use of the medicinal products concerned.

Manufacturers should arrange with their suppliers to obtain the appropriate type of glass container for the intended use. Suppliers should provide the raw and packaging materials in conformity with industrial norms. Classifications of types of

glass are given in the European and United States pharmacopoeias, whereas no such classification exists in the Japanese pharmacopoeia.

Glass can be tested for light transmission and hydrolytic resistance. In the Japanese pharmacopoeia, such tests are described only for glass containers for injection, whereas in the European and United States pharmacopoeias they are given for all types of glass containers.

2.1.2 Plastics

Some containers are now being made of plastics; the main use is for bags for parenteral solutions. Plastic containers have several advantages compared with glass containers:

- they are unbreakable
- they are collapsible
- they are light.

The European, Japanese and United States pharmacopoeias all describe materials of the same type, but there are considerable differences in the classification and presentation.

As far as tests are concerned, the three pharmacopoeias are extremely difficult to compare. The European pharmacopoeia is the most detailed and requires tests in relation to the use and routes of administration of the medicinal product. Moreover, the same concept is extended to bulk containers for active ingredients.

2.1.3 Metal

Metal containers are used solely for medicinal products for non- parenteral administration. They include tubes, packs made from foil or blisters, cans, and aerosol and gas cylinders. Aluminium and stainless steel are the metals of choice for both primary and secondary packaging for medicinal products. They have certain advantages and provide excellent tamper-evident containers.

Since metal is strong, impermeable to gases and shatterproof, it is the ideal packaging material for pressurized containers.

Descriptions and tests can be found in the norms and standards of the ISO; these have been established in collaboration with manufacturers. Requirements are not given in pharmacopoeias; the suitability of a particular material for a container is normally established by conducting stability studies in which the material is in contact with the drug in question.

2.2 Closures

Closures used for the purpose of covering drug containers after the filling process should be as inert as possible. They should not give rise to undesired interactions between the

contents and the outside environment, and should provide a complete seal. Besides their protective function, closures must also allow the easy and safe administration of the drug.

Depending on the application, closures may have to be pierced with a needle for intravenous sets. Such closures are made from elastomeric materials (rubbers), while those that cannot be pierced are generally made from plastics such as polyethylene or polypropylene.

Depending on the type of container, closures may have different shapes and sizes, e.g. stoppers for infusion or injection bottles or plungers for prefilled syringes. A special design of stopper may also be required for some pharmaceutical production processes such as lyophilization.

Closures, as primary packaging components, are of critical importance and must be carefully selected. They are an essential component of the container and, as such, an integral part of the drug preparation.

A container type which does not require a removable closure at the time of administration is usually preferred since such a container/ closure system avoids, or at least minimizes, the risk of biological and other contamination as well as tampering.

For parenteral preparations, the combination of glass containers and elastomeric closures, usually secured by an aluminium cap, is widely used. Typical examples are infusion bottles, injection vials and prefilled syringes. The rubber closures used within such a system must be carefully selected in accordance with the intended purpose. Most often, improper rubber closures are the cause of incompatibility between the packaging and the drug.

2.2.1 Rubber closures

Rubber consists of several ingredients, one of which is elastomer. Modern rubber compounds used in packaging pharmaceuticals contain only a limited number of ingredients, which are very difficult to extract. Closures made from such materials generally do not pose any problems, and can be used in contact with a large number of drug preparations.

Rubber closures for pharmaceutical use must meet the relevant requirements of the most important pharmacopoeias (the European, Japanese and United States pharmacopoeias). International standards have also been established (ISO 8871). It should be emphasized that the requirements of pharmacopoeias and standards must be seen as minimal requirements. The suitability of a rubber closure for a given application can only be established by means of stability studies.

2.2.2 Caps or overseals

Caps or overseals are used to secure the rubber closure to the container in order to maintain the integrity of the seal under normal conditions of transport, handling and storage during the intended shelf-life of the product. Such caps are usually made

of aluminium and can be equipped with a plastic top to facilitate opening. Caps also provide evidence of tampering: once opened or removed they cannot be repositioned. This is especially true for caps with a plastic top.

2.2.3 Special types of closure

Demographic trends are causing new problems for packaging designers. Thus while child-resistant closures safeguard children against drug intoxication, opening such packaging may prove difficult for the increasing number of elderly persons in the population.

Tamper-evident closures. Tampering includes three aspects, namely altering, pilfering and falsifying the pharmaceutical product.

To prevent tragic accidents and especially malicious tampering, manufacturers try to create safe packaging and governments continue to update regulations to include new tamper-evident technology. In 1975, the United States Food and Drug Administration issued a regulatory requirement for tamper-evident packaging to be used for ophthalmic preparations, thus ensuring that such preparations remained sterile until their use (12). This regulation specifies that the closures must be sealed in such a manner that the contents cannot be used without destroying the seal. In 1982, a further regulation (13) on tamper-evident packaging for OTC human drug products described such packaging as “having an indicator or barrier to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred”.

The concept of tamper-evident packaging is also found in the “General Notice” and “Requirements” of the United States pharmacopoeia, which stipulate that all OTC drugs must comply with the tamper-evident packaging and labelling requirements of the Food and Drug Administration, unless specifically exempted. Products covered by the regulation include all OTC drugs, toothpaste and topical dermatological products, oral cosmetic liquids, contact lens solutions and tablets.

In May 1992, the Food and Drug Administration (14) listed 11 technologies capable of satisfying the definition of tamper-evident packaging, while a twelfth was added for sealed cartons. The list includes film wrappers, blister packs, bubble packs, heat-shrunk bands or wrappers, paper foil or plastic packs, bottles with inner mouth seals, tape seals, breakable cap-ring systems, sealed tubes or plastic blindend heat-sealed tubes, sealed cartons, aerosol containers and all metal and composite cans.

Child-resistant closures. Tragic accidents involving the drug intoxication of children has led to new legislation making it difficult for drug packaging to be opened by young children, while allowing adults easy access. Such packaging is designated as child-resistant.

Certain protocols for child-resistant packaging were established in the United States in 1966. In 1970, the Poison-Prevention Packaging Act was passed and placed under the jurisdiction of the Food and Drug Administration. This Act was transferred

in 1973 to the Consumer Product Safety Commission, which is responsible for drugs and household substances (15). The use of child-resistant packaging has proved effective in reducing child mortality from intoxication by oral prescription drugs, and it is now recognized worldwide that children must be protected against such intoxication.

The ISO has published an internationally agreed standard test procedure for reclosable child-resistant packaging (16). In Europe several norms have been introduced, which complement the ISO standard (17, 18).

The European Committee for Standardization (CEN) has defined a child-resistant package as one “which makes it difficult for young children to gain access to the contents, but which is not too difficult for adults to use properly in accordance with the requirement of this European standard” (19).

The three most common reclosable child-resistant types of closure are the “press–turn”, the “squeeze–turn” and a combination lock.

To determine whether a packaging is child-resistant, it must be subjected to the ISO test procedure for reclosable child-resistant packaging (14).

Most designs that are child-resistant require two hands to open the closure. Such packaging can cause problems for elderly people, and can even lead to the deliberate purchase of drugs with packaging that is not child-resistant; alternatively, the child-resistant closure may not be replaced on the container. An optional “elderly adult test” has been inserted in the ISO standard to deal with this problem.

3. Quality assurance aspects of packaging

3.1 General considerations

To ensure that patients and consumers receive high-quality drugs, the quality management system must take the following considerations into account if the required quality of packaging is to be obtained:

- the requirements of the national authorities and the relevant legislation
- the product
- the production process
- the manufacturers’ internal policies (safety, marketing, etc.).

Bad packaging which is the result of deficiencies in the quality assurance system for packaging can have serious consequences, and packaging defects can create problems that may result in drug recalls. Such defects may include breakage, and problems relating to printing or inks, or errors on labels and package inserts (patient information leaflets). The use of GMP and quality control will prevent the release of a defective medicinal product.

Packaging processes and equipment need validation/qualification in the same way as any other part of processing within a pharmaceutical facility.

3.2 Quality control

Pharmacopoeial specifications and standards for quality control established by national drug quality control laboratories, as already mentioned, can only be regarded as general in character and must be interpreted as minimum standards. The essential part of quality control is performed by the manufacturer during the development, production, release and post-marketing surveillance of the entire medicinal product, i.e. the finished dosage form in its primary and secondary packaging. As pointed out by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-second meeting (1):

Quality control is the part of GMP concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. Quality control is not confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

In the production chain, quality control for packaging contains several critical points. The basic requirements for quality control are as follows (1):

- (a) Adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting and testing starting materials, packaging materials, and intermediate, bulk and finished products, and where appropriate for monitoring environmental conditions for GMP purposes.
- (b) Samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved of by the quality control department.
- (c) Test methods must be validated.
- (d) Records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated.
- (e) The finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container, and correctly labelled.
- (f) Records must be made of the results of inspecting and testing materials and intermediate, bulk and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures.

. . . The quality control department as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, to evaluate, maintain and store the reference standards for substances, to ensure the correct labelling of containers of materials and products, to ensure that the stability of the active pharmaceutical ingredients and products is monitored, to participate in the investigation of complaints related to the quality of the product, and to participate in the environmental monitoring. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

Tests and assays are normally carried out at room temperature (between 15 and 25 °C, or up to 30 °C in some climatic zones), unless otherwise indicated. *The international pharmacopoeia* gives alternative methods to be used if certain instruments are not available.

3.2.1 Sampling

Sampling is used to check the correctness of the label, packaging material or container reference, as well as in the acceptance of consignments, detecting adulteration of the medicinal product, obtaining a sample for retention, etc.

The sampling procedure must take into account the homogeneity and uniformity of the material so as to ensure that the sample is representative of the entire batch.

The sampling procedure should be described in a written protocol. Further details are given in “Sampling procedure for industrially manufactured pharmaceuticals” (20).

3.2.2 Testing programme

The testing programme for quality control purposes may vary from one manufacturer to another. Quality control tests are intended to check the identity of the material concerned. Complete pharmacopoeial or analogous testing may also be carried out, as may special tests, where necessary.

All written specifications for packaging materials and containers should include the nature, extent and frequency of routine tests. Routine tests vary according to the type of material and its immediate packaging, the use of the product, and the route of administration. Nevertheless, such tests usually include the following (21):

- visual inspection (cleanliness, defects)
- tests to identify the material
- dimensional tests
- physical tests
- chemical tests
- microbiological tests.

3.3 Inspection and audit

Self-inspection is covered in Appendix 3, which is taken from Annex 1 of the thirty-second report of the Committee (1).

3.3.1 Rules

It is extremely important to control the security and quality of packaging. The requirements to be met by packaging for pharmaceutical products are more stringent than those for the packaging of food products, although many similarities exist. The goal of inspection is to ascertain the quality of the products, and especially the quality of the packaging. Items for self-inspection include documentation, storage of starting materials and finished products, validation of programmes, production and in-process controls, calibration of instruments or measurement systems, control of labels, sanitation and hygiene, recall procedures, premises (including personnel facilities), and maintenance of buildings and equipment.

Labels play an important part in the quality of packaging. Packaging and labelling errors in the manufacture of pharmaceutical products are often reported.

3.3.2 Audits of suppliers

Pharmaceutical manufacturers are usually audited or inspected by national or international licensing authorities; the same applies to suppliers of starting materials, active pharmaceutical ingredients, excipients and packaging materials. All suppliers of pharmaceuticals and packaging materials play an important role in the chain of quality assurance of the final medicinal product.

Further details can be found in the twenty-fifth and thirtieth reports of the Committee (2, 22), and “General requirements for dosage forms” in *The international pharmacopoeia* (3).

4. Protection of the environment

The protection of the environment has become increasingly important in many countries in recent years. Greater attention has been paid to the disposal and recycling of waste, and legislation has been introduced in many countries.

4.1 Packaging waste

Pharmaceutical packaging represents a very small percentage of waste, but its disposal can cause problems for the environment. For this reason, the Committee, at its thirty-second meeting (1), decided that:

. . . Provisions should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials

should be stored in suitably designed, separated, enclosed cupboards, as required by national legislation.

. . . Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

Environmental problems result from the methods used for waste disposal, and will depend on the type of packaging waste concerned. Such waste may include:

- uncontaminated waste (assimilated to domestic waste: paper, cardboard, glass, plastic);
- contaminated waste (paper, cardboard, glass, plastic), e.g. waste that has been in contact with blood, blood-derived products, radioactive products or cytotoxic products.

The method of disposal will therefore vary but should always be in accordance with national legislation. Contaminated packaging is often incinerated. The methods of disposal of uncontaminated packaging are shown in Table 2.

Table 2
Methods of disposal of uncontaminated packaging

Material	Recycling	Landfill	Incineration
Paper, cardboard	+++	++	++
Plastics	++	+	+++
Glass	+++	++	NA
Rubber	+	++	+++
Metal	+++	+	NA

+++ : Highly recommended; ++ : recommended; + : acceptable; NA : not applicable.

4.2 Waste policies

Waste is created at all stages in the production, supply and use of a pharmaceutical product. At each step, care therefore needs to be taken, either by the manufacturer or the end-user, to protect the environment.

Environmental concerns in the international community have led to certain changes in the conditions for the licensing of medicines (23). Thus an environmental risk

assessment may have to be carried out in some cases in order to identify potential risks to the environment arising from the storage, use and disposal of medicinal products. The medicinal product as a whole may become the subject of the environmental risk assessment so that consideration has to be given not only to the active ingredient but also to the adjuvants/excipients in the formulation, and the primary and secondary packaging.

Another major environmental issue affecting certain types of pharmaceutical products concerns the chlorofluorocarbon (CFC) propellants, and the threat that they represent to the ozone layer (24). A European directive has been published on this subject (25).

In several European countries, manufacturers must dispose of their drug waste, or must pay a specialized company to do so for them, and are encouraged to salvage packaging waste. Faced with this problem, manufacturers and pharmacists have, respectively, introduced new directives and new process policies aimed at:

- *Reducing packaging.* Efforts should be made to reduce the volume and weight of packaging materials, and to eliminate packaging which is not essential for the protection of the contents of medicinal products.
- *Salvaging and recycling packaging.* The use of environmental- friendly packaging needs to be considered, i.e. recyclable or degradable packaging. (Valuable packaging materials, such as aluminium, have been extensively recycled for many years. Recently, paper, glass and plastic materials have joined the list of recyclable packaging materials.) However, materials that have been in contact with toxic or highly potent drugs require special consideration.
- *Eliminating and incinerating packaging.* Some plastic materials cannot be recycled and are therefore incinerated. The burning of polyvinyl chloride (PVC) is controversial since, if combustion is not complete, it causes a potential increase in the levels of dioxin in the environment. Incineration can be recommended if the combustion heat produced by it can also be used for other purposes. Developing countries are often short of incinerators. This method is nevertheless regarded as the best available for the elimination of contaminated packaging.

5. Quality specifications

5.1 Requirements in The international pharmacopoeia

5.1.1 Packaging materials

Monographs for inclusion in Volume 6 of *The international pharmacopoeia* (3) have been proposed for glass containers and rubber closures.

5.1.2 Requirements for dosage form containers

Every pharmaceutical preparation must comply with the labelling requirements laid down in the WHO guidelines on GMP for pharmaceutical products (1).

Tablets. These should be kept in well-closed containers and protected from light, moisture, crushing and mechanical shock. Any special storage conditions should be stated on the label. Tablets should be able to withstand handling, including packaging and transportation, without losing their integrity. Moisture-sensitive forms, such as effervescent tablets, should be stored in tightly closed containers or moisture-proof packs, and may require the use of separate packages containing water-adsorbent agents, such as silica gel.

Additional special recommendations for packaging, storage and transportation are specified in the relevant individual monographs.

For effervescent tablets, the label should state “Not to be swallowed directly”.

Capsules. These should be packaged and stored in a manner that protects them from microbial contamination. Capsules should be kept in well-closed containers. They should be protected from light, excessive moisture, or dryness, and should not be subjected to temperatures above 30 °C.

Additional special recommendations for packaging, storage and transportation are specified in the relevant individual monographs.

Parenteral preparations. These are usually supplied in glass ampoules, bottles or vials, plastic bottles or bags, and prefilled syringes, which are coloured in the case of light-sensitive substances.

Except where otherwise indicated in the relevant individual monographs, the containers for parenteral preparations should be made from a material that is sufficiently transparent to permit the visual inspection of the contents. They should not adversely affect the quality of the preparation, allow diffusion of any kind into or across the container, or release foreign substances into the preparation.

Closures for containers for parenteral preparations should be equipped with a firm seal to prevent the entry of microorganisms and other contaminants while permitting the withdrawal of a part or the whole of the contents without removal of the closure. They should not be made of materials that react with the contents, nor should they allow foreign substances to diffuse into the preparation. The elastomers of which the closure is made should be sufficiently firm to allow the passage of a needle with the least possible shedding of particles. Closures for multi-dose containers should be sufficiently elastic to allow the puncture to reseal when the needle is withdrawn and thus protect the contents from airborne contamination. A tamper-evident container is fitted with a device that reveals clearly whether it has ever been opened.

On visual inspection, solutions, reconstituted solutions and intravenous infusions (except dispersions) should be clear and free from visible particulate matter.

Topical semi-solid dosage forms. Containers for these dosage forms should be made from a material that does not adversely affect the quality of the preparation or

allow diffusion of any kind into or across the container into the preparation. Closures for these containers should be of a design that minimizes microbial contamination and be equipped with a device that reveals whether the container has ever been opened.

Containers for topical semi-solid dosage forms should protect the preparation from light, moisture, and damage during handling and transportation. The use of suitable metal or plastic flexible tubes is preferred. Preparations for nasal, aural, vaginal or rectal use should be supplied in containers adapted for the appropriate delivery of the product to the site of application, or should be supplied with a suitable applicator.

Topical semi-solid dosage forms should be kept in well-closed containers. The preparation should maintain its pharmaceutical integrity throughout the shelf-life when stored at the temperature indicated on the label; this should normally not exceed 25 °C. Special storage recommendations or limitations are indicated in the relevant individual monographs.

5.2 Pharmacopoeial requirements for containers in Europe, Japan and the United States

5.2.1 Glass containers

As previously mentioned in section 2.1.1, a classification of types of glass for containers for pharmaceutical products does not exist in the Japanese pharmacopoeia, while those given in the European and United States pharmacopoeias are very similar.

Both the European and United States pharmacopoeias provide specifications for glass containers for injections. The latter publication also gives specific guidance for the packaging, repackaging and dispensing of medicinal products. Both the European and United States pharmacopoeias also provide specifications for light-resistant containers and tightly or well-closed closures for capsules and tablets.

The European pharmacopoeia gives a general account of the requirements for glass containers for pharmaceutical use, together with those specifically applicable to glass containers for human blood and blood products.

5.2.2 Plastic containers

Many different plastics are used for containers for medicinal products and the requirements applicable to them differ greatly in the various pharmacopoeias. It is very difficult to compare the tests described. Other and possibly different requirements may be found in international standards.

5.2.3 Rubber closures

A comparison of the requirements for rubber closures is as difficult as that for plastic containers. The European and Japanese pharmacopoeias contain special requirements for rubber closures intended for containers of aqueous parenteral preparations. The

United States pharmacopoeia describes more generally the use of closures made from elastomers for injection bottles, but does not specify the preparations for which they can be used.

Similarities exist between the tests given in the European, Japanese and United States pharmacopoeias, but international standards also exist which differ considerably from one another.

5.3 International Standards

A list of recent International Standards on packaging is given in Appendix 4.

References

1. Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).
2. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirtieth report*. Geneva, World Health Organization, 1987 (WHO Technical Report Series, No. 748).
3. *The international pharmacopoeia, 3rd ed. Vol. 4. Tests, methods, and general requirements. Quality specifications for pharmaceutical substances, excipients, and dosage forms*. Geneva, World Health Organization, 1994.
4. Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996, Annex 5 (WHO Technical Report Series, No. 863).
5. Stability of drug dosage forms. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report*. Geneva, World Health Organization, 1990, Annex 1 (WHO Technical Report Series, No. 790).
6. WHA41.16. In: *Handbook of resolutions and decisions of the World Health Assembly and the Executive Board, Volume III*, 3rd ed. (1985–1992). Geneva, World Health Organization, 1993:89.
7. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report*. Geneva, World Health Organization, 1990 (WHO Technical Report Series, No. 790).
8. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996 (WHO Technical Report Series, No. 863).
9. *Report of the international workshop on counterfeit drugs, Geneva, 26–28 November 1997*. Geneva, World Health Organization, 1998 (unpublished document WHO/DRS/CFD/98.1; available from Essential Drugs and Medicines Policy, World Health Organization, 1211 Geneva 27, Switzerland).
10. *The rational use of drugs: report of the Conference of Experts, Nairobi, 25–29 November 1985*. Geneva, World Health Organization, 1987.
11. *Counterfeit drugs: guidelines for the development of measures to combat counterfeit drugs*. Geneva, World Health Organization, 1999 (unpublished document WHO/EDM/QSM/99.1; available from Essential Drugs and Medicines Policy, World Health Organization, 1211 Geneva 27, Switzerland).

12. **Department of Health and Human Services, Food and Drug Administration.** Section 200.50. Ophthalmic preparations and dispensers. In: *U.S. Code of Federal Regulations. Title 21. Food and drugs. Vol. 4. Parts 200 to 299.* Washington, DC, United States Government Printing Office, 2000:6–7.
13. **Department of Health and Human Services, Food and Drug Administration.** Section 211.132. Tamper-evident packaging requirements for over-the-counter (OTC) human drug products. In: *U.S. Code of Federal Regulations. Title 21. Food and drugs. Vol. 4. Parts 200 to 299.* Washington, DC, United States Government Printing Office, 2000:125–126.
14. **Department of Health and Human Services, Food and Drug Administration.** *Tamper-resistant packaging requirements for certain over-the-counter (OTC) human drug products.* Washington, DC, United States Government Printing Office, 1992 (FDA Compliance Policy Guide, 7132a.17).
15. **Department of Health and Human Services, Food and Drug Administration.** Part 1700. Poison-Prevention Act of 1970 Regulations. In: *U.S. Code of Federal Regulations. Title 16. Commercial practices. Chapter 2. Consumer Product Safety Commission.* Washington, DC, United States Government Printing Office, 1999:690–705.
16. *Child-resistant packaging — requirements and testing procedures for reclosable packages. International Standard ISO 8317.* Geneva, International Organization for Standardization, 1989.
17. *Specifications for packagings resistant to opening by children. British Standard BS 6652.* London, British Standards Institution, 1985.
18. *Packaging — child-resistant packages — requirements, testing procedures, non-reclosable packages for pharmaceutical products. DIN 55559.* Berlin, German Standardization Institute, 1998.
19. *Packaging — child-resistant packaging — requirements and testing procedures for non-reclosable packages for pharmaceutical products. European Protocol prEN862.* Brussels, European Committee for Standardization, 2000.
20. Sampling procedure for industrially manufactured pharmaceuticals. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report.* Geneva, World Health Organization, 1990, Annex 2 (WHO Technical Report Series, No. 790).
21. Plastic primary packaging materials. In: *The rules governing medicinal products in the European Union. Vol. 3. Guidelines on the quality, safety and efficacy of medicinal products for human use.* Brussels, European Commission, 1998:75–82.
22. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Twenty-fifth report.* Geneva, World Health Organization, 1975 (WHO Technical Report Series, No. 567).
23. Council Directive 93/39/EEC of 14 June 1993 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC in respect of medicinal products. *Official Journal of the European Communities*, 1993, 214:22–30.
24. Matters relating to the replacement of CFCs in medicinal products (3BR2a). In: *The rules governing medicinal products in the European Union. Vol. 3B. Safety, environment and information.* Brussels, European Commission, 1998.
25. *Assessment of potential risk to the environment posed by medicinal products. European Directive No. 5504/94.* London, Medicines Control Agency, 1994.

Bibliography

Good manufacturing practices

- **Department of Health and Human Services, Food and Drug Administration.** Part 210. Current good manufacturing practice in manufacturing, processing, packing, or holding of drugs; general. In: *U.S. Code of Federal Regulations. Title 21. Food and drugs. Vol. 4. Parts 200 to 299.* Washington, DC, United States Government Printing Office, 2000:113.
- Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report.* Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).
- Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.* Geneva, World Health Organization, 1996, Annex 7 (WHO Technical Report Series, No. 863).
- Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. In: *WHO Expert Committee on the Use of Essential Drugs. Sixth report.* Geneva, World Health Organization, 1995, Annex 3 (WHO Technical Report Series, No. 850).
- *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 1.* Geneva, World Health Organization, 1997.
- *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 2. Good manufacturing practices and inspection.* Geneva, World Health Organization, 1999.
- *The rules governing medicinal products in the European Union. Vol. IV. Good manufacturing practices: medicinal products for human and veterinary use.* Brussels, European Commission, 1998.
- *Regulations for buildings and facilities of pharmacies and manufacturing plants of drugs, medical devices, quasi-drugs and cosmetics. (MHW Ordinance No. 2, dated 1 February 1961; amended by MHW Ordinance No. 54, dated 28 March 2001.)* Tokyo, Ministry of Health, Labour and Welfare, 2001.
- *Regulations for manufacturing control and quality control of drugs and quasi-drugs. (MHW Ordinance No. 3, dated 27 January 1994; amended by MHW Ordinance No. 16, dated 12 March 1999.)* Tokyo, Ministry of Health and Welfare, 1999.

Pharmacopoeias

- *European pharmacopoeia*, 3rd ed. Strasbourg, Council of Europe, 1997; Supplements 1998, 1999.
- *The international pharmacopoeia*, 3rd ed. Vol. 4. *Tests, methods and general requirements. Quality specifications for pharmaceutical substances, excipients, and dosage forms.* Geneva, World Health Organization, 1994.
- *The Japanese pharmacopoeia*, 13th ed. Tokyo, Ministry of Health and Welfare, 1996; Supplement 1, 1998.
- *The United States pharmacopeia*, 23rd ed. Rockville, MD, The United States Pharmacopoeial Convention, 1995; Supplements 1–9, 1995–1998.

Guidelines and documents

- *Guideline for submitting documentation for packaging for human drugs and biologics.* Washington, DC, Center for Drug Evaluation and Research, Food and Drug Administration, 1987.

- *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Twenty-sixth report.* Geneva, World Health Organization, 1977 (WHO Technical Report Series, No. 614).
- *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirtieth report.* Geneva, World Health Organization, 1987 (WHO Technical Report Series, No. 748).
- *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report.* Geneva, World Health Organization, 1990 (WHO Technical Report Series, No. 790).
- *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report.* Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 823).
- *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.* Geneva, World Health Organization, 1996 (WHO Technical Report Series, No. 863).

Books

- **Banker GS, Rhodes CT, eds.** *Modern pharmaceuticals*, 3rd ed. Vol. 40. *Drugs and the pharmaceutical sciences*. New York, NY, Dekker, 1996.
- **Cooper J.** *Plastic containers for pharmaceuticals: testing and control*. Geneva, World Health Organization, 1974 (WHO Offset Publication, No. 4).
- **Gennaro AR, ed.** *Remington's pharmaceutical sciences*, 18th ed. Easton, PA, Mack, 1990.
- *[Guide to packaging.] Guide de l'emballage.* Paris, Usine Nouvelle (annual).
- **Jenkins WA, Osborn KR.** *Packaging drugs and pharmaceuticals*. Buffalo, NY, Technomic, 1993.
- **Leonard EA.** *Packaging: specifications, purchasing, and quality control*, 4th ed. New York, NY, Dekker, 1996.
- **Lockhart H, Paine FA.** *Packaging of pharmaceuticals and healthcare products*, 1st ed. Glasgow, Blackie Academic & Professional, 1996.
- **Reinhardt PA, Gordon JG.** *Infectious and medical waste management*. Chelsea, MI, Lewis Publishers, 1991.
- **Ross CF.** *Packaging of pharmaceuticals*. Melton Mowbray, Institute of Packaging, 1975.
- **Snyder D, ed.** *FDA-Speak. The Interpharm glossary of FDA acronyms and regulatory terms*. Buffalo, NY, Interpharm, 1992.
- **Snyder DE.** *Interpharm international dictionary of biotechnology and pharmaceutical manufacturing*. Buffalo, NY, Interpharm, 1992.

Reviews and articles

- **Casola AR.** FDA's guidelines for pharmaceutical packaging. *Pharmaceutical Engineering*, 1989, 9:15–19.
- Child-resistant containers. *Pharmaceutical Journal*, 1988, 241:219.
- **Choppen DF.** Packaging and labelling for patient and site compliance. *Clinical Research and Regulatory Affairs*, 1994, 11(1):61–65.
- **Department of Health and Human Services, Food and Drug Administration.** Section 211.132. Tamper-evident packaging requirements for over-the-counter (OTC) human drug products. In: *U.S. Code of Federal Regulations. Title 21. Food and drugs. Vol. 4. Parts 200 to 299*. Washington, DC, United States Government Printing Office, 2000:125–126.

- **Rodgers GB.** The safety effects of child-resistant packaging for oral prescription drugs: two decades of experience. *Journal of the American Medical Association*, 1996, 275:1661–1665.
- Tighter standards for blister packs wanted. *Pharmaceutical Journal*, 1995, 255:232.
- **USP Subcommittee on Packaging, Storage, and Distribution.** Survey on the practice of repackaging solid oral dosage forms in blister packs. *Pharmaceutical Forum*, 1996, 22(6):3265–3267.

Appendix 1

Storage areas¹

1. Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products.
2. Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.
3. Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.
4. Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.
5. There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.
6. Segregation should be provided for the storage of rejected, recalled or returned materials or products.
7. Highly active materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire or explosion should be stored in safe and secure areas.
8. Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labelling, and special attention should be paid to the safe and secure storage of these materials.

¹ Previously published in "Good manufacturing practices for pharmaceutical products". In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirtysecond report. Geneva*, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).

Appendix 2

Labels¹

1. All finished drug products should be identified by labelling, as required by the national legislation, bearing at least the following information:
 - (a) the name of the drug product;
 - (b) a list of the active ingredients (if applicable, with the International Nonproprietary Names), showing the amount of each present, and a statement of the net contents, e.g. number of dosage units, weight or volume;
 - (c) the batch number assigned by the manufacturer;
 - (d) the expiry date in an uncoded form;
 - (e) any special storage conditions or handling precautions that may be necessary;
 - (f) directions for use, and warnings and precautions that may be necessary; and
 - (g) the name and address of the manufacturer or the company or the person responsible for placing the product on the market.

¹ Previously published in "Good manufacturing practices for pharmaceutical products". In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).

Appendix 3

Self-inspection and quality audits¹

1. *Principle.* The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and quality control. The self-inspection programme should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively; all recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up programme.

Items for self-inspection

2. Written instructions for self-inspection should be established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items:
 - (a) personnel
 - (b) premises including personnel facilities
 - (c) maintenance of buildings and equipment
 - (d) storage of starting materials and finished products
 - (e) equipment
 - (f) production and in-process controls
 - (g) quality control
 - (h) documentation
 - (i) sanitation and hygiene
 - (j) validation and revalidation programmes
 - (k) calibration of instruments or measurements systems
 - (l) recall procedures
 - (m) complaints management

¹ Previously published in "Good manufacturing practices for pharmaceutical products". In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirtysecond report*. Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).

- (n) labels control
- (o) results of previous self-inspections and any corrective steps taken.

Self-inspection team

3. Management should appoint a self-inspection team from local staff who are expert in their own fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

Frequency of self-inspection

4. The frequency at which self-inspections are conducted may depend on company requirements.

Self-inspection report

5. A report should be made at the completion of a self-inspection. The report should include:
 - (a) self-inspection results
 - (b) evaluation and conclusions
 - (c) recommended corrective actions.

Follow-up action

6. The company management should evaluate both the self-inspection report and the corrective actions as necessary.

Quality audit

7. It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors.

Suppliers' audits

8. The quality control department should have responsibility together with other relevant departments for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.
9. Before suppliers are approved and included in the specifications they should be evaluated. The evaluation should take into account a supplier's history and the nature of the materials to be supplied. If the audit is required, it should determine the supplier's ability to conform with GMP standards for active pharmaceutical ingredients.

Appendix 4

International standards on packaging

A list is given below of the standards on packaging issued by the International Organization for Standardization (ISO), as of 10 October 1998, starting with the four main standards, after which they are listed in numerical order.

Quality systems — model for quality assurance in design, development, production, installation and servicing. International Standard ISO 9001. 1994.

Quality systems — model for quality assurance in production, installation and servicing. International Standard ISO 9002. 1994.

Quality systems — model for quality assurance in final inspection and test. International Standard ISO 9003. 1994.

Quality management and quality systems elements. Part 1: Guidelines. International Standard ISO 9004-1. 1994.

Quality management and quality systems elements. Part 2: Guidelines for service. International Standard ISO 9004-2. 1994.

Quality management and quality systems elements. Part 3: Guidelines for processed materials. International Standard ISO 9004-3. 1994.

Quality management and quality systems elements. Part 4: Guidelines for quality improvement. International Standard ISO 9004-4. 1994.

Reusable all-glass or metal-and-glass syringes for medical use. Part 1: Dimensions. International Standard ISO 595-1. 1986.

Reusable all-glass or metal-and-glass syringes for medical use. Part 2: Design, performance requirements and tests. International Standard ISO 595-2. 1987.

Transfusion equipment for medical use. Part 1: Glass transfusion bottles, closures and caps. International Standard ISO 1135-1. 1987.

Plastics collapsible containers for human blood and blood components. International Standard ISO 3826. 1993.

Injection containers for injectables and accessories. Part 1: Injection vials made of glass tubing. International Standard ISO 8362-1. 1989.

Injection containers for injectables and accessories. Part 2: Closures for injection vials. International Standard ISO 8362-2. 1988.

Injection containers for injectables and accessories. Part 3: Aluminium caps for injection vials. International Standard ISO 8362-3. 1989.

Injection containers for injectables and accessories. Part 4: Injection vials made of moulded glass. International Standard ISO 8362-4. 1989.

Injection containers for injectables and accessories. Part 5: Freeze-drying closures for injection vials. International Standard ISO 8362-5. 1995.

Injection containers for injectables and accessories. Part 6: Caps made of aluminium-plastics combinations for injection vials. International Standard ISO 8362-6. 1992.

Injection containers for injectables and accessories. Part 7: Injection caps made of aluminium-plastics combinations without overlapping plastics part. International Standard ISO 8362-7. 1995.

Infusion equipment for medical use. Part 4: Infusion sets for single use, gravity feed. International Standard ISO 8536-4. 1998.

Infusion equipment for medical use. Part 5: Burette-type infusion sets. International Standard ISO 8536-5. 1992.

Infusion equipment for medical use. Part 6: Freeze-drying closures for infusion bottles. International Standard ISO 8536-6. 1995.

Infusion equipment for medical use. Part 7: Caps made of aluminium-plastics combinations for infusion bottles. International Standard ISO 8536-7. 1992.

Sterile single-use syringes, with or without needle, for insulin. International Standard ISO 8537. 1991.

Elastomeric parts for aqueous parenteral preparations. International Standard ISO 8871. 1990.

Aluminium caps for transfusion, infusion and injection bottles — general requirements and test methods. International Standard ISO 8872. 1988.

Injection equipment for medical use. Part 1: Ampoules for injectables. International Standard ISO 9187-1. 2000.

Injection equipment for medical use. Part 2: One-point-cut (OPC) ampoules. International Standard ISO 9187-2. 1993.

Dental cartridge syringes. International Standard ISO 9997. 1999.

Caps made of aluminium–plastics combinations for infusion bottles and injection vials — requirements and test methods. International Standard ISO 10985. 1999.

Prefilled syringes. Part 1: Glass cylinders for dental local anaesthetic cartridges. International Standard ISO 11040-1. 1992.

Prefilled syringes. Part 2: Plungers and discs for dental local anaesthetic cartridges. International Standard ISO 11040-2. 1994.

Prefilled syringes. Part 3: Aluminium caps for dental local anaesthetic cartridges. International Standard ISO 11040-3. 1993.

Prefilled syringes. Part 4: Glass barrels for injectables. International Standard ISO 11040-4. 1996.

Prefilled syringes. Part 5: Plungers for injectables. International Standard ISO 11040-5. 1996.

Containers and accessories for pharmaceutical preparations. Part 1: Drop-dispensing bottles. International Standard ISO 11418-1. 1996.

Containers and accessories for pharmaceutical preparations. Part 2: Screw-neck bottles for syrups. International Standard ISO 11418-2. 1996.

Containers and accessories for pharmaceutical preparations. Part 3: Screw-neck bottles (vials) for solid and liquid dosage forms. International Standard ISO 11418-3. 1996.

Containers and accessories for pharmaceutical preparations. Part 4: Tablet bottles. International Standard ISO 11418-4. 1996.

Containers and accessories for pharmaceutical preparations. Part 5: Dropper assemblies. International Standard ISO 11418-5. 1997.

Containers and accessories for pharmaceutical preparations. Part 7: Screw-neck vials made of glass tubing for liquid dosage forms. International Standard ISO 11418-7. 1998.

Pen-injectors for medical use. Part 1: Requirements and test methods. International Standard ISO 11608-1. 2000.

Pen-injectors for medical use. Part 2: Needles — requirements and test methods. International Standard ISO 11608-2. 2000.

Pen-injectors for medical use. Part 3: Finished cartridges — requirements and test methods. International Standard ISO 11608-3. 2000.

Pen systems. Part 1: Glass cylinders for pen-injectors for medical use. International Standard ISO 13926-1. 1998.

Pen systems. Part 2: Plungers and discs for pen-injectors for medical use. International Standard ISO 13926-2. 1999.

Disposable hanging devices for transfusion and infusion bottles — requirements and test methods. International Standard ISO 15010. 1998.

2.5 Recommendations for quality requirements when plant-derived artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients^{1,2}

Annex 6, WHO Technical Report Series, 992, 2015

1. Introduction	261
2. Characterization of artemisinin	262
3. Tests and specifications for artemisinin starting material	264
References	267

¹ Originally published as Annex 6 in WHO Technical Report Series, No. 970, 2012: Recommendations for quality requirements when artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients.

² Also published in the "Supplementary information" section of *The International Pharmacopoeia*.

1. Introduction

The harmonized good manufacturing practices (GMP) (1, 2) describe requirements for the production of active pharmaceutical ingredients (APIs). The applicability of these requirements begins with a defined starting material as follows:

“An API starting material is a raw material, intermediate, or an API that is used in the production and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials normally have defined chemical properties and structure.”

The focus of GMP for APIs is for field inspector use, rather than in applications for marketing authorization. It defines what may be considered as a starting material and provides guidance on where GMP is applied. The GMP guidelines do not apply to steps taken prior to the first introduction of the defined starting material. The manufacturer should designate and document the rationale for the point at which production of the API begins. For a synthesis process, this is known as the point at which the starting materials are entered into processes.

From a regulatory standpoint, the use of API starting materials marks the beginning of the detailed description of the process. The applicant for marketing authorization should propose and justify which substance should be considered as the API starting material, e.g. incorporated as a significant structural fragment into the structure of the active substance.

In practice the designation of a starting material may be difficult. The number of steps separating the starting material from the final API is an issue to be decided on a case-by-case basis, subject to the manufacturer's proposal and assessors' evaluation. Since a designated starting material may be obtained from multiple sources, it is necessary to have well-defined quality requirements to ensure that the APIs produced meet specifications. Establishing these requirements may involve a compromise between the desire for a pure starting material and the impact of this on cost of API production. Impurities can be tolerated in the starting material if the API manufacturing process has been shown to efficiently remove them. Redundant purification steps may reduce the yield of the final API and thus further increase its cost.

Artemisinin derivatives used in artemisinin-based combination therapy (ACT) are synthesized from artemisinin in one or two synthetic steps. Artemisinin is typically produced as an isolate from *Artemisia annua* L. Artemisinin complies with the definition of a “starting material”, as defined above and described in certain national, regional and international guidelines. It is:

- a material used in the production of the API that is incorporated into the API as a significant structural element;
- commercially available;
- a compound whose name, chemical structure, chemical and physical characteristics, properties and impurity profile are well defined; and
- obtained by commonly known procedures.

As artemisinin is extracted from plant material and prior intermediates are thus not available, it is logical to designate this compound as the starting material for its derivatives.

A monograph appears in *The International Pharmacopoeia* for artemisinin used as an API. However, at present, artemisinin is mainly used as a starting material for artemisinin-derived APIs, and not as an API.

The level of quality of the artemisinin should be acceptable for its intended use as the starting material for the production of artemisinin derivatives. The specifications presented below take into account an acceptable balance of benefit versus risk between the quality of artemisinin used as a starting material and the quality required for artemisinin derivatives for use as APIs.

However, competent authorities may accept other impurity profile levels depending on the capability of the manufacturing process to lead to artemisinin-derived APIs at least compliant with the relevant monographs of *The International Pharmacopoeia*.

The purpose of this document is to offer a global approach to defining the level of quality requirements of artemisinin when used as a starting material for the production of its API derivatives used in ACT formulations. It does not apply to cases where artemisinin is used as an API. It is intended that the recommendations for requirements outlined in this document will apply to artemisinin extracted from *Artemisia annua* L. regardless of variations in agricultural environment or variations in extraction and purification steps. In addition, in order to ensure appropriate quality of the derived APIs, the manufacturer may add additional tests, such as tests for residual solvents and heavy metals, among others, and/or require tighter specifications. For artemisinin produced using synthetic chemical processes or by fermentation other requirements may be applicable.

2. Characterization of artemisinin

Provided that artemisinin intended for use as a starting material has been correctly identified, the major quality concern is the presence and level of impurities with the potential to affect the purity of subsequent API derivatives. Impurities may originate from the plant extracts or arise from the purification process or from degradation.

Different biosynthetic routes may be used at different stages in the plant's development and there are claims of variability between growing regions and environments. Despite a lack of consensus on a single biosynthetic route, several potential impurities are common to different routes. These include artemisinic acid, dihydroartemisinic acid, arteannuin B and artemisitene. Of these only artemisitene has been reported in isolated artemisinin. Recent work (3,4) has contributed towards a clearer understanding of existing impurities and their analysis.

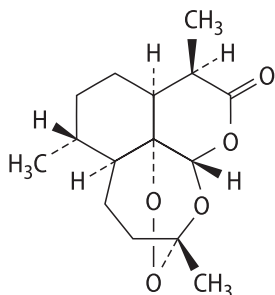
Examination of a wide variety of artemisinin samples produced in various regions indicated the consistent presence of two impurities: artemisitene and an artemisinin diastereomer with the stereochemistry inverted at C-9 (9-epi-artemisinin). A possible concern is that artemisinin impurities may not be detected with high-performance liquid chromatography analysis using ultraviolet detection, as used in the majority of testing laboratories. Recent work (5) using more sensitive general detection by mass spectrometry, however, demonstrated that additional impurities occur only in trace amounts. Isolated artemisinin is very stable. The potential degradants proposed on the basis of mechanistic studies do not occur at temperatures below 100 °C. These degradants are not observed in isolated artemisinin.

In the chemical conversion of the artemisinin starting material to its API derivatives (e.g. artesunate), the artemisinin diastereomeric impurity may be converted to a corresponding diastereomer at the C-9 position in the API derivative. However, these resulting diastereomers have not been observed in isolated APIs. The fate of artemisitene is less clear as it may be converted to the same intermediate as artemisinin.

Artemisitene-derived impurities have not been observed in artemisinin derivative APIs. Proposed limits for these impurities are based on historical results. The specifications for artemisinin starting material are based on experience with artemether and artesunate. For a new artemisinin-derived API the suitability of the specifications to control potential impurities arising during its synthesis should be demonstrated.

As the artemisinin extraction processes use solvents like dichloromethane, chloroform, ether and others, residual solvents should be indicated on the certificate of analysis issued by the supplier.

3. Tests and specifications for artemisinin starting material



Relative molecular mass: 282.3

Chemical name: (3*R*,5*aS*,6*R*,8*aS*,9*R*,12*S*,12*aR*)-3,6,9-trimethyloctahydro-3,12-epoxyprano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one; CAS Reg. No. 63968-64-9.

Description: Colourless needles or a white to almost white to slightly yellow, crystalline powder.

Category: Starting material for the synthesis of artemisinin derivative APIs.

Storage: Artemisinin should be kept in a well-closed container, protected from light.

Requirements

Artemisinin contains not less than 95.0% and not more than the equivalent of 102.0% of $\text{C}_{15}\text{H}_{22}\text{O}_5$ calculated with reference to the dried substance.

Identity tests

Carry out the examination as described under 1.7 *Spectrophotometry in the infrared region* of *The International Pharmacopoeia* (6). The infrared absorption spectrum is concordant with the spectrum obtained from artemisinin RS or with the *reference spectrum* of artemisinin in *The International Pharmacopoeia*.

Specific optical rotation: Use a 10 mg/mL solution in dehydrated ethanol R;
 $[\alpha]_{\text{D}}^{20^\circ\text{C}} = +75^\circ$ to $+78^\circ$

Loss on drying: Dry to constant mass at 80 °C; it loses not more than 10.0 mg/g.

Related substances

Note: It may be possible to justify other limits when artemisinin as a starting material is used in a particular synthesis and manufacturing process, by validation of the levels and limits of the impurities in the final API.

Carry out the test as described under 1.14.4 *High performance liquid chromatography of The International Pharmacopoeia* (6). Use the chromatographic conditions and prepare solutions (1) and (2) as described below under “Assay”. For solution (3) dilute 1 mL of solution (1) to 100 mL with the mobile phase.

Inject separately 20 µL of solutions (1), (2) and (3). Record the chromatograms for about 1.5 times the retention time of artemisinin. In the chromatogram obtained with solution (2) artemisitene (impurity A) is eluted at the relative retention of about 0.79 with reference to artemisinin (retention time about 10 minutes). The test is not valid unless the resolution between the peak of artemisitene and the peak of artemisinin is at least 4. The chromatogram obtained with solution (1) may show a peak due to impurity B eluting at a retention of about 0.85 with reference to artemisinin.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 0.027, is not greater than 0.15 times the area of the peak in the chromatogram obtained with solution (3) (0.2%);
- the area of any peak corresponding to impurity B is not greater than the area of the peak in the chromatogram obtained with solution (3) (1.0%);
- the area of any peak other than the principal peak is not greater than 0.5 times the area of the peak in the chromatogram obtained with solution (3) (0.5%);
- the sum of the corrected area of any peak corresponding to impurity A and the areas of all the peaks, apart from the principal peak, is not greater than 3 times the area of the peak obtained with solution (3) (3.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak obtained with solution (3) (0.1%).

Assay

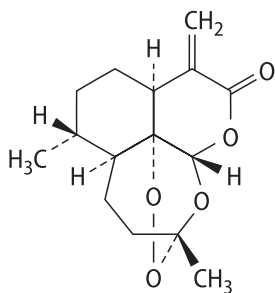
Carry out the test as described under 1.14.4 *High performance liquid chromatography of The International Pharmacopoeia* (6), using a stainless steel column (15 cm × 4.6 mm) packed with 5 µm particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups. The mobile phase consists of a 50:50 mixture of acetonitrile and water, pumped at a flow rate of 1.0 mL/minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 210 nm.

Prepare the following solutions. For solution (1) prepare a 5.0 mg/mL solution of the test substance in the mobile phase. For solution (2) prepare a 5.0 mg/mL solution of artemisinin RS in the mobile phase.

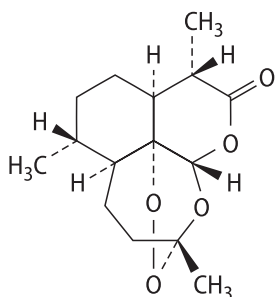
Inject separately 20 μL of solutions (1) and (2). Record the chromatograms for about 1.5 times the retention time of artemisinin. In the chromatogram obtained with solution (2) artemisitene (impurity A) is eluted at the relative retention of 0.79 with reference to artemisinin (retention time about 10 minutes). The test is not valid unless the resolution between the peak of artemisitene and the peak of artemisinin is at least 4. The chromatogram obtained with solution (1) may show a peak due to impurity B eluting at a retention of about 0.85 with reference to artemisinin.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the content of $\text{C}_{15}\text{H}_{22}\text{O}_5$ with reference to the dried substance.

Impurities



(3*R*,5*aS*,6*R*,8*aS*,12*S*,12*aR*)-3,6-dimethyl-9-methylideneoctahydro-3,12-epoxypyran[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (artemisitenene)



(3*R*,5*aS*,6*R*,8*aS*,9*S*,12*S*,12*aR*)-3,6,9-trimethyloctahydro-3,12-epoxypyran[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (9-*epi*-artemisinin)

References

1. WHO good manufacturing practices for active pharmaceutical ingredients. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report*. Geneva, World Health Organization, 2010, Annex 2 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y).
2. *International Conference on Harmonisation (ICH) Topic Q7: Note for guidance on good manufacturing practice for active pharmaceutical ingredients*. London, EMEA, 2006 (CPMP/ICH/4106/00); <https://www.ich.org/page/quality-guidelines>.
3. Lapkin AA et al. Development of HPLC analytical protocols for quantification of artemisinin in biomass and extracts. *Journal of Pharmaceutical and Biomedical Analysis*, 2009, 49:908–915.
4. Stringham RW et al. High performance liquid chromatographic evaluation of artemisinin, raw material in the synthesis of artesunate and artemether. *Journal of Chromatography A*, 2009, 1216:8918–8925.
5. Stringham RW et al. Verification of the identities of impurities in artemisinin and correction of their elution order in high performance liquid chromatography. *Journal of Chromatography A*, 2011, 1218:6838–6842.
6. *The International Pharmacopoeia*, 4th Edition, Vol. 1: General notices; monographs for pharmaceutical substances (A–O) and Vol. 2: Monographs for pharmaceutical substances (P–Z); monographs for dosage forms and radiopharmaceutical preparations; methods of analysis; reagents. Geneva, World Health Organization, 2006, also available in CD-ROM format and online:
 - *The International Pharmacopoeia*, 4th Edition, First Supplement. Geneva, World Health Organization, 2008; <http://apps.who.int/phint/en/p/docf/>, also available in CD-ROM format;
 - *The International Pharmacopoeia*, 4th Edition, First, Second, Third and Fourth Supplements, 2014, available on CD-ROM.

2.6 Recommendations on risk of transmitting animal spongiform encephalopathy agents via medicinal products

Annex 1, WHO Technical Report Series, 908, 2003

Products with risk of transmitting agents of animal spongiform encephalopathies are those derived from tissues or secretions of animals susceptible to transmissible spongiform encephalopathies other than by experimental challenge. This definition applies to all substances or preparations obtained from such animals and to all substances or preparations where products obtained from such animals are included as active substances or excipients or have been used during production, e.g. as raw or source materials, starting materials or reagents.

Materials of animal origin should be avoided whenever possible. However, if used, manufacturers should be aware of the risk and have a system in place to minimize it, especially since international trading patterns, often include the processing and re-export of products, so that their origin may not be traceable.

In order to minimize the risk of transmitting animal spongiform encephalopathy agents via medicinal products, manufacturers should follow the recommendations of the Joint Technical Consultation on Bovine Spongiform Encephalopathy, public health, animal health and trade, convened by the WHO, the Food and Agriculture Organization of the United Nations and the Office International des Epizooties 11–14 June 2001 in Paris.¹

¹ *Proceedings — Joint WHO/FAO/OIE Technical Consultation on BSE: public health, animal health and trade.* Paris: Office International des Epizooties, World Health Organization, Food and Agriculture Organization, World Organisation for Animal Health; 2002.

3. Marketing authorization: bioequivalence

3.1 Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability

Annex 8, WHO Technical Report Series, 1052, 2024

Republication of *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability*, WHO Technical Report Series No. 1003, Annex 6.

Background

Following the publication of the *WHO guideline on Biopharmaceutics Classification System-based biowaivers*, the relevant sections from this guideline have been removed, including the appendix *Equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the Biopharmaceutics Classification System*.

Background	269
1. Introduction	272
2. Glossary	273
3. Documentation of equivalence for marketing authorization	276
4. When equivalence studies are not necessary	277
5. When equivalence studies are necessary and types of study required	279
5.1 In vivo studies	279
5.2 In vitro studies	280

6. In vivo equivalence studies in humans: general considerations	280
6.1 Provisions for studies in humans	280
6.2 Justification of human bioequivalence studies	280
6.3 Selection of investigators	281
6.4 Study protocol	281
7. Pharmacokinetic comparative bioavailability (bioequivalence) studies in humans	281
7.1 Design of pharmacokinetic studies	281
7.1.1 Alternative study designs for studies in patients	282
7.1.2 Considerations for active pharmaceutical ingredients with long elimination half lives	282
7.1.3 Considerations for multiple-dose studies	283
7.1.4 Considerations for modified-release products	283
7.2 Subjects	284
7.2.1 Number of subjects	284
7.2.2 Dropout and withdrawal	285
7.2.3 Exclusion of subject data	285
7.2.4 Selection of subjects	286
7.2.5 Monitoring the health of subjects during the study	286
7.2.6 Considerations for genetic phenotyping	287
7.3 Investigational product	287
7.3.1 Multisource pharmaceutical product	287
7.3.2 Choice of comparator product	287
7.4 Study conduct	288
7.4.1 Selection of strength	288
7.4.2 Non-linear pharmacokinetics	288
7.4.3 Study standardization	288
7.4.4 Coadministration of food and fluid with the dose	289
7.4.5 Washout interval	290
7.4.6 Sampling times	290
7.4.7 Sample fluids and their collection	291
7.4.8 Parameters to be assessed	291
7.4.9 Studies of metabolites	292
7.4.10 Measurement of individual enantiomers	293
7.5 Quantification of active pharmaceutical ingredient	293
7.6 Statistical analysis	295
7.7 Acceptance ranges	297
7.8 Reporting of results	298
7.9 Special considerations	299
7.9.1 Fixed-dose combination products	299
7.9.2 Clinically important variations in bioavailability	299
7.9.3 Highly variable active pharmaceutical ingredients	299
8. Pharmacodynamic equivalence studies	301
9. Clinical equivalence studies	303

10. In vitro equivalence testing	305
10.1 In vitro equivalence testing in the context of the Biopharmaceutics Classification System	305
10.2 Qualification for a biowaiver based on the Biopharmaceutics Classification System	306
10.3 In vitro equivalence testing based on dose proportionality of formulations	306
10.3.1 Proportional formulations	306
10.3.2 Qualification for biowaivers based on dose proportionality of formulations	306
10.3.3 Dissolution profile comparison for biowaivers based on dose proportionality of formulations	308
10.4 In vitro equivalence testing for non-oral dosage forms	308
10.5 In vitro equivalence testing for scale-up and post-approval changes	311
References	311
Appendix 1 Recommendations for conducting and assessing comparative dissolution profiles	314

1. Introduction

These guidelines provide recommendations to regulatory authorities when defining requirements for approval of multisource (generic) pharmaceutical products in their respective countries. The guidance provides appropriate in vivo and in vitro requirements to assure interchangeability of the multisource product without compromising the safety, quality and efficacy of the pharmaceutical product.

National regulatory authorities should ensure that all pharmaceutical products subject to their control conform to acceptable standards of safety, efficacy and quality, and that all premises and practices employed in the manufacture, storage and distribution of these products comply with good manufacturing practice standards so as to ensure the continued conformity of the products with these requirements until they are delivered to the end user.

All pharmaceutical products, including multisource products, should be used in a country only after approval by the national or regional authority.

Regulatory authorities should require the documentation of a multisource pharmaceutical product to meet the following:

- good manufacturing practices
- quality control specifications
- pharmaceutical product interchangeability.

Multisource pharmaceutical products need to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator's (comparator) product. In addition, reasonable assurance must be provided that the multisource product is therapeutically equivalent to and interchangeable with the comparator product. For some classes of products, including – most evidently – aqueous parenteral solutions, interchangeability is adequately assured by assessment of the composition, implementation of good manufacturing practices, and evidence of conformity with appropriate specifications, including relevant pharmacopoeial specifications. For a wide range of pharmaceutical products, the concepts and approaches covered by these guidelines will enable national regulatory authorities to decide whether a given multisource product can be approved. This guidance is generally applicable to orally administered multisource products as well as to non-orally administered pharmaceutical products for which systemic exposure measures are suitable for documenting bioequivalence (for example, transdermal delivery systems and certain parenteral, rectal and nasal pharmaceutical products). Some information applicable to locally acting products is also provided in this document. For other classes of product, including many biologicals such as vaccines, animal sera, products derived from human blood and plasma, and products manufactured by biotechnology, as well as non-biological complex products, the concept of interchangeability raises issues that are

beyond the scope of this document, and these products are consequently excluded from consideration.

To ensure interchangeability, the multisource product must be therapeutically equivalent to the comparator product. Types of *in vivo* equivalence studies include comparative pharmacokinetic studies, comparative pharmacodynamic studies and comparative clinical studies.

Direct demonstration of therapeutic equivalence through a comparative clinical trial is rarely a practical choice, as these trials tend to be insensitive to differences in formulation and usually require a very large number of patients. Further, such studies in humans can be financially daunting, are often unnecessary and may be unethical. For these reasons, the science of bioequivalence testing has been developed over the past 50 years. According to the tenets of this science, therapeutic equivalence can be assured when the multisource product is both pharmaceutically equivalent and bioequivalent.

Assuming that, in the same subject, an essentially similar plasma concentration time course will result in essentially similar concentrations at the sites of action and thus in an essentially similar therapeutic outcome, pharmacokinetic data may be used instead of therapeutic results. Further, in selected cases, *in vitro* comparison of the dissolution profiles of the multisource product with those of the comparator product may be sufficient to provide an indication of equivalence.

It should be noted that interchangeability includes the equivalence of the dosage form as well as of the indications and instructions for use. Alternative approaches to the principles and practices described in this document may be acceptable, provided they are supported by adequate scientific justification. These guidelines should be interpreted and applied without prejudice to obligations incurred through the existing international Agreement on Trade-Related Aspects of Intellectual Property Rights (1).

2. Glossary

Some important terms used in these guidelines are defined below. They may have different meanings in other contexts.

bioavailability. The rate at and extent to which the active moiety is absorbed from a pharmaceutical dosage form and becomes available at the sites of action. Reliable measurements of active pharmaceutical ingredient concentrations at the sites of action are usually not possible. The substance in the systemic circulation, however, is considered to be in equilibrium with the substance at the sites of action. Bioavailability can therefore be defined as the rate at and extent to which the active pharmaceutical ingredient or active moiety is absorbed from a pharmaceutical dosage form and becomes available in the systemic circulation. Based on pharmacokinetic and clinical considerations, it is generally accepted that, in the same subject, an essentially similar plasma concentration time course will result in an essentially similar concentration time course at the sites of action.

bioequivalence. Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities, in terms of rate ($C_{\max}$ and $t_{\max}$) and extent of absorption (area under the curve), after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.

biological pharmaceutical product. A biological pharmaceutical product is a synonym for “biological product” or “biological” (as described in the reports of the Expert Committee on Biological Standardization in the World Health Organization (WHO) Technical Report Series). The definition of a pharmaceutical substance used in treatment, prevention or diagnosis as a “biological” has been variously based on criteria related to its source, its amenability to characterization by physicochemical means alone, and the requirement for biological assays or arbitrary systems of classification applied by regulatory authorities. For the purposes of WHO, including the current document, the list of substances considered to be biologicals is derived from their earlier definition as “substances which cannot be fully characterized by physicochemical means alone and which therefore require the use of some form of bioassay”. However, developments in the utility and applicability of physicochemical analytical methods, improved control of biological and biotechnology-based production methods, and an increased applicability of chemical synthesis to larger molecules have made it effectively impossible to base a definition of a biological on any single criterion related to method of analysis, source or method of production. Nevertheless, many biologicals are produced using in vitro culture systems.

Biopharmaceutics Classification System. The Biopharmaceutics Classification System is a scientific framework for classifying active pharmaceutical ingredients based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the pharmaceutical product and the critical examination of the excipients of the pharmaceutical product, the Biopharmaceutics Classification System takes into account the major factors that govern the rate and extent of active pharmaceutical ingredient absorption (exposure) from immediate-release oral solid dosage forms: excipient composition, dissolution, solubility and intestinal permeability.

biowaiver. The regulatory pharmaceutical product approval process whereby the dossier (application) is approved based on evidence of equivalence rather than through in vivo equivalence testing.

comparator product. The comparator product is a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established. If the innovator product is no longer marketed in the jurisdiction, the selection principle, as described in *Guidance on the selection of*

comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products,¹ should be used to identify a suitable alternative comparator product.

dosage form. The form of the finished pharmaceutical product (for example, tablet, capsule, suspension or suppository).

equivalence requirements. In vivo or in vitro testing requirements for approval of a multisource pharmaceutical product for a marketing authorization.

equivalence test. A test that determines the equivalence between the multisource product and the comparator product using in vivo or in vitro approaches.

fixed-dose combination. A combination of two or more active pharmaceutical ingredients in a fixed ratio of doses. This term is used generically to mean a particular combination of active pharmaceutical ingredients irrespective of the formulation or brand. It may be administered as single entity products given concurrently or as a finished pharmaceutical product.

fixed-dose combination finished pharmaceutical product. A finished pharmaceutical product that contains two or more active pharmaceutical ingredients.

generic product. See “multisource pharmaceutical product”.

innovator pharmaceutical product. Generally, the innovator pharmaceutical product is that which was first authorized for marketing, on the basis of complete documentation of quality, safety and efficacy.

interchangeable pharmaceutical product. A product that is therapeutically equivalent to a comparator product and can be interchanged with the comparator in clinical practice.

in vitro equivalence dissolution test. A dissolution test that includes comparison of the dissolution profile between the multisource product and the comparator product, typically in at least three media: pH 1.2, pH 4.5 and pH 6.8 buffer solutions.

in vitro quality control dissolution test. A dissolution test procedure identified in the pharmacopoeia for routine quality control of product batches, generally a single time point dissolution test for immediate-release products and a three or more time points dissolution test for modified release products.

¹ Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. WHO Technical Report Series No. 992, Annex 8. Geneva: World Health Organization; 2015.

multisource pharmaceutical product. A pharmaceutically equivalent or pharmaceutically alternative product that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

non-biological. Not involving or derived from biology or living organisms.

pharmaceutical alternative. A product is a pharmaceutical alternative if it contains the same active pharmaceutical moiety or moieties but differs in dosage form (for example, tablets versus capsules), strength, or chemical form (for example, different salts or different esters). Pharmaceutical alternatives deliver the same active moiety by the same route of administration but are otherwise not pharmaceutically equivalent. They may or may not be bioequivalent or therapeutically equivalent to the comparator product.

pharmaceutical equivalence. Products are pharmaceutical equivalents if they contain the same molar amount of the same active pharmaceutical ingredients in the same dosage form, if they meet comparable standards, and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the active pharmaceutical ingredient solid-state properties, the excipients, the manufacturing process or other variables can lead to differences in product performance.

If an excipient serves multiple functions (for example, microcrystalline cellulose as a filler and as a disintegrant), then the most conservative recommended range should be applied (for example, $\pm 1.0\%$ for microcrystalline cellulose should be applied in this example). The relative concentration of an excipient present in two aqueous solution finished pharmaceutical products is considered to be similar if the difference is $\leq 10\%$.

therapeutic equivalence. Two pharmaceutical products are considered to be therapeutically equivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and, after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same when administered to patients by the same route under the conditions specified in the labelling. This can be demonstrated by appropriate equivalence studies, such as pharmacokinetic, pharmacodynamic, clinical or in vitro studies.

3. Documentation of equivalence for marketing authorization

Multisource pharmaceutical products must be shown, either directly or indirectly, to be therapeutically equivalent to the comparator product if they are to be considered interchangeable. Suitable test methods to assess equivalence are:

- comparative pharmacokinetic studies in humans, in which the active pharmaceutical ingredient (API) or its metabolites are measured as a function of time in an accessible biological fluid such as blood, plasma, serum or urine to obtain pharmacokinetic measures, such as area under the curve (AUC) and C_{max}, that reflect the systemic exposure;
- comparative pharmacodynamic studies in humans;
- comparative clinical trials;
- comparative in vitro tests.

The applicability of each of these four methods is discussed below. Detailed information is provided on conducting an assessment of equivalence studies using pharmacokinetic measurements and in vitro methods, which are currently the methods most often used to document equivalence for most orally administered pharmaceutical products for systemic exposure.

Acceptance of any test procedure in the documentation of equivalence between two pharmaceutical products by a national regulatory authority depends on many factors, including the characteristics of the API and the pharmaceutical product. Where an API produces measurable concentrations in an accessible biological fluid, such as plasma, comparative pharmacokinetic studies can be performed. This type of study is considered to be the gold standard in equivalence testing; however, where appropriate, in vitro testing, for example Biopharmaceutics Classification System (BCS)-based biowaivers for immediate-release pharmaceutical products, can also assure equivalence between the multisource product and the comparator product (see sections 5 and 10). Where an API does not produce measurable concentrations in an accessible biological fluid and a BCS-based biowaiver is not an option, comparative pharmacodynamics studies may be an alternative method for documenting equivalence. Further, in certain cases when it is not possible to assess equivalence through other methods, comparative clinical trials may be considered appropriate.

The criteria that indicate when equivalence studies are or are not necessary are discussed in sections 4 and 5 of these guidelines.

4. When equivalence studies are not necessary

In the following circumstances, multisource pharmaceutical products are considered to be equivalent without the need for further documentation.

- (a) When the pharmaceutical product is to be administered parenterally (for example, intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations to those in the comparator product. Certain excipients

(such as buffer, preservative and antioxidant) may be different provided it can be shown that the changes in these excipients would not affect the safety or efficacy of the pharmaceutical product. The same principles are applicable for parenteral oily solutions but, in this case, the use of the same oily vehicle is essential. Similarly, for micellar solutions, solutions containing complexing agents or solutions containing co solvents of the same qualitative and quantitative composition of the functional excipients are necessary in order to waive equivalence studies. The change of other excipients should be critically reviewed.

- (b) When pharmaceutically equivalent products are solutions for oral use (for example, syrups, suspensions and tinctures), contain the API in the same molar concentration as the comparator product, and contain the same functional excipients in similar concentrations (if the API is BCS class I) and the same excipients in similar concentrations (for APIs from other BCS classes).
- (c) When pharmaceutically equivalent products are in the form of powders for reconstitution as an aqueous solution and the resultant solution meets either criterion (a) or criterion (b) above.
- (d) When pharmaceutically equivalent products are gases.
- (e) When pharmaceutically equivalent products are otic or ophthalmic products prepared as aqueous solutions and contain the same APIs in the same molar concentration and the same excipients in similar concentrations. Certain excipients (such as preservative, buffer, substance to adjust tonicity or thickening agent) may be different provided their use is not expected to affect bioavailability, safety or efficacy of the product.
- (f) When pharmaceutically equivalent products are topical products prepared as aqueous solutions and contain the same APIs in the same molar concentration and the same excipients in similar concentrations (note that a waiver would not apply to other topical dosage forms such as gels, emulsions or suspensions, but might be applicable to oily solutions if the vehicle composition is sufficiently similar).
- (g) When pharmaceutically equivalent products are aqueous solutions for nebulization or nasal drops, intended to be administered with essentially the same device, contain the same APIs in the same concentration, and contain the same excipients in similar concentrations (note that this waiver does not apply to other dosage forms such as suspensions for nebulization, nasal drops where the API is in suspension, nasal sprays in solution or suspension, dry powder inhalers or pressurized metered dose inhalers in solution or suspension). The pharmaceutical product may include different excipients provided their use is not expected to affect bioavailability, safety or efficacy of the product.

For situations (b), (c), (e), (f) and (g) above it is incumbent upon the applicant to demonstrate that the excipients in the pharmaceutically equivalent product are the same and that they are in concentrations similar to those in the comparator product or, where applicable (that is, (a), (e) and (g)), that their use is not expected to affect the bioavailability, safety or efficacy of the product. In the event that the applicant cannot provide this information and the national regulatory authority does not have access to the relevant data, it is incumbent upon the applicant to perform appropriate studies to demonstrate that differences in excipients or devices do not affect product performance.

5. When equivalence studies are necessary and types of study required

Except for the cases discussed in section 4, these guidelines recommend that documentation of equivalence with the comparator product be required by registration authorities for a multisource pharmaceutical product. Studies must be carried out using the product intended for marketing (see also subsection 7.3).

5.1 In vivo studies

For certain APIs and dosage forms, in vivo documentation of equivalence, through either a pharmacokinetic comparative bioavailability (bioequivalence) study, a comparative pharmacodynamic study or a comparative clinical trial, is regarded as especially important. In vivo documentation of equivalence is necessary when there is a risk that possible differences in bioavailability may result in therapeutic inequivalence (2). Examples are as follows:

- (a) oral, immediate-release pharmaceutical products with systemic action, except for the conditions outlined in section 10;
- (b) non-oral, non-parenteral pharmaceutical products designed to act systemically (such as transdermal patches, suppositories, nicotine chewing gum, testosterone gel and skin-inserted contraceptives);
- (c) modified-release pharmaceutical products designed to act systemically, except for the conditions outlined in section 10;
- (d) fixed-dose combination products with systemic action, where at least one of the APIs requires an in vivo study (3);
- (e) non-solution pharmaceutical products, which are for non-systemic use (for example, for oral, nasal, ocular, dermal, rectal or vaginal application) and are intended to act without systemic absorption.

In the case of non-solution pharmaceutical products for non-systemic use, the equivalence is established through, for example, comparative clinical or

pharmacodynamic studies, local availability studies or in vitro studies. In certain cases, measurement of the concentration of the API may still be required for safety reasons, that is, in order to assess unintended systemic absorption.

5.2 In vitro studies

For certain APIs and dosage forms, in vitro documentation of equivalence may be appropriate. In vitro approaches for systemically acting oral products are discussed in section 10.

6. In vivo equivalence studies in humans: general considerations

6.1 Provisions for studies in humans

Pharmacokinetic, pharmacodynamic and comparative clinical trials are clinical studies and should therefore be carried out in accordance with the provision and prerequisites for a clinical study, as outlined in the WHO *Guidelines for good clinical practice for trials on pharmaceutical products* (4), and with WHO good laboratory practices (5). Additional guidance for organizations performing in vivo equivalence studies is available from WHO (6).

All research involving human subjects should be conducted in accordance with the ethical principles contained in the current version of the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, including respect for persons, beneficence (“maximize benefits and minimize harms and wrongs”) and non-maleficence (“do no harm”), as defined by the International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences, or laws and regulations of the country in which the research is conducted, whichever represents the greater protection for study subjects.

6.2 Justification of human bioequivalence studies

Most pharmacokinetic and pharmacodynamic equivalence studies are non-therapeutic studies in which no direct clinical benefit accrues to the subject.

It is important for anyone preparing a trial of a medicinal product in humans that the specific aims, problems and risks or benefits of the proposed human study be thoroughly considered and that the chosen design be scientifically sound and ethically justified. It is assumed that people involved in the planning of a study are familiar with the pharmacokinetic theories underlying bioavailability and bioequivalence studies. The overall design of the bioequivalence study should be based on the knowledge of the pharmacokinetics, pharmacodynamics and therapeutics of the API. Information about manufacturing procedures and data from tests performed on the product batch to be used in the study should establish that the product under investigation is of suitable quality.

6.3 Selection of investigators

The investigators should have the appropriate expertise, qualifications and competence to undertake the proposed study. Prior to the trial, the investigators and the sponsor should draw up an agreement on the protocol, monitoring, auditing, standard operating procedures, and allocation of trial-related responsibilities. The identity and duties of the individuals responsible for the study and safety of the subjects participating in the study must be specified. The logistics and premises of the trial site should comply with requirements for the safe and efficient conduct of the trial.

6.4 Study protocol

A bioequivalence study should be carried out in accordance with a protocol agreed upon and signed by the investigator and the sponsor. The protocol and its attachments or appendices should state the aim of the study and the procedures to be used, the reasons for proposing the study to be undertaken in humans, the nature and degree of any known risks, assessment methodology, criteria for acceptance of bioequivalence, the groups from which it is proposed that trial subjects be selected, and the means for ensuring that they are adequately informed before they give their consent. The investigator is responsible for ensuring that the protocol is strictly followed. Any changes required must be agreed on and signed by the investigator and sponsor and appended as amendments, except when necessary to eliminate an apparent immediate hazard or danger to a trial subject.

The protocol, attachments and appendices should be scientifically and ethically appraised by one or (if required by local laws and regulations) more review bodies (for example, institutional review board, peer review committee, ethics committee or national regulatory authority) constituted appropriately for these purposes and independent of the investigators and sponsor.

The signed and dated study protocol should be approved by the national regulatory authority before commencing the study, if required by national and regional laws and regulations. The study report forms an integral part of the registration dossier of the multisource product in order to obtain the marketing authorization for the multisource product.

7. Pharmacokinetic comparative bioavailability (bioequivalence) studies in humans

7.1 Design of pharmacokinetic studies

Bioequivalence studies are designed to compare the in vivo performance of a multisource product with that of a comparator product. Such studies on products designed to deliver the API for systemic exposure serve two purposes:

- as a surrogate for clinical evidence of the safety and efficacy of the multisource product;
- as an in vivo measure of pharmaceutical quality.

The design of the study should maximize the sensitivity to detect any difference between products, minimize the variability that is not caused by formulation effects and eliminate bias as far as possible. Test conditions should reduce variability within and between subjects. In general, for a bioequivalence study involving a multisource product and a comparator product, a randomized, two-period, two-sequence, single-dose, crossover study conducted with healthy volunteers is the preferred study design. In this design each subject is given the multisource product and the comparator product in randomized order. An adequate washout period should follow the administration of each product.

It should be noted, however, that under certain circumstances an alternative, well established and statistically appropriate study design may be more suitable.

7.1.1 Alternative study designs for studies in patients

For APIs that are very potent or too toxic to administer in the highest strength to healthy volunteers (for example, because of the potential for serious adverse events or because the trial necessitates a high dose), it is recommended that the study be conducted using the API at a lower strength in healthy volunteers. For APIs that show unacceptable pharmacological effects in healthy volunteers, even at lower strengths, a study conducted in patients may be required. Depending on the dosing posology this may be a multiple-dose, steady-state study. As above, such studies should employ a crossover design if possible; however, a parallel group design study in patients may be required in some situations. The use of such an alternative study design should be fully justified by the sponsor and should include patients whose disease process is stable for the duration of the bioequivalence study, if possible.

7.1.2 Considerations for active pharmaceutical ingredients with long elimination half lives

A single-dose, crossover bioequivalence study for an orally administered product with a long elimination half-life is preferred, provided an adequate washout period between administrations of the treatment is possible. The interval between study days should be long enough to permit elimination of essentially all of the previous dose from the body. Ideally the interval should not be less than five terminal elimination half-lives of the active compound or metabolite, if the latter is measured. If the crossover study is problematic owing to a very long elimination half-life, a bioequivalence study with a parallel design may be more appropriate. A parallel design may also be necessary when comparing some depot formulations.

For both crossover and parallel design studies of oral products, sample collection time should be adequate to ensure completion of gastrointestinal transit (approximately two to three days) of the pharmaceutical product and absorption of the API. Blood sampling should be conducted for up to 72 hours following administration, but sampling beyond this time is not generally necessary for immediate-release products.

The number of subjects should be derived from statistical calculations, but generally more subjects are needed for a parallel study design than for a crossover study design.

7.1.3 Considerations for multiple-dose studies

In certain situations multiple-dose studies may be considered appropriate. Multiple-dose studies in patients are most useful in cases where the API being studied is considered to be too potent or too toxic to be administered to healthy volunteers, even in single doses (see also subsection 7.1.1). In this case a multiple-dose, crossover study in patients may be performed without interrupting therapy.

The dosage regimen used in multiple-dose studies should follow the usual dosage recommendations.

Other situations in which multiple-dose studies may be appropriate are as follows:

- cases where the analytical sensitivity is too low to adequately characterize the pharmacokinetic profile after a single dose;
- for extended-release dosage forms with a tendency to accumulate (in addition to single-dose studies).

In steady-state studies, the washout of the last dose of the previous treatment can overlap with the approach to steady state of the second treatment, provided the approach period is sufficiently long (at least five times the terminal half-life). Appropriate dosage administration and sampling should be carried out to document the attainment of a steady state.

7.1.4 Considerations for modified-release products

Modified-release products include extended-release products and delayed-release products. Extended-release products are variously known as controlled-release, prolonged-release and sustained-release products.

Owing to the more complex nature of modified-release products relative to immediate-release products, additional data are required to ensure the bioequivalence of two modified-release products. Factors such as the coadministration of food, which influences API bioavailability and also, in certain cases, bioequivalence, must be taken into consideration. The presence of food can affect product performance both by influencing the release of the API from the formulation and by causing physiological

changes in the gastrointestinal tract. In this regard a significant concern with regard to modified-release products is the possibility that food may trigger a sudden and abrupt release of the API leading to “dose dumping”. This would most likely be manifested as a premature and abrupt rise in the plasma concentration time profile. Therefore, bioequivalence studies conducted under both fasted and fed conditions are required for orally administered, modified-release pharmaceutical products. Unless single-dose studies are not possible for reasons such as those discussed in subsection 7.1.1, single-dose, crossover bioequivalence studies conducted under both fasted and fed conditions comparing the highest strength of the multisource product and the comparator product must be performed to demonstrate bioequivalence. Single-dose studies are preferred to multiple-dose studies, as single-dose studies are considered to provide more sensitive measurement of the release of API from the pharmaceutical product into the systemic circulation. In addition to single-dose studies, multiple-dose studies may be considered for extended-release dosage forms with a tendency to accumulate; for example, after a single dose of the highest strength the AUC for the dosing interval covers < 90% of the AUC extrapolated to infinity. The comparator product in these studies should be a pharmaceutically equivalent, modified-release product. The bioequivalence criteria for modified-release products are essentially the same as for conventional release dosage forms except that acceptance criteria should also be applied to $C_{\min}$ ($C_{\tau_{\text{min}}}$) in the case of multiple-dose studies. As release mechanisms of pharmaceutical products become more complex, as in the case of products with an immediate-release and modified-release component, additional parameters such as partial AUC measures may be necessary to ensure the bioequivalence of two products.

The fed-state bioequivalence study should be conducted after the administration of an appropriate standardized meal at a specified time (usually not more than 30 minutes) before taking the pharmaceutical product. A meal that will promote the greatest change in gastrointestinal tract conditions relative to the fasted state should be given (see subsection 7.4.4 for more recommendations on the content of the meal). The composition of the meal should take local diet and customs into consideration. The composition and caloric breakdown of the test meal should be provided in the study protocol and report.

7.2 Subjects

7.2.1 Number of subjects

The number of subjects required for a bioequivalence study is determined by:

- the error variance (coefficient of variation) associated with the primary parameters to be studied, as estimated from a pilot experiment, from previous studies or from published data;
- the significance level desired (5%);

- the statistical power desired;
- the mean deviation from the comparator product compatible with bioequivalence and with safety and efficacy;
- the need for the 90% confidence interval for the geometric mean ratio to be within bioequivalence limits, normally 80–125%, for log-transformed data.

The number of subjects to be recruited for the study should be estimated by considering the standards that must be met using an appropriate method – see, for example, Julious (7). In addition, a number of extra subjects should be recruited, dosed appropriately, and their samples analysed based on the expected rate of dropout or withdrawal, which depends on the safety and tolerability profile of the API. The number of subjects recruited should always be justified by the sample size calculation provided in the study protocol. A minimum of 12 subjects is required.

In some situations, reliable information concerning the expected variability in the parameters to be estimated may not be available. In such situations a two-stage sequential study design can be employed as an alternative to conducting a pilot study (see subsection 7.6.1 for more information).

7.2.2 Dropout and withdrawal

Sponsors should select a sufficient number of study subjects to allow for possible dropout or withdrawal. Because replacement of subjects during the study could complicate the statistical model and analysis, dropouts generally should not be replaced. Reasons for withdrawal (for example, adverse reaction or personal reasons) must be reported. If a subject is withdrawn due to an adverse event after receiving at least one dose of the study medication, the subject's plasma or serum concentration data should be provided.

The concentration–time profiles of subjects who exhibit predose concentrations higher than 5% of the corresponding $C_{\max}$ should be excluded from the statistical analysis. The concentration–time profiles of subjects who exhibit predose concentrations equal to or less than 5% of the corresponding $C_{\max}$ should be included in the statistical analysis without correction.

7.2.3 Exclusion of subject data

Extreme values can have a significant impact on bioequivalence study data because of the relatively small number of subjects typically involved; however, it is rarely acceptable to exclude data. Potential reasons for excluding subject data and the procedure to be followed should be included in the study protocol. Exclusion of data for statistical or pharmacokinetic reasons alone is not acceptable. Retesting of subjects is not recommended.

7.2.4 Selection of subjects

Bioequivalence studies should generally be performed with healthy volunteers. Clear criteria for inclusion and exclusion should be stated in the study protocol. If the pharmaceutical product is intended for use in both sexes, the sponsor should include both males and females in the study. The potential risk to women will need to be considered on an individual basis and, if necessary, they should be warned of any possible dangers to the fetus if they should become pregnant. The investigators should ensure that female volunteers are not pregnant or likely to become pregnant during the study. Confirmation should be obtained by urine tests just before administration of the first and last doses of the product under study.

Generally, subjects should be aged between 18 and 55 years and their weight should be within the normal range, with a body mass index between 8 and 30 kilograms per square metre (kg/m^2). The subjects should have no history of alcohol or drug abuse problems and should preferably be non-smokers.

The volunteers should be screened for their suitability using standard laboratory tests, a medical history and a physical examination. If necessary, special medical investigations may be carried out before and during studies, depending on the pharmacology of the individual API being investigated, for example, an electrocardiogram if the API has a cardiac effect. The ability of the volunteers to understand and comply with the study protocol has to be assessed. Subjects who are being or have previously been treated for any gastrointestinal problems or convulsive, depressive or hepatic disorders, and in whom there is a risk of a recurrence during the study period, should be excluded.

If a parallel design study is planned, standardization of the two groups of subjects is important in order to minimize variation not attributable to the investigational products (see subsection 7.2.6).

If the aim of the bioequivalence study is to address specific questions (such as bioequivalence in a special population), the selection criteria should be adjusted accordingly.

7.2.5 Monitoring the health of subjects during the study

In keeping with guidelines for good clinical practice (4), the health of volunteers should be monitored during the study so that the onset of side-effects, toxicity or any intercurrent disease may be recorded and appropriate measures taken. The incidence, severity, seriousness and duration of any adverse event observed during the study must be reported. The probability that an adverse event is due to the finished pharmaceutical product (FPP) should be judged by the investigator. Health monitoring before, during and after the study must be carried out under the supervision of a qualified medical practitioner licensed in the jurisdiction in which the study is conducted.

7.2.6 Considerations for genetic phenotyping

Phenotyping for metabolizing activity can be important for studies with high-clearance APIs that are metabolized by enzymes that are subject to genetic polymorphism, such as propranolol. In such cases, slow metabolizers will have a higher bioavailability of the API, while the bioavailability of possible active metabolites will be lower. Phenotyping of subjects can be considered for studies of APIs that show phenotype-linked metabolism and for which a parallel group design is to be used, because it allows fast and slow metabolizers to be evenly distributed between the two groups of subjects. Phenotyping could also be important for safety reasons and for determination of sampling times and washout periods in crossover design studies.

7.3 Investigational product

7.3.1 Multisource pharmaceutical product

The multisource pharmaceutical product used in the bioequivalence studies for registration purposes should be identical to the planned commercial pharmaceutical product. Therefore, not only the composition and quality characteristics (including stability) but also the manufacturing methods (including equipment and procedures) should be the same as those to be used in the future routine production runs. Test products must be manufactured under good manufacturing practice regulations. Batch control results, lot number, manufacturing date and, if possible, expiry date for the multisource product should be stated. Samples should ideally be taken from batches of industrial scale. When this is not feasible, pilot or small-scale production batches may be used, provided that they are not smaller than 10% of expected full production batches, or 100 000 units, whichever is larger, and are produced with the same formulation and similar equipment and process to that planned for commercial production batches. A biobatch of less than 100 000 units may be accepted provided that this is the proposed production batch size, with the understanding that future scale-up for production batches will not be accepted unless supported by *in vitro* or *in vivo* data, as applicable.

7.3.2 Choice of comparator product

The innovator pharmaceutical product is usually the most logical comparator product for a multisource pharmaceutical product because its quality, safety and efficacy should have been well assessed and documented in pre-marketing studies and post-marketing monitoring schemes. Preferably this will mean employing the innovator product available on the market when studying multisource products for national and regional approval. There will be situations, however, where this is not feasible. Detailed guidance for the selection of comparator products for use in national and regional applications is provided in the comparator guidance (8).

It is recommended that potency and *in vitro* dissolution characteristics of the multisource and the comparator pharmaceutical products be ascertained prior

to the performance of an equivalence study. Content of the API of the comparator product should be close to the label claim and the difference between two products being compared should not be more than $\pm 5\%$. If, because of the lack of availability of different batches of the comparator product, it is not possible to study batches with potencies within $\pm 5\%$, potency correction may be required on the statistical results from the bioequivalence study.

7.4 Study conduct

7.4.1 Selection of strength

In bioequivalence studies, the molar equivalent dose of multisource and comparator product must be used. For a series of strengths that can be considered proportionally formulated (see subsection 10.3), the strength with the greatest sensitivity for bioequivalence assessment should be administered as a single unit. This will usually be the highest marketed strength. A higher dose – that is, more than one dosage unit – may be employed when analytical difficulties exist. In this case, the total single dose should not exceed the maximal daily dose of the dosage regimen. In certain cases, a study performed with a lower strength can be considered acceptable if this lower strength is chosen for reasons of safety or if the API is highly soluble and its pharmacokinetics are linear over the therapeutic range.

7.4.2 Non-linear pharmacokinetics

When the API in a series of strengths, which are considered proportionally formulated, exhibits non-linear pharmacokinetics over the range of strengths, special consideration is necessary when selecting the strength for study.

For APIs exhibiting non-linear pharmacokinetics within the range of strengths, resulting in greater than proportional increases in AUC with increasing dose, the comparative bioavailability study should be conducted on at least the highest marketed strength.

For APIs with non-linear pharmacokinetics within the range of strengths due to saturable absorption and resulting in less than proportional increases in AUC with increasing dose, the bioequivalence study should be conducted on at least the lowest strength (or a strength in the linear range).

For APIs with non-linear pharmacokinetics within the range of strengths due to limited solubility of the API and resulting in less than proportional increases in AUC with increasing dose, bioequivalence studies should be conducted on at least the lowest strength (or a strength in the linear range) and the highest strength.

7.4.3 Study standardization

Standardization of study conditions is important to minimize variability other than in the pharmaceutical products. Standardization between study periods is critical to a

successful study. Standardization should cover exercise, diet, fluid intake and posture, as well as restriction of the intake of alcohol, caffeine, certain fruit juices and concomitant medicines for a specified period before and during the study.

Volunteers should not take any other medicine, alcoholic beverages or over-the-counter medicines and supplements for an appropriate interval before or during the study. In the event of emergency, the use of any non-study medicine must be reported (dose and time of administration).

Physical activity and posture should be standardized as far as possible to limit their effects on gastrointestinal blood flow and motility. The same pattern of posture and activity should be maintained for each day of the study. The time of day at which the study product is to be administered should be specified.

7.4.4 Coadministration of food and fluid with the dose

FPPs are usually given after an overnight fast of at least 10 hours and participants are allowed free access to water. On the morning of the study no water is allowed during the hour prior to FPP administration. The dose should be taken with a standard volume of water (usually 150–250 millilitres). Two hours after FPP administration, water is again permitted as often as desired. A standard meal is usually provided four hours after FPP administration. All meals should be standardized and the composition stated in the study protocol and report.

There are situations when the investigational products should be administered following consumption of a meal (under fed conditions). These situations are described below.

Immediate-release formulations

Fasted-state studies are generally preferred. However, when the product is known to cause gastrointestinal disturbances if given to subjects in the fasted state, or if the labelling of the comparator product restricts administration to subjects in the fed state, then a fed-state study becomes the preferred approach.

For products with specific formulation characteristics (such as microemulsions or solid dispersions), bioequivalence studies performed under both fasted and fed conditions are required, unless the product is only taken in a fasted or fed state.

Typically, a meal meeting the composition recommendations identified in the following subsection on “Modified-release formulations” should be employed in fed-state studies. The exact composition of the meal may depend on local diet and customs, as determined by the national regulatory authority. For studies conducted with immediate-release products there may be situations where it is appropriate to employ a predose meal with a different caloric or fat content from a meal meeting the composition recommendations identified in the following subsection.

The test meal should be consumed beginning 30 minutes prior to administration of the FPP.

Modified-release formulations

In addition to a study conducted under fasted conditions, food effect studies are necessary for all multisource, modified-release formulations to ensure that the interaction between the varying conditions in the gastrointestinal tract and the product formulations does not differentially impact the performance of the multisource and comparator products. The presence of food can affect product performance both by influencing the release of the API from the formulation and by causing physiological changes in the gastrointestinal tract. A significant concern with regard to modified-release products is the possibility that food may trigger a sudden and abrupt release of the API, leading to “dose dumping”. In these cases, the objective is to select a meal that will challenge the robustness of the new multisource formulation to prandial effects on bioavailability. To achieve this, a meal that will provide a maximal perturbation to the gastrointestinal tract relative to the fasted state should be employed; for example, a high-fat (approximately 50% of the total caloric content of the meal), high-calorie (approximately 800 to 1000 kilocalories) test meal has been recommended (2). The meal selected should take into account local customs and diet. The caloric breakdown of the test meal should be provided in the study report.

The subject should start eating the meal 30 minutes before the FPP is administered and complete eating the meal prior to FPP administration.

7.4.5 Washout interval

The interval (washout period) between doses of each formulation should be long enough to permit the elimination of essentially all of the previous dose from the body. The washout period should be the same for all subjects and should normally be more than five times the median terminal half-life of the API. Consideration should be given to extending this period in some situations, for example if active metabolites with longer half-lives are produced or if the elimination rate of the API has high variability between subjects. In this second case, a longer washout period should be considered to allow for the slower elimination in subjects with lower elimination rates. Just prior to administration of the treatment during the second study period, blood samples should be collected and assayed to determine the concentration of the API or metabolites. The minimum washout period should be at least seven days unless a shorter period is justified by a short half-life. The adequacy of the washout period can be estimated from the predose concentrations of the API in the second study period and should be less than 5% of the observed $C_{\max}$.

7.4.6 Sampling times

Blood samples should be taken at a frequency sufficient for assessing $C_{\max}$, AUC and other parameters. Sampling points should include a predose sample, at least one or two points before $C_{\max}$, two points around $C_{\max}$ and three or four points during the

elimination phase. Consequently, at least seven sampling points will be necessary for estimation of the required pharmacokinetic parameters. For most APIs the number of samples necessary will be higher to compensate for between-subject differences in absorption and elimination rate and thus enable accurate determination of the maximum concentration of the API in the blood ($C_{\max}$) and terminal elimination rate constant in all subjects. Generally, sampling should continue for long enough to ensure that 80% of the $AUC_{0-\infty}$ can be accrued, but it is not necessary to sample for more than 72 hours. The exact duration of sample collection depends on the nature of the API and the input function from the administered dosage form.

7.4.7 Sample fluids and their collection

Under normal circumstances, blood should be the biological fluid sampled to measure the concentrations of the API. In most cases the API or its metabolites are measured in serum or plasma. If it is not possible to measure the API in blood, plasma or serum, the API is excreted unchanged in the urine and there is a proportional relationship between plasma and urine concentrations; urine can be sampled for the purpose of estimating exposure. The volume of each urine sample must be measured at the study centre, where possible immediately after collection, and the measurements included in the report. The number of samples should be sufficient to allow the estimation of pharmacokinetic parameters. However, in most cases the exclusive use of urine excretion data should be avoided, as this does not allow estimation of the $t_{\max}$ and the maximum concentration. Blood, plasma, serum and urine samples should be processed and stored under conditions that have been shown not to cause degradation of the analytes. Details of these conditions should be included in the analytical validation report (see subsection 7.5).

The sample collection methodology must be specified in the study protocol.

7.4.8 Parameters to be assessed

In bioavailability studies, the shape and area under the plasma concentration versus time curves are mostly used to assess rate ($C_{\max}$, $t_{\max}$) and extent (AUC) of exposure. Sampling points or periods should be chosen such that the concentration versus time profile is sufficiently defined to allow calculation of relevant parameters. For single-dose studies, the following parameters should be measured or calculated:

- Area under the plasma, serum or blood concentration–time curve from time zero to time t (AUC_{0-t}), where t is the last sampling time point with a measurable concentration of the API in the individual formulation tested. The method of calculating AUC values should be specified. Non-compartmental methods should be used for pharmacokinetic calculations in bioequivalence studies.
- $C_{\max}$ is the maximum or peak concentration observed, representing peak exposure of API (or metabolite) in plasma, serum or whole blood.

Usually AUC_{0-t} and C_{max} are considered to be the most relevant parameters for assessment of bioequivalence. In addition, it is recommended that the following parameters be estimated:

- Area under the plasma, serum or blood concentration–time curve from time zero to time infinity ($AUC_{0-\infty}$) representing total exposure, where $AUC_{0-\infty} = AUC_{0-t} + C_{last}/K_e$; C_{last} is the last measurable analyte concentration and K_e is the terminal or elimination rate constant calculated according to an appropriate method.
- t_{max} is the time after administration of the FPP at which C_{max} is observed.

For additional information the elimination parameters can be calculated:

- $t_{1/2}$ is the plasma (serum, whole blood) half-life.

For multiple-dose studies conducted with modified-release products, the following parameters should be calculated:

- AUC_{τ} is AUC over one dosing interval (τ) at steady state.
- C_{max} .
- C_{min} (C_{τ}) is concentration at the end of a dosing interval.
- Peak trough fluctuation is percentage difference between C_{max} and C_{min} .

As release mechanisms of pharmaceutical products become more complex – for example, products with an immediate-release and a modified-release component – additional parameters, such as partial AUC measures, may be necessary to ensure the bioequivalence of two products.

When urine samples are used, cumulative urinary recovery (A_e) and maximum urinary excretion rate are employed instead of AUC and C_{max} .

7.4.9 Studies of metabolites

Generally, evaluation of bioequivalence will be based on the measured concentrations of the API released from the dosage form rather than the metabolite. The concentration–time profile of the API is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution and elimination.

In rare cases it may be necessary to measure concentrations of a primary active metabolite rather than those of the API if concentrations of the API are too low to allow reliable analytical measurement in blood, plasma or serum for an adequate length of time, or when the parent compound is unstable in the biological matrix.

It is important to decide beforehand and state in the study protocol which chemical entities (API or metabolite) will be analysed in the samples and to identify the analyte whose data will be used to assess bioequivalence.

It is also important to note that measurement of one analyte, API or metabolite carries the risk of making a type 1 error (the consumer's risk) to remain at the 5% level. However, if more than one of several analytes is selected retrospectively as the bioequivalence determinant, then both the consumer and producer risks change (9). The analyte whose data will be used to assess bioequivalence cannot be changed retrospectively.

When measuring active metabolites, washout period and sampling times may need to be adjusted to enable adequate characterization of the pharmacokinetic profile of the metabolite.

7.4.10 Measurement of individual enantiomers

A non-stereoselective assay is acceptable for most bioequivalence studies. A stereospecific assay measuring the individual enantiomers should be employed when the enantiomers exhibit different pharmacokinetic properties or different pharmacodynamic properties, and the exposure of the enantiomers, as estimated by their AUC ratio or $C_{\max}$ ratio, changes when there is a change in the rate of absorption.

7.5 Quantification of active pharmaceutical ingredient

For the measurement of concentrations of the active compound or metabolites in biological matrices, such as serum, plasma, blood and urine, the applied bioanalytical method should be well characterized, fully validated and documented to a satisfactory standard in order to yield reliable results.

The validation of bioanalytical methods and the analysis of subject samples for clinical trials in humans should be performed following the principles of good clinical practice, good laboratory practice and the most up-to-date guidelines from stringent regulatory authorities on the topic of bioanalytical method validation.

State-of-the-art principles and procedures for bioanalytical method validation and analysis of study samples should be employed. The main characteristics of a bioanalytical method that are essential to ensure the acceptability of the performance and the reliability of analytical results are:

- selectivity;
- lower limit of quantification;
- the response function and calibration range (calibration curve performance);
- accuracy;
- precision;
- matrix effects;
- stability of the analytes in the biological matrix;

- stability of the analytes and of the internal standard in the stock and working solutions, and in extracts throughout the entire period of storage and processing conditions.

In general:

- The analytical method should be able to differentiate the analyte of interest and, if employed, the internal standard from endogenous components in the matrix or other components in the sample.
- The lower limit of quantification, being the lowest concentration of analyte in a sample, should be estimated to prove that the analyte at this concentration can be quantified reliably, with an acceptable accuracy and precision.
- The response of the instrument with regard to the concentration of analyte should be known and should be evaluated over a specified concentration range. The calibration curve should be prepared in the same matrix as the matrix of the intended subject samples by spiking the blank matrix with known concentrations of the analyte. A calibration curve should consist of a blank sample, a zero sample and six to eight non-zero samples covering the expected range.
- Within-run and between-run accuracy and precision should be assessed on samples spiked with known amounts of the analyte and the quality control samples, at a minimum of three different concentrations.
- Matrix effects should be investigated when using mass spectrometric methods.
- Stability of the analyte in the stock solution and in the matrix should be proven, covering every step taken during sample preparation and sample analysis, as well as the storage conditions used.
- When more than one analyte is present in subject samples, it is recommended that the stability of the analytes in the matrix be demonstrated in the presence of the other analytes under standard conditions such as freeze–thaw testing, short-term room temperature storage and long-term freezer storage.
- Where changes are made to an analytical method that has already been validated, a full validation may not be necessary, depending on the nature of the changes implemented. A partial validation may be acceptable.
- A cross-validation is needed in cases where data are obtained from different methods within and across studies or when data are obtained within a study from different laboratories applying the same method.

- Analysis of subject samples should be carried out after validation of the analytical method. Before the start of the analysis of the subject samples, the performance of the bioanalytical method should have been verified.
- Calibration and quality control standards should be processed in an identical manner and at the same time as the subject's samples from the same run.
- Reasons for reanalysis, reinjection and reintegration of subject samples should be predefined in the protocol, study plan or standard operating procedures. Reinjection of a full analytical run or of individual calibration standard samples or quality control samples, simply because the calibration or quality controls failed, without any identified analytical cause, is considered unacceptable. For bioequivalence studies, reanalysis, reinjection or reintegration of subject samples for reasons related to pharmacokinetic fit is normally not acceptable, as this may affect and bias the outcome of such a study.
- When analysing subject samples, the precision and accuracy of the method should be confirmed by reanalysing subject samples in a separate analytical run on a different day (incurred samples reanalysis). Incurred samples reanalysis should be performed for each bioequivalence trial. The extent of testing done should be based on an in-depth understanding of the analytical method and analyte used.
- The samples from one subject (all periods) should be analysed in the same analytical run if possible.

Validation procedures, methodology and acceptance criteria should be specified in the analytical protocol or the standard operating procedures. All experiments used to support claims or draw conclusions about the validity of the method should be described in a report (method validation report).

The results of subject sample determination should be given in the analytical report together with calibration and quality control sample results, repeat analyses, reinjections and reintegrations (if any), and a representative number of sample chromatograms.

7.6 Statistical analysis

The primary concern in bioequivalence assessment is to limit the risk of a false declaration of equivalence. Statistical analysis of the bioequivalence trial should demonstrate that a clinically significant difference in bioavailability between the multisource product and the comparator product is unlikely. The statistical procedures should be specified in the protocol before the data collection starts.

The statistical method for testing bioequivalence is based on the determination of the 90% confidence interval for the ratio of the log-transformed population

means (multisource or comparator) for the pharmacokinetic parameters under consideration and by carrying out two one-sided tests at the 5% level of significance (10). To establish bioequivalence, the calculated confidence interval should fall within a preset bioequivalence limit. The procedures should lead to a decision scheme that is symmetrical with respect to the formulations being compared (that is, leading to the same decision whether the multisource formulation is compared to the comparator product or the comparator product to the multisource formulation).

All concentration-dependent pharmacokinetic parameters (for example, AUC and $C_{\max}$) should be log-transformed using either common logarithms to the base 10 or natural logarithms. The choice of either common or natural logs should be consistent and should be stated in the study report.

Logarithmically transformed, concentration-dependent pharmacokinetic parameters should be analysed using analysis of variance (ANOVA). Normally, the ANOVA model should include formulation, period, sequence and subject factors. Parametric methods, that is, those based on normal distribution theory, are recommended for the analysis of log-transformed bioequivalence measures.

The general approach is to construct a 90% confidence interval for the quantity $\mu_T - \mu_R$ and to reach a conclusion of pharmacokinetic equivalence if this confidence interval is within the stated limits. The nature of parametric confidence intervals means that this is equivalent to carrying out two one-sided tests of the hypothesis at the 5% level of significance (10, 11). The antilogs of the confidence limits obtained constitute the 90% confidence interval for the ratio of the geometric means between the multisource and comparator products. The same procedure should be used for analysing parameters from steady-state trials or cumulative urinary recovery, if required.

For $t_{\max}$, descriptive statistics should be given. Where $t_{\max}$ is considered clinically relevant, the median and range of $t_{\max}$ should be compared between test and comparator to exclude numerical differences with clinical importance. A formal statistical comparison is rarely necessary. Generally, the sample size is not calculated to have enough statistical power for $t_{\max}$. However, if $t_{\max}$ is to be subjected to a statistical analysis, this should be based on non-parametric methods and should be applied to untransformed data. A sufficient number of samples around predicted maximal concentrations should have been taken to improve the accuracy of the $t_{\max}$ estimate. For parameters describing the elimination phase ($t_{1/2}$), only descriptive statistics should be given. See subsection 7.2.3 for information on the handling of extreme data.

Exclusion of data for statistical or pharmacokinetic reasons alone is not acceptable.

Two-stage sequential design

In some situations reliable information concerning the expected variability in the parameters to be estimated may not be available. In such situations a two-stage sequential study design can be employed, such that an accurate estimate of the variability can be

determined in the first stage of the study. The number of subjects employed in the first stage is generally based on the most likely intrasubject variance estimate, with some added subjects to compensate for dropout. The analysis undertaken at the end of the first stage is treated as an interim analysis. If bioequivalence is proven at this point, the study can be terminated. If bioequivalence is not proven at the end of the first stage, the second stage is conducted employing an appropriate number of additional subjects, as determined based on the variance estimates and point estimate calculated from the stage 1 data. At the end of the second stage, the results from both groups combined are used in the final analysis. In order to use a two-stage design, adjustments must be made to protect the overall type 1 error rate and maintain it at 5%. To do this, both the interim and final analyses must be conducted at adjusted levels of significance, with the confidence intervals calculated using the adjusted values.

It is recommended that the same alpha for both stages be employed. This gives an alpha of 0.0294 for this case (12); however, the amount of alpha to be spent at the time of the interim analysis can be set at the study designer's discretion. For example, the first stage may be planned as an analysis where no alpha is spent in the interim analysis since the objective of the interim analysis is to obtain information on the point estimate difference and variability and where all the alpha is spent in the final analysis with the conventional 90% confidence interval. In this case, no test against the acceptance criteria is made during the interim analysis and bioequivalence cannot be proven at that point. The proposed statistical plan must be clearly defined in the study protocol, including the adjusted significance level that is to be employed during each analysis.

A factor for stage should be included in the ANOVA model for the final analysis of the combined data from the two stages.

This approach can be employed in both crossover and parallel study designs.

7.7 Acceptance ranges

AUC_{0-t} - ratio

The 90% confidence interval for this measure of relative bioavailability should lie within a bioequivalence range of 80.00–125.00%. If the API is determined to possess a narrow therapeutic index, the bioequivalence acceptance range should be restricted to 90.00–111.11%.

The same criterion applies to the parameter AUC τ in multiple-dose studies and for partial AUCs if they are necessary for comparative testing of a modified-release product.

C_{max} ratio

For maximal concentration data, the acceptance limit of 80.00–125.00% should be applied to the 90% confidence interval for the mean C_{max} ratio. However, this measure of relative bioavailability is inherently more variable than, for example, the AUC ratio,

and in certain cases this variability can make proving bioequivalence challenging (see subsection 7.9.3 for information on an approach for proving bioequivalence when the intrasubject variability for the $C_{\max}$ parameter is high). If the API is determined to possess a narrow therapeutic index, the bioequivalence acceptance range may need to be restricted to 90.00–111.11%, if appropriate. The same criterion applies to the parameters $C_{\max}$ and C_{tau} in multiple-dose studies.

$t_{\max}$ difference

Statistical evaluation of $t_{\max}$ makes sense only if there is a clinically relevant claim for rapid onset of action or concerns about adverse effects. In such a case, comparison of the median and range data for each product should be undertaken. For other pharmacokinetic parameters the same considerations as outlined above apply.

7.8 Reporting of results

The report of a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation in compliance with good clinical practice and good laboratory practice rules. The relevant International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline (13) can be used in the preparation of the study report. The responsible investigators should sign the respective sections of the report. Names and affiliations of the responsible investigators, site of the study and period of its execution should be stated.

The names and batch numbers of the pharmaceutical products used in the study, as well as the composition of the test products, should be given. Results of in vitro dissolution tests conducted in media with pHs of 1.2, 4.5 and 6.8 and the quality control media, if different, should be provided. In addition, the applicant should submit a signed statement confirming that the test product is identical to the pharmaceutical product that is submitted for registration.

The bioanalytical validation report should be attached. This report should include the information recommended in the stringent regulatory authority guidance chosen as a guide for the bioanalytical portion of a study (see subsection 7.5).

All results should be presented clearly. All concentrations measured in each subject and the sampling time should be tabulated for each formulation. Tabulated results showing API concentration analyses according to analytical run (including runs excluded from further calculations, together with all calibration standards and quality control samples from the respective run) should also be presented. The tabulated results should present the date of run, subject, study period, product administered (multisource or comparator) and time elapsed between FPP administration and blood sampling, in a clear format. The procedure for calculating the parameters used (for example, AUC) from the raw data should be stated. Any deletion of data should be documented and justified.

Individual blood concentration–time curves should be plotted on a linear-linear and log-linear scale. All individual data and results should be given, including information on subjects who dropped out. The dropouts or withdrawn subjects should be reported and accounted for. All adverse events that occurred during the study should be reported, together with the study physician's classification of the events. Further, any treatments given to address adverse events should be reported.

Results of all measured and calculated pharmacokinetic parameters should be tabulated for each subject–formulation combination, together with descriptive statistics. The statistical report should be sufficiently detailed to enable the statistical analyses to be repeated if necessary. If the statistical methods applied deviate from those specified in the study protocol, the reasons for the deviations should be stated.

7.9 Special considerations

7.9.1 Fixed-dose combination products

If the bioequivalence of fixed-dose combination products is assessed by in vivo studies, the study design should follow the same general principles as described in previous sections. The multisource fixed-dose combination product should be compared with the pharmaceutically equivalent comparator fixed-dose combination product. In certain cases (for example, when no comparator fixed-dose combination product is available on the market) separate products administered in free combination can be used as a comparator (3). Sampling times should be chosen to enable the pharmacokinetic parameters of all APIs to be adequately assessed. The bioanalytical method should be validated with respect to all analytes measured in the presence of the other analytes. Statistical analyses should be performed with pharmacokinetic data collected on all active ingredients; the 90% confidence intervals of the test/comparator ratio of all active ingredients should be within acceptance limits.

7.9.2 Clinically important variations in bioavailability

Innovators should make every effort to provide formulations with good bioavailability characteristics. If a better formulation is later developed by the innovator, this should then serve as the comparator product. A new formulation with a bioavailability outside the acceptance range for an existing pharmaceutical product is not interchangeable by definition.

7.9.3 Highly variable active pharmaceutical ingredients

A “highly variable API” has been defined as an API with an intrasubject variability of > 30% in terms of the ANOVA coefficient of variation (CV) (14). Proving the bioequivalence of FPPs containing highly variable APIs can be problematic because the higher the ANOVA CV, the wider the 90% confidence interval. Thus large numbers of subjects must be enrolled in studies involving highly variable APIs to achieve adequate statistical power.

Although there is variability in how regulatory authorities deal with the issue of highly variable APIs, the most rigorous of the current approaches involve the scaling of bioequivalence acceptance criteria based on the intrasubject standard deviation observed in the relevant parameters for the comparator product (15–17). Of the two most common assessment parameters, $C_{\max}$ is subject to the highest variability and hence is the parameter for which a modified approach is most needed.

For highly variable FPPs it is recommended that a three-way partial replicate (where the comparator product is administered twice) or a four-way fully replicated crossover bioequivalence study be conducted and reference-scaled average bioequivalence be employed to widen the acceptance interval for the $C_{\max}$ parameter, if the intrasubject variability for $C_{\max}$ following replicate administrations of the comparator product is > 30%. If this is the case, the acceptance criteria for $C_{\max}$ can be widened to a maximum of 69.84–143.19%. The applicant should justify that the calculated intrasubject variability is a reliable estimate and that it is not the result of outliers.

The extent of the widening of the acceptance interval for $C_{\max}$ is defined based upon the intrasubject variability seen in the bioequivalence study using scaled average bioequivalence according to $[U, L] = \exp [\pm k \cdot sWR]$, where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and sWR is the intrasubject standard deviation of the log-transformed values of $C_{\max}$ of the reference product. Table A8.2 gives examples of how different levels of variability lead to different acceptance limits using this methodology.

Table A8.2
Acceptance limits for different levels of variability

Intrasubject CV (%)	Lower limit	Upper limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥ 50	69.84	143.19

$$CV(\%) = \sqrt{(e^{\{S_{WR}\}^2} - 1)}$$

The geometric mean ratio for $C_{\max}$ should lie within the conventional acceptance range of 80.00–125.00%.

The standard bioequivalence acceptance criterion for AUC should be maintained without scaling. If the intrasubject variability for $C_{\max}$ following replicate administration

of the comparator, is found to be $< 30\%$, standard bioequivalence acceptance criteria should be applied to both AUC and $C_{\max}$ without scaling.

For multiple-dose studies, a similar approach can be applied to the following parameters if the intrasubject variability for the parameter is found to be $> 30\%$: $C_{\max}$, C_{tau} and partial AUCs if required. The standard bioequivalence acceptance criterion will apply to AUC τ without scaling.

The approach to be employed should be clearly defined prospectively in the study protocol. The regulatory authority of the country to which the study data will be submitted should be consulted before commencing the study to confirm that the proposed approach is acceptable for that jurisdiction.

8. Pharmacodynamic equivalence studies

Studies in healthy volunteers or patients using pharmacodynamic measurements may be used for establishing equivalence between two pharmaceutical products when the pharmacokinetic approach is not feasible. Pharmacodynamic equivalence studies may become necessary if quantitative analysis of the API or metabolites in blood, serum, plasma or urine cannot be made with sufficient accuracy and sensitivity; however, this is extremely unlikely given current technology. Furthermore, pharmacodynamic equivalence studies in humans are required if measurements of API concentrations cannot be used as surrogate end-points for the demonstration of efficacy and safety of the particular pharmaceutical product, as is the case with pharmaceutical products designed to act locally. However, local availability studies based on pharmacokinetic studies alone or in combination with in vitro dissolution studies are being considered as surrogate end-points for the demonstration of equivalent biopharmaceutical quality and release at the site of action for some products acting locally. In addition, bioequivalence studies are also required in order to demonstrate equivalent systemic exposure for systemic safety purposes.

Pharmacodynamic studies are not recommended for orally administered pharmaceutical products for systemic action when the API is absorbed into the systemic circulation and a pharmacokinetic approach can be used to assess systemic exposure and establish bioequivalence. This is because the sensitivity to detect differences between products in their biopharmaceutical quality, release and absorption is lower with pharmacodynamic or clinical end-points. As the dose–response curve for pharmacodynamics or clinical end-points is usually flatter than the relationship between dose and pharmacokinetic parameters, it is essential to ensure the internal validity of the study by showing assay sensitivity, that is, the ability to distinguish the response obtained by adjacent doses (twofold or even fourfold difference in dose). It is essential to perform the comparison at the dose level at which the dose–response is steepest, which may require first doing a pilot study for its identification. Furthermore, variability in pharmacodynamic measures is usually greater than that in pharmacokinetic measures.

In addition, pharmacodynamic measures are often subject to significant placebo effects, which add to the variability and complicate experimental design. The result is often that huge numbers of patients would have to be enrolled in pharmacodynamic studies to achieve adequate statistical power.

If pharmacodynamic studies are to be used, they must be performed as rigorously as bioequivalence studies and the principles of good clinical practice must be followed (4).

The following requirements must be recognized when planning, conducting and assessing the results of a study intended to demonstrate equivalence by measuring pharmacodynamic responses.

- The response measured should be a pharmacological or therapeutic effect that is relevant to the claims of efficacy and safety.
- The methodology must be validated for precision, accuracy, reproducibility and specificity.
- Neither the multisource product nor the comparator product should produce a maximal response during the course of the study, since it may be impossible to detect differences between formulations given.
- The response should be measured quantitatively, preferably under double-blind conditions, and be recordable by an instrument that produces and records the results of repeated measurements to provide a record of the pharmacodynamic events, which are substitutes for measurements of plasma concentrations. Where such measurements are not possible, recordings on visual analogue scales may be used. Where the data are limited to qualitative (categorized) measurements, appropriate special statistical analysis will be required.
- Participants should be screened prior to the study to exclude non-responders. The criteria by which responders are distinguished from non-responders must be stated in the protocol.
- In situations where an important placebo effect can occur, comparison between pharmaceutical products can only be made by a priori consideration of the potential placebo effect in the study design. This may be achieved by adding a third phase with placebo treatment during the design of the study.
- The underlying pathology and natural history of the condition must be considered in the study design. There should be confirmation that the baseline conditions are reproducible.
- A crossover design can be used. Where this is not appropriate, a parallel group study design should be chosen.

The basis for the selection of the multisource and comparator products should be the same as described in subsection 7.3.

In studies in which continuous variables can be recorded, the time course of the intensity of the action can be described in the same way as in a study in which plasma concentrations are measured and parameters can be derived that describe the area under the effect–time curve, the maximum response, and the time at which the maximum response occurred.

The comparison between the multisource product and the comparator product can be performed in two different ways:

- **Dose-scale analysis or relative potency.** This is defined as the ratio of the potency of the multisource product to that of the comparator product. It is a way of summarizing the relationship between the dose–response curves of the multisource and comparator products.
- **Response-scale analysis.** This consists of demonstration of equivalence (for at least two dose levels) at the pharmacodynamic end-point.

For either approach to be acceptable, a minimum requirement is that the study has assay sensitivity. To meet this requirement, at least two non-zero levels need to be studied and one dose level needs to be shown to be superior to the other.

Therefore, it is recommended that unless otherwise justified more than one dose of both the multisource product and the comparator product are studied. However, it is essential that doses on the steep part of the dose–response curve are studied. If the chosen dose is too low on the dose–response curve, then demonstrating equivalence between two products is not convincing, as this dose could be subtherapeutic. Equally, if a dose at the top of the dose–response curve is included, similar effects will be seen for doses much higher than that studied, and hence demonstrating equivalence at this dose level would also not be convincing.

The results using both approaches should be provided. In both cases the observed confidence intervals comparing multisource and comparator products should lie within the chosen equivalence margins to provide convincing evidence of equivalence. As for bioequivalence studies, 90% confidence intervals should be calculated for relative potency, whereas 95% confidence intervals should be calculated for the response-scale analysis. It should be noted that the acceptance range as applied for bioequivalence assessment may not be appropriate. For both approaches the chosen equivalence ranges should be prespecified and appropriately justified in the protocol.

9. Clinical equivalence studies

In some instances (see example (e) in subsection 5.1, “In vivo studies”) plasma concentration time–profile data may not be suitable for assessing equivalence between two formulations. Although in some cases pharmacodynamic equivalence studies can

be an appropriate tool for establishing equivalence, in others this type of study cannot be performed because of a lack of meaningful pharmacodynamic parameters that can be measured; a comparative clinical trial then has to be performed to demonstrate equivalence between two formulations. However, it is preferable to assess equivalence by performing a pharmacokinetic equivalence study rather than a clinical trial that is less sensitive and would require a huge number of subjects to achieve adequate statistical power. For example, it has been calculated that 8600 patients would be required to give adequate statistical power to detect a 20% improvement in response to the study API compared with a placebo (18, 19). Similarly, it was calculated that 2600 myocardial infarct patients would be required to show a 16% reduction in risk. A comparison of two formulations of the same API based on such end-points would require even greater numbers of subjects (19).

If a clinical equivalence study is considered as being undertaken to prove equivalence, the same statistical principles apply as for the bioequivalence studies, although a 95% confidence interval might be necessary for pharmacodynamic and clinical end-points in contrast to the 90% confidence level employed conventionally for pharmacokinetic studies. The number of patients to be included in the study will depend on the variability of the target parameters and the acceptance range and is usually much higher than the number of subjects needed in bioequivalence studies.

The methodology for establishing equivalence between pharmaceutical products by means of a clinical trial with a therapeutic end-point conducted in patients is not yet as far advanced as that for bioequivalence studies. However, some important items that need to be defined in the protocol can be identified as follows.

- The target parameters that usually represent relevant clinical end-points from which the onset, if applicable and relevant, and intensity of the response are to be derived.
- The size of the acceptance range has to be defined case by case, taking into consideration the specific clinical conditions. These include the natural course of the disease, the efficacy of available treatments and the chosen target parameter. In contrast to bioequivalence studies (where a conventional acceptance range is applied), the size of the acceptance range in clinical trials should be set individually according to the therapeutic class and indications.
- The currently used statistical method is the confidence interval approach.
- The confidence intervals can be derived from either parametric or non-parametric methods.
- Where appropriate, a placebo arm should be included in the design.
- In some cases it is relevant to include safety end-points in the final comparative assessments.

The selection basis for the multisource and comparator products should be the same as described in subsection 7.3.

10. In vitro equivalence testing

Over the past three decades, dissolution testing has evolved into a powerful tool for characterizing the quality of oral pharmaceutical products. The dissolution test, at first exclusively a quality control test, is now emerging as a surrogate equivalence test for certain categories of orally administered pharmaceutical products. For these products (typically solid oral dosage forms containing APIs with suitable properties), similarity in in vitro dissolution profiles, in addition to excipient comparisons and a risk-benefit analysis, can be used to document equivalence of a multisource product with a comparator product.

It should be noted that although the dissolution tests recommended in *The International Pharmacopoeia* (20) for quality control have been designed to be compatible with the biowaiver dissolution tests, they do not fulfil all the requirements for evaluating equivalence of multisource products with comparator products. Dissolution tests for quality control purposes, including those described in other pharmacopoeias, do not address all test conditions required for evaluating equivalence of multisource products and should not be applied for this purpose.

10.1 In vitro equivalence testing in the context of the Biopharmaceutics Classification System

The Biopharmaceutics Classification System (BCS)-based biowaiver approach is intended to reduce the need for in vivo bioequivalence studies, as it can provide a surrogate for in vivo bioequivalence. In vivo bioequivalence studies may be exempted if an assumption of equivalence in in vivo performance can be justified by satisfactory in vitro data. The BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the APIs.

The BCS categorizes APIs into one of four BCS classes, as follows:

- class I: high solubility, high permeability
- class II: low solubility, high permeability
- class III: high solubility, low permeability
- class IV: low solubility, low permeability.

Guidance providing recommendations to support the biopharmaceutics classification of APIs and the BCS-based biowaiver of bioequivalence studies for FPPs can be found in the *WHO guideline on Biopharmaceutics Classification System-based biowaivers*.

10.2 Qualification for a biowaiver based on the Biopharmaceutics Classification System

Guidance providing recommendations to support the biopharmaceutics classification of APIs and the BCS-based biowaiver of bioequivalence studies for FPPs can be found in the *WHO guideline on Biopharmaceutics Classification System-based biowaivers*.

10.3 In vitro equivalence testing based on dose proportionality of formulations

Under certain conditions, approval of different strengths of a multisource product can be considered on the basis of dissolution profiles if the formulations have proportionally similar compositions.

10.3.1 Proportional formulations

For the purpose of this guidance, proportional formulations can be defined in two ways, based on the strength of dosage forms.

- (a) All active and inactive ingredients are exactly in the same proportions in the different strengths (for example, a tablet of 50 milligram (mg) strength has exactly half of all the active and inactive ingredients contained in a tablet of 100 mg strength and twice what would be contained in a tablet of 25 mg strength). For immediate-release products, coating components, capsule shell, colour agents and flavours are not generally required to meet this requirement.
- (b) For an FPP, where the amount of the API in the dosage form is relatively low (up to 10 mg per dosage unit or not more than 5% of the weight of the dosage form), the total weight of the dosage form remains similar for all strengths.

For (b) a waiver is considered:

- if the amounts of the different excipients or capsule contents are the same for the strengths concerned and only the amount of the API has changed;
- if the amount of filler is changed to account for the change in amount of API. The amounts of other core excipients or capsule content should be the same for the strengths concerned.

10.3.2 Qualification for biowaivers based on dose proportionality of formulations

Immediate-release tablets

A biowaiver based on dose proportionality of formulations for a series of strengths of a multisource product, when the pharmaceutical products are manufactured with the same manufacturing process, may be granted when:

- an in vivo equivalence study has been performed on at least one of the strengths of the formulation (as described in subsection 7.4.1, the strength studied will usually be the highest strength, unless a lower strength is chosen for reasons of safety or the API is highly soluble and displays linear pharmacokinetics);
- all strengths are proportionally similar in formulation to that of the strength studied;
- the dissolution profiles for the different strengths are similar at pH 1.2, 4.5, 6.8 and for the quality control media, unless justified by the absence of sink conditions.

If the different strengths of the test product do not show similar dissolution profiles owing to the absence of sink conditions in any of the above media, this should be substantiated by showing similar dissolution profiles when testing the same dose per vessel (for example, two tablets of 5 mg versus one tablet of 10 mg) or by showing the same behaviour in the comparator product.

As for the BCS-based biowaiver, if both strengths release 85% or more of the label amount of the API in 15 minutes, using all three dissolution media as recommended in the *WHO guideline on Biopharmaceutics Classification System-based biowaivers*, the profile comparison with an f_2 test is unnecessary.

In the case where an immediate-release dosage form with several strengths deviates from proportionality a bracketing approach is possible, so that only two strengths representing the extremes need to be studied in vivo.

If approval of one strength of a product is based on a BCS-based biowaiver instead of an in vivo equivalence study, other strengths in the series of strengths should also be assessed based on BCS-based biowaivers as opposed to a biowaiver based on dose proportionality.

Delayed-release tablets and capsules

For delayed-release tablets, for a series of strengths of a multisource product where the strengths are proportionally similar in formulation to that of the strength studied in an in vivo equivalence study, a lower strength can be granted a biowaiver if it exhibits similar dissolution profiles, $f_2 \geq 50$, in the recommended test condition for delayed-release product, for example, dissolution test in acid medium (pH 1.2) for 2 hours followed by dissolution in pH 6.8. When evaluating proportionality in composition, it is recommended to consider the proportionality of gastro-resistant coating with respect to the surface area (not to core weight) to have the same gastro-resistance (mg/cm^2).

For delayed-release capsules where different strengths have been achieved solely by means of adjusting the number of beads containing the API, similarity in the dissolution profile of the new (lower) strength to that of the approved strength ($f_2 > 50$)

under the test conditions recommended for delayed-release products (see above) is sufficient for a biowaiver.

Extended-release tablets and capsules

For extended-release tablets, when there is a series of strengths of a multisource product that are proportionally similar in their active and inactive ingredients and have the same API release mechanism, in vivo bioequivalence studies should be conducted with the highest proposed strength. Subsequently, lower strengths in the series can be granted a biowaiver if they exhibit similar dissolution profiles to the highest strength, $f_2 \geq 50$, in three different pH buffers (between pH 1.2 and 7.5) and the quality control media by the recommended test method.

For extended-release tablets with an osmotic pump release mechanism, the dissolution profile comparison ($f_2 \geq 50$) under one recommended test condition is sufficient for a biowaiver based on dose proportionality of formulation.

For extended-release beaded capsules where different strengths have been achieved solely by means of adjusting the number of beads containing the API, a dissolution profile comparison ($f_2 \geq 50$) under one recommended test condition is sufficient for a biowaiver based on dose proportionality of formulation.

10.3.3 Dissolution profile comparison for biowaivers based on dose proportionality of formulations

As for biowaivers based on the BCS, a model-independent mathematical approach (for example, f_2 test) can be used for comparing the dissolution profiles of two products. The dissolution profiles of the two products (reference strength and additional strength) should be measured under the same test conditions. The dissolution sampling times for both reference strength and additional strength profiles should be the same. For example:

- for immediate-release products, 5, 10, 15, 20, 30, 45 and 60 minutes;
- for 12-hour extended-release products, 1, 2, 4, 6, 8 and 12 hours;
- for 24-hour extended-release products, 1, 2, 4, 6, 8, 16 and 24 hours.

For the application of the f_2 value, see Appendix 1.

10.4 In vitro equivalence testing for non-oral dosage forms

In the case of intravenous micellar solutions with the same qualitative and quantitative composition of the surfactant, but significant changes to other excipients, an in vitro comparison might avoid the need for in vivo studies if a similar micellar system and API release from the micelle after dilution of the FPP or API administration into the blood system is ensured (21).

Locally applied, locally acting products in the form of aqueous suspensions containing the same API in the same molar concentration and essentially the same excipients in comparable concentrations might be waived from the demonstration of equivalence by means of local availability, pharmacodynamic or clinical studies if in vitro characterization is able to ensure a similar crystallographic structure and particle size distribution as well as any other in vitro test specific for each dosage form, for example dissolution. The methodological details for the techniques mentioned below are not covered in these guidelines. Additional information regarding these techniques should be sought from guidelines produced by stringent regulatory authorities or from state-of-the-art literature.

- (a) Suspensions for nebulization with the same qualitative and quantitative composition as the comparator product might be waived from in vivo studies if the particles in the suspensions are shown to have the same crystallographic structure and particle size distribution as those from the comparator product, as well as comparability in any other appropriate in vitro test, for example dissolution. In addition, the nebulized droplets should exhibit a similar aerodynamic particle size distribution to that of the comparator product.
- (b) Suspensions for nebulization with different qualitative and quantitative composition might be granted a waiver if, in addition to the requirements defined above under (a), the difference in excipient composition does not alter the nebulizer efficiency (for example, by the presence or absence of a different surfactant or preservative) or the aerodynamic particle size distribution (for example, altering product hygroscopicity by the presence of a different amount of salt as isotonic agent). To this end, the appropriate state-of-the-art in vitro test should be conducted to ensure product equivalence. Any difference in excipients should be critically reviewed because certain excipients that are considered irrelevant in other dosage forms (for example, preservative, substance to adjust tonicity or thickening agent) may affect safety or efficacy of the product.
- (c) Nasal drops where the API is in suspension with the same qualitative and quantitative composition as the comparator product might be waived from in vivo studies if the particles in suspension are shown to have the same crystallographic structure and similar particle size distribution to that of the comparator product, as well as comparability in any other appropriate in vitro test, such as dissolution.
- (d) Nasal drops where the API is in suspension, with qualitative or quantitative differences in excipient composition with respect to the comparator product, might be waived from in vivo studies if, in addition to the requirements defined above under (c), the difference in excipient composition does not affect efficacy and safety (for example, a different preservative may affect the

safety profile due to greater irritation of the nasal passages and a different viscosity or thixotropy may affect the residence time in the site of action). Therefore any difference in excipients should be critically reviewed.

- (e) Nasal sprays in solution with the same qualitative and quantitative composition in excipients can be granted waivers based on a battery of in vitro tests as defined by stringent regulatory authorities (22).
- (f) Nasal sprays in solution with qualitative and quantitative differences in the excipient composition might be waived if, in addition to showing similarity in the battery of in vitro tests referenced under (e), differences in excipients are critically reviewed as described above under (d).
- (g) Nasal sprays in suspension with the same qualitative and quantitative composition in excipients might be waived if, in addition to the battery of in vitro tests referenced above under (e), the particles in suspension are shown to have the same crystallographic structure and similar particle size distribution, as well as comparability in any other appropriate in vitro test, such as dissolution.
- (h) Nasal sprays in suspension with qualitative and quantitative differences in excipient composition might be waived if, in addition to the battery of in vitro tests referenced above under (e) and (g), differences in excipients are critically reviewed as described above under (d).
- (i) In the case of pressurized metered-dose inhalers in solution or suspension, in vivo studies might be waived if similarity is shown in a battery of in vitro tests as described in specific guidelines produced by stringent regulatory authorities (23). A waiver of in vivo studies for a dry powder inhaler is not considered feasible unless the device for the dry powder inhaler is identical to the comparator.
- (j) For pharmaceutically equivalent topical gel products, equivalence can be demonstrated by means of in vitro membrane diffusion studies when the products contain essentially the same excipients in comparable concentrations and the APIs in the product are in solution (24).
- (k) Otic and ophthalmic suspensions with the same qualitative and quantitative composition in excipients might be granted a waiver if the particles in suspension are shown to have the same crystallographic structure and similar particle size distribution, as well as comparability in any other appropriate in vitro test, such as dissolution.
- (l) Products acting locally in the gastrointestinal tract containing highly soluble APIs (as defined by the BCS) in immediate-release dosage forms might be waived from in vivo equivalence studies based on the same dissolution requirements as are applied for the BCS-based biowaiver.

10.5 In vitro equivalence testing for scale-up and post-approval changes

Although these guidelines refer primarily to registration requirements for multisource pharmaceutical products, it should be noted that under certain conditions, following permissible changes to formulation or manufacturing after FPP approval, in vitro dissolution testing may also be suitable to confirm similarity of product quality and performance characteristics. More information on when dissolution testing may be used to support product variations is provided in WHO guidance on variations in pharmaceutical products.

References

1. Agreement on Trade-Related Aspects of Intellectual Property Rights. Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization, 1994. Geneva: World Trade Organization (https://www.wto.org/english/tratop_e/trips_e/trips_e.htm, accessed 5 February 2024).
2. Guidance for industry: bioavailability and bioequivalence studies for orally administered medicine products – general considerations. Rockville (MD): Department of Health and Human Services, United States Food and Drug Administration; 2003.
3. Guidelines for registration of fixed-dose combination medicinal products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-ninth report. WHO Technical Report Series No. 929, Annex 5. Geneva: World Health Organization; 2005.
4. Guidelines for good clinical practice for trials on pharmaceutical products. In: WHO Expert Committee on the Selection and use of Essential Medicines: sixth report. WHO Technical Report Series No. 850, Annex 3. Geneva: World Health Organization; 1995.
5. Handbook. Good laboratory practice (GLP). Quality practices for regulated non-clinical research and development, second edition. Geneva: World Health Organization, on behalf of the Special Programme for Research and Training in Tropical Diseases; 2009.
6. Guidance for organizations performing in vivo bioequivalence studies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. WHO Technical Report Series No. 996, Annex 9. Geneva: World Health Organization; 2016.
7. Julious SA. Sample sizes for clinical trials with normal data. *Stat Med*. 2004;23(12):1921–86.
8. Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. WHO Technical Report Series No. 992, Annex 8. Geneva: World Health Organization; 2015.
9. Midha KK, Rawson MJ, Hubbard JW. Commentary: the role of metabolites in bioequivalence. *Pharm Res*. 2004;21(8):1331–44.
10. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinet Biopharm*. 1987;15(6): 657–80.
11. Westlake WJ. Bioavailability and bioequivalence of pharmaceutical formulations. In: Peace KE, editor. *Biopharmaceutical statistics for drug development*. New York: Marcel Dekker; 1988:329–52.

12. Pocock SJ. Group sequential methods in the design and analysis of clinical trials. *Biometrika*. 1977;64(2):191–9.
13. ICH E3: Structure and content of clinical study reports. Scientific guideline. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Secretariat/IFPMA; 1995.
14. Blume HH, Midha KK. Bio-International 92, Conference on bioavailability, bioequivalence and pharmacokinetic studies. *J Pharm Sci*. 1993;82(11):1186–9.
15. Tothfalusi L, Endrenyi L, Midha KK, Rawson MJ, Hubbard JW. Evaluation of bioequivalence of highly variable drugs and drug products. *Pharm Res*. 2001;18(6):728–33.
16. Tothfalusi L, Endrenyi L, Midha KK. Scaling or wider bioequivalence limits for highly variable drugs and for the special case of C(max). *Int J Clin Pharmacol Ther*. 2003;41(5):217–25.
17. Tothfalusi L, Endrenyi L. Limits for scaled average bioequivalence of highly variable drugs and drug products. *Pharm Res*. 2003;20(3):382–9.
18. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. II. Unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. *JAMA*. 1988;260(15):2259–63.
19. The Studies of Left Ventricular Dysfunction (SOLVD) Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325:293–302. doi:10.1056/NEJM199108013250501.
20. The International Pharmacopoeia, 11th edition. Geneva: World Health Organization; 2023 (<https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/international-pharmacopoeia>, accessed 13 January 2024).
21. Guideline on the investigation of bioequivalence. London: Committee for Medicinal Products for Human Use, European Medicines Agency; 2010.
22. Compilation of individual product specific guidance on demonstration of bioequivalence. London: European Medicines Agency; 2014.
23. Draft guidance for industry: bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action. Rockville (MD): United States Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research; 2003.
24. Guidance for industry: nonsterile semisolid dosage forms scale-up and postapproval changes: chemistry, manufacturing, and controls; in vitro release testing and in vivo bioequivalence documentation. Rockville (MD): United States Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research; 1997.

Further reading

- Committee for Medicinal Products for Human Use/European Medicines Agency. 2009. Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD). CPMP/EWP/4151/00 rev 1. London: CHMP/EMA.
- European Medicines Agency. 2010. Reflection paper on guidance for laboratories that perform the analysis or evaluation of clinical trial samples. EMA/INS/GCP/532137/2010. London: EMA.
- Fares HM, Zats JL. 1995. Measurement of drug release from topical gels using two types of apparatus. *Pharm Tech*. 19:52–8.

- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 1996. ICH E6. Good clinical practice: consolidated guidance. Geneva: ICH.
- Moore JW, Flanner HH. 1996. Mathematical comparison of curves with an emphasis on in vitro dissolution profiles. *Pharm Tech*. 20:64–74.
- Shah VP, Tsong Y, Sathe P, Liu JP. 1998. In vitro dissolution profile comparison: statistics and analysis of the similarity factor, f_2 . *Pharm Res*. 15:889–96.
- World Health Organization. 2007. Guidance on variations to a prequalified product dossier. In: WHO Expert Committee on the Selection and use of Essential Medicines: forty-first report. WHO Technical Report Series No. 943, Annex 6. Geneva: WHO.
- World Health Organization. 2009. Good clinical laboratory practice (GCLP). Geneva: World Health Organization, on behalf of the Special Programme for Research and Training in Tropical Diseases.
- World Health Organization. 2016. WHO general guidance on variations to multisource pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. WHO Technical Report Series No. 996, section 11. Geneva: WHO.

Appendix 1

Recommendations for conducting and assessing comparative dissolution profiles

The dissolution measurements of the two FPPs (for example, test and comparator or two different strengths) should be made under the same test conditions. A minimum of three time points (zero excluded) should be included, the time points for both reference (comparator) and test product being the same. The sampling intervals should be short for a scientifically sound comparison of the profiles (for example, 5, 10, 15, 20, 30, 45 and 60 minutes for an immediate-release dosage form). The 15-minute time point is critical to determine whether a product is very rapidly dissolving and to determine whether f_2 must be calculated. For extended-release FPPs, the time points should be set to cover the entire duration of expected release, for example, in addition to earlier time points: samples at 1, 2, 3, 5 and 8 hours should be collected for a 12-hour release, and additional test intervals would be necessary for longer duration of release.

Studies should be performed in at least three media covering the physiological range, including pH 1.2 hydrochloric acid, pH 4.5 buffer and pH 6.8 buffer. *The International Pharmacopoeia* buffers are recommended; other pharmacopoeial buffers with the same pH and buffer capacity are also acceptable. Water may be considered as an additional medium, especially when the API is unstable in the buffered media to the extent that the data are unusable.

If both the test and reference (comparator) products show more than 85% dissolution in 15 minutes, the profiles are considered similar (no calculations required). Otherwise:

- Similarity of the resulting comparative dissolution profiles should be calculated using the following equation that defines a similarity factor (f_2):

$$f_2 = 50 \text{ LOG } \{ [1 + 1/n \sum_{t=1}^n (R_t - T_t)^2]^{-0.5} \times 100 \},$$

where R_t and T_t are the mean per cent API dissolved in reference (comparator) and test product, respectively, at each time point. An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar.

- A maximum of one time point should be considered after 85% dissolution of the reference (comparator) product has been reached.
- In the case where 85% dissolution cannot be reached owing to poor solubility of the API or the release mechanism of the dosage form, the dissolution should be conducted until an asymptote (plateau) has been reached.

- At least 12 units should be used for determination of each profile. Mean dissolution values can be used to estimate the similarity factor, f_2 . To use mean data the percentage coefficient of variation at time points up to 10 minutes should be not more than 20% and at other time points should be not more than 10%.
- When delayed-release products (for example, enteric coated) are being compared, the recommended conditions are acid medium (pH 1.2) for 2 hours and buffer pH 6.8 medium.
- When comparing extended-release beaded capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the API, one condition (normally the release condition) will suffice.
- Surfactants should be avoided in comparative dissolution testing.

A statement that the API is not soluble in any of the media is not sufficient, and profiles in the absence of surfactant should be provided. The rationale for the choice and concentration of surfactant should be provided. The concentration of the surfactant should be such that the discriminatory power of the test will not be compromised.

3.2 Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products

Annex 8, WHO Technical Report Series, 992, 2015

1. Introduction	317
2. Background	317
3. General principles	319
References	320

1. Introduction

In recent years the need for the regulation and assurance of quality of medicines has continued to increase. Large numbers of multisource (generic) medicines are being produced by many different companies and in different countries; this may result in different products. On a global level there is thus a need to address not only the quality, safety and efficacy of multisource products that are exported and imported, but also their possible interchangeability.

In light of the various approaches in scientific and regulatory environments, the feasibility of developing a system of international comparator products was considered in the past. This initiative led to the recommendations published in 2002 entitled, *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products* (1). Since the guidance was published, the World Health Organization (WHO) Model List of Essential Medicines (EML) has been revised several times and many of the products originally listed are no longer marketed and/or available as indicated in the list, which means that the list of international comparators recommended by the WHO Expert Committee on Preparations for Pharmaceutical Specifications needs updating.

In view of the complexity of the list of comparators it was decided to prepare two new, separate, guidance documents: one on the selection of comparator products, including the general guidance on how to select comparator products, and the second one comprising the international list of comparator products. The aim was to facilitate the updating and maintenance process.

2. Background

The *Guidelines on registration requirements to establish interchangeability for multisource (generic) pharmaceutical products* (2) are designed to provide recommendations to national regulatory authorities and manufacturers on the requirements for approval of multisource (generic) pharmaceutical products in their respective countries. The guidance provides appropriate in vivo and in vitro requirements to assure interchangeability of the multisource product.

Multisource pharmaceutical products need to conform to the same appropriate standards of quality, efficacy and safety as those applicable to the innovator's product. In addition, reasonable assurance should be provided that the multisource product is therapeutically equivalent and interchangeable with the comparator product. For some classes of products including, for example, parenteral formulations of highly water-soluble compounds, interchangeability is adequately assured by implementation of good manufacturing practices (GMP) and provision of evidence of conformity with relevant pharmacopoeial specifications.

This guidance document provides an update of the previously published list (1) and the respective chapter on selection of comparator products (3, 4). The information could also be used for medicine procurement purposes.

The historical development of comparator product criteria is summarized in Table A8.1.

Table A8.1

Historical development of comparator product criteria

Year	Development	Description
Pre-1996	International Conference of Drug Regulatory Authorities (ICDRA) (1991 and 1994) recommended development of global standards and requirements for interchangeability of multisource products; WHO initiated the process	No agreement on the criteria for selecting a list of international comparator products or any list of such products exists. The comparator product chosen is either the most widely used (leading) product on the market or the product that was first introduced in that market. For this reason, among others, significant differences could exist between the comparator products used in different countries
1996	The question of choice of reference product was raised	<i>Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability</i> (WHO Technical Report Series, No. 863), Annex 9, including Appendix 7 on "Choice of reference product"
2002	WHO issued the first list of <i>International comparator products for equivalence assessment of interchangeable multisource (generic) products</i>	<i>Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products</i> (WHO Technical Report Series, No. 902), Annex 11
2006	"In order of preference" principle in comparator product selection was clarified	<i>Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability</i> (WHO Technical Report Series, No. 937), Annex 7

3. General principles

The comparator product is defined as a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice.

As a general principle, multisource products should comply with the same standards of quality, safety and efficacy as are applicable to the corresponding comparator product. In addition, quality attributes of a multisource product should be tested against the comparator product with which it should be interchangeable.

The selection of the comparator pharmaceutical product is usually made at the national or regional level by the national or regional regulatory authority.

The innovator product is usually the most logical comparator product because its quality, safety and efficacy should have been well assessed in pre- and post-marketing studies and, in addition, the data on its safety and efficacy are usually linked to a pharmaceutical product with defined specifications for quality and performance. However, these products may not always be easy to obtain or may no longer be available on the market. The comparator product chosen is therefore often the most widely used product (market leader) or the product that was first introduced in that market. For this reason, among others, significant differences may exist between the comparator products used in different countries.

In principle, a national regulatory authority has several options for selection of a comparator product. These are listed below in order of preference:

1. the innovator product for which quality, safety and efficacy has been established if this product has been granted a national marketing authorization (*nationally authorized innovator*);
2. national market leader product for which a national marketing authorization has been granted;
3. the WHO-recommended comparator product included in the International list of comparator products (1) or, if different and if it exists for the active pharmaceutical ingredient in question, the one suggested within the context of the Prequalification Team;
4. an innovator product approved by a stringent regulatory authority, i.e. a country associated to The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH);
5. a product that has been granted approval in an ICH-associated country;
6. in the case that no innovator or comparator product can be identified according to the above, the choice of the comparator should be made carefully and should be comprehensively justified by the applicant. In this case, the most important selection criteria in order of preference are:

- prequalification by WHO,
- extensive documented use in clinical trials reported in peer-reviewed scientific journals,
- a long and unproblematic period of post-market surveillance.

Additionally, these comparators should conform to all appropriate compendial quality standards.

It is important to note that a product that has been approved based on comparison with a comparator product that has no national marketing authorization in the country which approved the multisource product, including the study for interchangeability, may or may not be interchangeable with currently marketed domestic products.

The choice of comparator product should be justified by the applicant. The country of origin of the comparator product should be reported together with the product's lot number and expiry date. Consultation with the relevant regulatory authority before purchase of the comparator product is strongly recommended.

Information specifically related to the selection of comparator products for use in studies to be conducted for submission to the WHO Prequalification Team – Medicines is available on the WHO website (<https://extranet.who.int/prequal/medicines/welcome-medicines-prequalification>) and in the WHO comparator document (1).

References

1. Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-sixth report. Geneva: World Health Organization; 2002: Annex 11 (WHO Technical Report Series, No. 902; https://iris.who.int/bitstream/handle/10665/42424/WHO_TRS_902.pdf?sequence=1&isAllowed=y).
2. Guidelines on registration requirements to establish interchangeability for multisource (generic) pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2014: Annex 7 (WHO Technical Report Series, No. 992; https://iris.who.int/bitstream/handle/10665/176954/9789240693968_eng.pdf?sequence=1&isAllowed=y).
3. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fortieth report. Geneva: World Health Organization; 2006: Annex 7 (WHO Technical Report Series, No. 937; https://apps.who.int/iris/bitstream/handle/10665/43443/WHO_TRS_937_eng.pdf?sequence=1).
4. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Revision. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2014: Annex 7 (WHO Technical Report Series, No. 992; https://iris.who.int/bitstream/handle/10665/176954/9789240693968_eng.pdf?sequence=1&isAllowed=y).

3.3 WHO guideline on Biopharmaceutics Classification System-based biowaivers Annex 7, WHO Technical Report Series, 1052, 2024

Background

A recommendation was made to the World Health Organization (WHO) Norms and Standards for Pharmaceuticals Team by the group of experts participating at the Joint Meeting on Regulatory Guidance for Multisource Products (1–3 November 2022), as well as by other parties, including the WHO Prequalification Team, to update the WHO Biopharmaceutics Classification System (BCS)-based biowaiver requirements (associated section within the overarching WHO *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability*) (1) in order to harmonize those guidelines with those stated in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline M9 on *Biopharmaceutics classification system-based biowaivers*, adopted in November 2019 (2).

The WHO guideline on *Biopharmaceutics Classification System-based biowaivers* will supersede the BCS-based biowaiver section of the WHO *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (1). The purpose of this document is to provide recommendations to support the biopharmaceutics classification of active pharmaceutical ingredients (APIs) and the BCS-based biowaiver of bioequivalence studies for finished pharmaceutical products (FPPs).

Background	321
1. Introduction	323
2. Scope	323
3. Glossary	324
4. Biopharmaceutics classification of the API	326
4.1 Solubility	326
4.2 Permeability	327
4.3 API stability in the gastrointestinal tract	327
5. Eligibility of an FPP for a BCS-based biowaiver	328
5.1 Excipients	328
5.2 In vitro dissolution	331
6. Documentation	333
References	334
Appendix 1 Caco-2 cell permeability assay method considerations	335
Appendix 2 Further information on the assessment of excipient differences	339
Appendix 3 Equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the Biopharmaceutics Classification System	343

This text is based on the ICH guideline M9: *Biopharmaceutics Classification System-based biowaivers*, November 2019.

1. Introduction

Two finished pharmaceutical products (FPPs) containing the same active moiety of the active pharmaceutical ingredient (API) are considered bioequivalent if their bioavailabilities (rate and extent of API absorption) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance (that is, similarity in terms of safety and efficacy). In in vivo bioequivalence studies, the pivotal pharmacokinetic parameters maximum concentration ($C_{\max}$) and area under the concentration time curve (AUC) are generally used to assess the rate and extent of drug absorption.

The Biopharmaceutics Classification System (BCS)-based biowaiver approach is intended to reduce the need for in vivo bioequivalence studies, as it can provide a surrogate for in vivo bioequivalence. In vivo bioequivalence studies may be exempted if an assumption of equivalence in in vivo performance can be justified by satisfactory in vitro data. The BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the APIs. The BCS categorizes APIs into one of four BCS classes, as follows:

- class I: high solubility, high permeability
- class II: low solubility, high permeability
- class III: high solubility, low permeability
- class IV: low solubility, low permeability.

This guidance provides recommendations to support the biopharmaceutics classification of APIs and the BCS-based biowaiver of bioequivalence studies for FPPs. The BCS-based biowaiver principles may be applied to bioequivalence purposes not explicitly specified in the guideline, provided they can be supported by a thorough scientific rationale.

2. Scope

BCS-based biowaivers may be used to substantiate in vivo bioequivalence. Examples include the comparison between products used during clinical development through commercialization, post-approval changes, and applications for generic products in accordance with regional regulations.

The BCS-based biowaiver is only applicable to immediate-release, solid orally administered dosage forms or suspensions designed to deliver the API to the systemic circulation. FPPs, having a narrow therapeutic index, are excluded from consideration for a BCS-based biowaiver in this guidance. Fixed-dose combination products are eligible for a BCS-based biowaiver when all APIs contained in the combination product meet the criteria, as defined in sections 4 and 5 of this guidance.

3. Glossary

The definitions given below apply to the terms used in this document. They have been aligned to the extent possible with the terminology in related WHO guidelines and good practices included in the WHO Quality Assurance of Medicines Terminology Database – List of Terms and related guidelines,¹ but may have different meanings in other contexts.

active pharmaceutical ingredient. Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to provide pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

bioavailability. The rate at and extent to which the active moiety is absorbed from a pharmaceutical dosage form and becomes available at the sites of action. Reliable measurements of active pharmaceutical ingredient concentrations at the sites of action are usually not possible. The substance in the systemic circulation, however, is considered to be in equilibrium with the substance at the sites of action. Bioavailability can therefore be defined as the rate at and extent to which the active pharmaceutical ingredient or active moiety is absorbed from a pharmaceutical dosage form and becomes available in the systemic circulation. Based on pharmacokinetic and clinical considerations, it is generally accepted that, in the same subject, an essentially similar plasma concentration time course will result in an essentially similar concentration time course at the sites of action.

bioequivalence. Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities, in terms of rate ($C_{\max}$ and $t_{\max}$) and extent of absorption (area under the curve), after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.

Biopharmaceutics Classification System. The Biopharmaceutics Classification System is a scientific framework for classifying active pharmaceutical ingredients based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the pharmaceutical product and the critical examination of the excipients of the pharmaceutical product, the Biopharmaceutics Classification System takes into account the major factors that govern the rate and extent of active pharmaceutical ingredient absorption (exposure) from immediate-release oral solid dosage forms: excipient composition, dissolution, solubility and intestinal permeability.

¹ <https://www.who.int/publications/m/item/quality-assurance-of-medicines-terminology-database>.

biowaiver. The regulatory pharmaceutical product approval process whereby the dossier (application) is approved based on evidence of equivalence rather than through in vivo equivalence testing.

comparator product. The comparator product is a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established. If the innovator product is no longer marketed in the jurisdiction, the selection principle, as described in *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products*,² should be used to identify a suitable alternative comparator product.

dosage form. The form of the finished pharmaceutical product (for example, tablet, capsule, suspension or suppository).

equivalence requirements. In vivo or in vitro testing requirements for approval of a multisource pharmaceutical product for a marketing authorization.

finished pharmaceutical product. A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling.

fixed-dose combination product. A finished pharmaceutical product that contains two or more active pharmaceutical ingredients.

generic product. See “multisource pharmaceutical product”.

innovator pharmaceutical product. Generally, the innovator pharmaceutical product is that which was first authorized for marketing, on the basis of complete documentation of quality, safety and efficacy.

interchangeable pharmaceutical product. A product that is therapeutically equivalent to a comparator product and can be interchanged with the comparator in clinical practice.

multisource pharmaceutical product. A pharmaceutically equivalent or pharmaceutically alternative product that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

² Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. WHO Technical Report Series No. 992, Annex 8. Geneva: World Health Organization; 2015.

4. Biopharmaceutics classification of the API

BCS-based biowaivers are applicable to FPPs where the APIs exhibit high solubility and either high permeability (BCS class I) or low permeability (BCS class III).

A biowaiver is applicable when the APIs in the test and comparator products are identical. A biowaiver may also be applicable if test and comparator products contain different salts, provided that both belong to BCS class I (high solubility and high permeability). A biowaiver is not applicable when the test product contains an ester, ether, isomer, mixture of isomers, complex or derivative of an API different from that of the comparator product, since these differences may lead to different bioavailabilities not deducible by means of experiments used in the BCS-based biowaiver concept. Prodrugs may be considered for a BCS-based biowaiver when absorbed as the prodrug.

4.1 Solubility

An API is classified as highly soluble if the highest single therapeutic dose is completely soluble in 250 millilitres (mL) or less of aqueous media over the pH range 1.2–6.8 at 37 (± 1) °C.

The applicant is expected to establish experimentally the solubility of the API over the pH range 1.2–6.8 at 37 (± 1) °C. At least three pHs within this range, including buffers at pH 1.2, 4.5 and 6.8, should be evaluated. In addition, solubility at the pH of lowest solubility of the API should be evaluated if it is within the specified pH range.

Solubility should be evaluated by a method appropriate to the properties of the API.

Equilibrium solubility experiments may be performed using a shake flask technique or an alternative method, if justified. Small volumes of solubility media may be employed if the available experimental apparatus will permit it. The pH for each test solution should be measured after the addition of the API and at the end of the equilibrium solubility study to ensure that the solubility measurement is conducted under the specified pH. The experiment should be conducted over a suitable time frame to reach equilibrium and the pH should be adjusted during this period as necessary.

Alternatively, when an equilibrium solubility study is not feasible due to the high amount of API required for the experiment, or when it is not possible to maintain the pH of the medium with pharmacopoeial buffers, solubility experiments where the highest therapeutic single dose (or a slightly higher amount to avoid recovery problems in the experiments) is examined in a 250 mL volume, or a proportionally smaller amount examined in a proportionally smaller volume of buffer, can be considered (3).

The lowest measured solubility over the pH range 1.2–6.8 will be used to classify the API.

A minimum of three replicate determinations at each solubility condition or pH using appropriate pharmacopoeial media is necessary to demonstrate solubility using a suitably validated method.

In addition, adequate stability of the API in the solubility media covering the gastrointestinal transit time should be demonstrated. In cases where the API is not stable, with >10% degradation over the extent of the solubility assessment, solubility cannot be adequately determined, and thus the API cannot be classified. In addition to experimental data, literature data may be provided to substantiate and support solubility determinations, keeping in mind that peer-reviewed articles may not contain the necessary details of the testing to make a judgement regarding the quality of the studies.

4.2 Permeability

The assessment of permeability should preferentially be based on the extent of absorption derived from human pharmacokinetic studies (for example, absolute bioavailability or mass balance).

High permeability can be concluded when the absolute bioavailability is $\geq 85\%$. High permeability can also be concluded if $\geq 85\%$ of the administered dose is recovered in urine as unchanged (parent drug) or as the sum of parent drug, phase 1 oxidative and phase 2 conjugative metabolites. Regarding metabolites in faeces, only oxidative and conjugative metabolites can be considered. Metabolites produced through reduction or hydrolysis should not be included unless it can be demonstrated that they are not produced prior to absorption (for example, by microbial action within the gastrointestinal tract). An unchanged drug in faeces cannot be counted towards the extent of absorption unless appropriate data support the conclusion that the amount of parent drug in faeces to be accounted for absorbed drug material is from biliary excretion, intestinal secretion or originates from an unstable metabolite (such as glucuronide, sulphate or N-oxide that has been converted back to the parent by the action of microbial organisms).

Human in vivo data derived from published literature (for example, product knowledge and bioavailability studies) may be acceptable, keeping in mind that peer-reviewed articles may not contain the necessary details of the testing to make a judgement regarding the quality of the results.

Permeability can be also assessed by validated and standardized in vitro methods using Caco 2 cells (see Appendix 1). The results from Caco-2 permeability assays should be discussed in the context of available data on human pharmacokinetics. If high permeability is inferred by means of an in vitro cell system, permeability independent of active transport should be proven as outlined in Appendix 1 on Caco 2 cell permeability assay method considerations.

If high permeability is not demonstrated, the API is considered to have low permeability for BCS classification purposes.

4.3 API stability in the gastrointestinal tract

Additional data to document the API's stability in the gastrointestinal tract should be provided if mass balance studies are used to demonstrate high permeability, unless $\geq$

85% of the dose is recovered as an unchanged drug in urine. Demonstration of stability in the gastrointestinal tract is required if in vitro Caco-2 studies are used to support high permeability. Stability in the gastrointestinal tract may be documented using pharmacopoeial or simulated gastric and intestinal fluids. Other relevant methods may be used with suitable justification. API solutions should be incubated at 37 °C for a period that is representative of the in vivo contact of the API with these fluids (that is, 1 hour in gastric fluid and 3 hours in intestinal fluid). API concentrations should then be determined using a suitably validated analytical method. Significant degradation (> 10%) of an API precludes BCS high-permeability classification.

5. Eligibility of an FPP for a BCS-based biowaiver

An FPP is eligible for a BCS-based biowaiver provided that the APIs satisfy the criteria regarding solubility and permeability (BCS class I and class III), the FPP is an immediate-release oral dosage form with systemic action, and the FPP is the same dosage form and strength as the comparator product.

FPPs with buccal or sublingual absorption are not eligible for a BCS-based biowaiver application. Furthermore, the BCS-based biowaiver approach is applicable only when the mode of administration includes water. If administration without water is also intended (for example, orodispersible products), a bioequivalence study in which the product is dosed without water should be conducted.

In order for an FPP to qualify for a BCS-based biowaiver, criteria with respect to the composition (excipients) and in vitro dissolution performance of the FPP should be satisfied. The FPP acceptance criteria are described in subsections 5.1 and 5.2 below.

5.1 Excipients

Ideally, the composition of the test product should mimic that of the comparator product. However, where excipient differences exist, they should be assessed for their potential to affect in vivo absorption. This should include consideration of the API properties as well as excipient effects. To be eligible for a BCS-based biowaiver, the applicant should justify why the proposed excipient differences will not affect the absorption profile of the API under consideration (that is, rate and extent of absorption, using a mechanistic and risk-based approach). The decision tree for performing such an assessment is outlined in Figures 1 and 2 in Appendix 2.

The possible effects of excipients on aspects of in vivo absorption such as solubility, gastrointestinal motility, transit time and intestinal permeability, including transporter mechanisms, should be considered. Excipients that may affect absorption include sugar alcohols, such as mannitol, sorbitol and surfactants (for example, sodium lauryl sulfate). The risk that a given excipient will affect the absorption of an API should be assessed mechanistically by considering:

- the amount of excipient used;
- the mechanism by which the excipient may affect absorption;
- absorption properties (rate, extent and mechanism of absorption) of the API.

The amount of excipients that may affect absorption in the test and comparator formulations should be addressed during product development, such that excipient changes are kept to a minimum. Small amounts included in the tablet coating, or levels below documented thresholds of effect for the specific API, are of less concern.

By definition, BCS class I APIs are highly absorbed and have neither solubility- nor permeability-limited absorption. Therefore, they generally represent a low-risk group of compounds in terms of the potential for excipients to affect absorption, compared to other BCS classes. Consideration of excipient effects for BCS class I-containing FPPs should focus on potential changes in the rate or extent of absorption. For example, if it is known that the API has high permeability due to active uptake, excipients that can inhibit uptake transporters are likely to be of concern. For BCS class I APIs that exhibit slow absorption, the potential for a given excipient to increase absorption rate should also be considered. These excipients that may affect absorption should be considered as detailed in Fig. 1, Appendix 2.

For BCS class I APIs, qualitative and quantitative differences in excipients are permitted, except for excipients that may affect absorption, which should be qualitatively the same and quantitatively similar (that is, within $\pm 10\%$ of the amount of excipient in the comparator product). Additionally, the cumulative difference for excipients that may affect absorption should be within $\pm 10\%$.

BCS class III APIs are considered to be more susceptible to the effects of excipients. These APIs are not considered highly permeable, and may have site specific absorption, so there are a greater number of mechanisms through which excipients can affect their absorption than for BCS class I APIs. For BCS class III APIs, all of the excipients should be qualitatively the same and quantitatively similar (except for film coating or capsule shell excipients). Excipients that may affect absorption should be qualitatively the same and quantitatively similar (that is, within $\pm 10\%$ of the amount of excipient in the comparator product), and the cumulative difference for these excipients should be within $\pm 10\%$. The acceptable differences in excipients are defined in Table A7.1. Examples of acceptable differences in excipients are shown in Appendix 2. Differences in colorants and flavouring may be permitted when these constitute very small amounts of the formulation. For the types of excipients not listed in Table A7.1, the same rule should be applied as for the excipients that may affect absorption.

It is known that in some cases the absolute amount of an excipient present in the gastrointestinal tract is relevant to whether that excipient will exert an effect on absorption, for example, an effect on relevant transporters. Since the allowable differences for BCS class III APIs defined in Table A7.1 are based on percentage difference relative to core weight (w/w), it is possible for absolute amounts of excipients in two formulations to differ significantly while still maintaining proportionality within the limits expressed

in Table A7.1. Control over differences in absolute amount of excipients where it is known that effects on absorption can be observed (for example, amounts of surfactants) is provided in Table A7.1; however, possible effects of other excipients is not controlled. Therefore, to control for possible excipient effects based on absolute amount differences between products, the total core weight of the proposed product should not deviate by more than 20% from the total core weight of the comparator product.

It is recognized that there are limitations to the application of Table A7.1 (for example, difficulty in determining the film coat weight for the comparator product). Table A7.1 is provided as a target to give clarity to applicants. Deviations from this will require appropriate justification, based on the principles described above.

Table A7.1

Criteria expected to demonstrate quantitative similarity for products containing BCS class III APIs

Within the context of quantitative similarity, differences in excipients for FPPs containing BCS class III APIs should not exceed the following targets:	
Excipient class	Percentage of the amount of excipient in the comparator
Excipients that may affect absorption	
Per excipient:	10%
Sum of differences:	10%
	Percentage difference relative to core weight ^a (w/w)
Major excipients types:	
Filler	10%
Disintegrant	
Starch	6%
Other	2%
Binder	1%
Lubricant	
Stearates	0.5%
Other	2%
Glidant	
Talc	2%
Other	0.2%
Total % change permitted for all excipients (including excipients that may affect absorption):	10%

^a Core does not include tablet film coat or capsule shell.

BCS-based biowaivers are applicable to fixed-dose combination products that are the same dosage form and strength. Fixed-dose combination product formulations containing only BCS class I APIs should meet criteria regarding excipients for a BCS class I API. Fixed-dose combination product formulations containing only BCS class III APIs, or BCS class I and BCS class III APIs, should meet criteria regarding excipients for a BCS class III API.

5.2 In vitro dissolution

When applying the BCS-based biowaiver approach, comparative in vitro dissolution tests should be conducted using one batch representative of the proposed commercial manufacturing process for the test product relative to the comparator product. The test product should originate from a batch of at least one tenth of production scale or 100 000 units, whichever is greater, unless otherwise justified. During a (clinical) development phase, smaller batch sizes may be acceptable, if justified. The API content or potency of the comparator product should be close to the label claim, and the difference in API content or potency between the test and comparator products should be not more than 5%. The comparative in vitro dissolution tests should use pharmacopoeial apparatus and suitably validated analytical methods.

The following conditions should be employed in the comparative dissolution studies to characterize the dissolution profile of the product.

- Apparatus: paddle or basket.
- Volume of dissolution medium: 900 mL or less (it is recommended to use the volume selected for the quality control test).
- Temperature of the dissolution medium: 37 ($\pm$ 1) °C.
- Agitation: paddle apparatus – 50 revolutions per minute (rpm); basket apparatus – 100 rpm.
- At least 12 units of comparator and test product should be used for each dissolution profile determination.
- Media: three buffers: pH 1.2, pH 4.5, and pH 6.8. Pharmacopoeial buffers should be employed. Additional investigation may be required at the pH of minimum solubility (if different from the buffers above).
- Organic solvents are not acceptable and no surfactants should be added.
- The sampling intervals employed in dissolution studies should be short for a scientifically sound comparison of the performance of the test and comparator products (for example, 5, 10, 15, 20 and 30 minutes).
- Samples should be filtered during collection, unless in situ detection methods are used. For this purpose, filters should be employed in line, at the end of the sampling probe, or both during sample collection.

- The pH of each dissolution medium should be maintained throughout the test. The pH of each dissolution medium should be measured at the beginning (prior to introduction of the testing unit) and at the end of each dissolution test.
- For gelatin capsules, or tablets with gelatin coatings where cross-linking has been demonstrated, the use of enzymes may be acceptable, if appropriately justified.

Dissolution profiles for the test and comparator products should be generated in the same laboratory by the same staff at the same time using the same equipment. Compilation of historical data is not acceptable.

When high variability or coning is observed in the paddle apparatus at 50 rpm for both comparator and test products, the use of the basket apparatus at 100 rpm is recommended. Additionally, alternative methods (such as the use of sinkers or other appropriately justified approaches) may be considered to overcome issues such as coning, if scientifically substantiated. All experimental results should be provided.

To qualify for a BCS-based biowaiver for BCS class I APIs, both the test product and comparator product should display either very rapid ($\geq 85\%$ for the mean percent dissolved in ≤ 15 minutes) in vitro dissolution characteristics, or rapid ($\geq 85\%$ for the mean percent dissolved in ≤ 30 minutes) and similar in vitro dissolution characteristics (that is, based on f_2 comparison), under all of the defined conditions. In cases where one product has rapid dissolution and the other has very rapid dissolution, similarity of the profiles should be demonstrated as below.

For the comparison of dissolution profiles, where applicable, the similarity factor (f_2) should be estimated by using the following formula:

$$f_2 = 50 \cdot \log \{ [1 + (1/n) \sum_{t=1}^n (R_t - T_t)^2]^{-0.5} \cdot 100 \}.$$

In this equation f_2 is the similarity factor, n is the number of time points, R_t is the mean percent comparator API dissolved at time t after initiation of the study, and T_t is the mean percent test API dissolved at time t after initiation of the study.

The evaluation of the f_2 is based on the following conditions.

- A minimum of three time points (zero excluded).
- The time points should be the same for the two products.
- Mean of the individual values for every time point for each product.
- Not more than one mean value of $\geq 85\%$ dissolved for either of the products.
- To allow the use of mean data, the coefficient of variation (%CV) should not be more than 20% at early time points (up to 10 minutes) and should not be more than 10% at other time points.

Two dissolution profiles are considered similar when the f_2 value is ≥ 50 . When both test and comparator products demonstrate that $\geq 85\%$ of the labelled amount of the API is dissolved in 15 minutes, comparison with an f_2 test is unnecessary and the dissolution profiles are considered similar. When the %CV for the mean data is too high based on the requirements listed above, f_2 calculation is considered unreliable. In such cases, an alternative method for the assessment of similarity in dissolution profiles, such as the bootstrap 90% confidence interval of expected f_2 , should be employed in keeping with regional expectations for dissolution similarity assessment.

To qualify for a BCS-based biowaiver for BCS class III APIs, both the test product and comparator product should display very rapid ($\geq 85\%$ for the mean percent dissolved in ≤ 15 minutes) in vitro dissolution characteristics under the defined conditions.

For fixed-dose combination product formulations, dissolution profiles should meet the criteria for all APIs in the fixed-dose combination product. Fixed-dose combination product formulations containing only BCS class I APIs should meet dissolution criteria for a BCS class I API. Fixed-dose combination product formulations containing only BCS class III APIs should meet dissolution criteria for a BCS class III API. For fixed-dose combination products containing both BCS class I and BCS class III APIs, the dissolution criteria for the applicable BCS class for each component should be applied.

For products with more than one strength, the BCS approach should be applied for each strength. It is required that test and comparator product dissolution profiles are compared at each strength.

6. Documentation

The applicant should provide complete information on the critical quality attributes of the test APIs and FPP and as much information as possible for the comparator product, including polymorphic form and enantiomeric purity; and any information on bioavailability or bioequivalence problems with the APIs or FPP, including literature surveys and applicant-derived studies. All study protocols and reports should be provided. Information on validated test methods should be appropriately detailed according to current regulatory guidance and policies.

The reporting format should include tabular and graphical presentations showing individual and mean results and summary statistics.

The report should include all excipients and their qualitative and, where appropriate, quantitative differences between the test and comparator products.

A full description of the analytical methods employed, including validation and qualification of the analytical parameters, should be provided. A detailed description of all test methods and media, including test and comparator batch information (unit dose (strength and assay), batch number, manufacturing date, batch size and, where known, expiry date) should also be provided. The dissolution report should include a thorough

description of experimental settings and analytical methods, including information on the dissolution conditions such as apparatus, de-aeration, filtration during sampling and volume.

In addition, complete information with full description of the methods applied should be provided for the Caco-2 cell permeability assay method, if applicable (see Appendix 1).

References

1. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. WHO Technical Report Series No. 1003, Annex 6. Geneva: World Health Organization; 2017 (<https://www.who.int/publications/m/item/annex-6-trs-1003> accessed 4 February 2024).
2. Biopharmaceutics classification system-based biowaivers. ICH harmonised guideline M9, current step 4 version, November 2019. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2019 (https://database.ich.org/sites/default/files/M9_Guideline_Step4_2019_1116.pdf, accessed 4 February 2024).
3. Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. WHO Technical Report Series No. 1019, Annex 4. Geneva: World Health Organization; 2019 (<https://www.who.int/publications/m/item/annex-4-trs-1019> accessed 5 February 2024).

Appendix 1

Caco-2 cell permeability assay method considerations

Permeability assays employing cultured Caco-2 epithelial cell monolayers derived from a human colon adenocarcinoma cell line are widely used to estimate intestinal drug absorption in humans. Caco-2 cells undergo spontaneous morphological and biochemical enterocytic differentiation and express cell polarity with an apical brush border, tight intercellular junctions and several active transporters as in the small intestine. Due to a potential for low or absent expression of efflux (for example, P-gp, BCRP, MRP2) and uptake (for example, PepT1, OATP2B1, MCT1) transporters, the use of Caco-2 cell assays as the sole data in support of high permeability for BCS classification is limited to passively transported drugs (see “Assay considerations” below).

Method validation

The suitability of the Caco-2 cell assays for Biopharmaceutics Classification System (BCS) permeability determination should be demonstrated by establishing a rank-order relationship between experimental permeability values and the extent of drug absorption in human subjects using model drugs of zero, low (< 50%), moderate (50–84%), and high ($\geq 85\%$) permeability. A sufficient number of model drugs are recommended for the validation to characterize high, moderate and low permeability (a minimum of five for each), plus a zero-permeability marker; examples are provided in Table 1. Further, a sufficient number (minimum of three) of cell assay replicates should be employed to provide a reliable estimate of drug permeability. The established relationship should permit differentiation between low, moderate- and high-permeability drugs.

Caco-2 cell monolayer integrity should be confirmed by comparing transepithelial electrical resistance (TEER) measures or other suitable indicators, prior to and after an experiment.

In addition, cell monolayer integrity should be demonstrated by means of compounds with proven zero permeability (refer to Table 1).

Reporting of the method validation should include a list of the selected model drugs along with data on extent of absorption in humans (mean, standard deviation, coefficient of variation) used to establish suitability of the method, permeability values for each model drug (mean, standard deviation, coefficient of variation), permeability class of each model drug, and a plot of the extent of absorption as a function of permeability (mean $\pm$ standard deviation or 95% confidence interval), with identification of the high-permeability class boundary and selected high-permeability model drug used to classify the test API.

In addition, a description of the study method, drug concentrations in the donor fluid, description of the analytical method and equation used to calculate permeability should be provided. Additionally, information on efflux potential (for example, bidirectional transport data) should be provided for a known substrate.

Table 1
Examples of model APIs for permeability assay method validation

Group	API
High permeability ($f_a \geq 85\%$)	Antipyrine Caffeine Ketoprofen Naproxen Theophylline Metoprolol Propranolol Carbamazepine Phenytoin Disopyramide Minoxidil
Moderate permeability ($f_a = 50\text{--}84\%$)	Chlorpheniramine Creatinine Terbutaline Hydrochlorothiazide Enalapril Furosemide Metformin Amiloride Atenolol Ranitidine
Low permeability ($f_a < 50\%$)	Famotidine Nadolol Sulpiride Lisinopril Acyclovir Foscarnet Mannitol Chlorothiazide Polyethylene glycol 400 Enalaprilat

Table 1 *continued*

Group	API
Zero permeability	FITC-Dextran Polyethylene glycol 4000 Lucifer yellow Inulin Lactulose
Efflux substrates	Digoxin Paclitaxel Quinidine Vinblastine

Assay considerations

Passive transport of the test compound should be demonstrated. This may be verified using a suitable assay system that expresses known efflux transporters, such as by demonstrating independence of measured in vitro permeability on initial drug concentration, for example, 0.01, 0.1 and 1 times the highest strength dissolved in 250 mL, or on transport direction (efflux ratio, such as ratio of apparent permeability (P_{app}) between the basolateral-to-apical and apical-to-basolateral directions < 2 for the selected drug concentrations).

$$\text{Efflux ratio} = P_{\text{appBL} \rightarrow \text{AP}} / P_{\text{appAP} \rightarrow \text{BL}}$$

Functional expression of efflux transporters should be verified by using bidirectional transport studies demonstrating asymmetric permeability of selected efflux transporter substrates (for example, digoxin, vinblastine or rhodamine 123, at non-saturating concentrations).

The test API concentrations used in the permeability studies should be justified. A validated Caco-2 method used for drug permeability determinations should employ conditions established during the validation and include a moderate-permeability and a high-permeability model drug in the donor fluid along with the test drug as internal standards to demonstrate consistency of the method. The choice of internal standards should be based on compatibility with the test drug (that is, they should not exhibit any significant physical, chemical or permeation interactions). The permeability of the internal standards may be determined following evaluation of the test drug in the same monolayers or monolayers in the same plate, when it is not feasible to include internal standards in the same cell culture well as the test drug permeability evaluation. The permeability values of the internal standards should be consistent between different tests, including those conducted during method validation. Acceptance criteria should be set for the internal standards and model efflux drug. Mean drug and internal standards

recovery at the end of the test should be assessed. For recoveries < 80%, a mass balance evaluation should be conducted including measurement of the residual amount of drug in the cell monolayer and testing apparatus.

Evaluation of the test drug permeability for BCS classification may be facilitated by selection of a high-permeability internal standard with permeability in close proximity to the moderate- or high-permeability class boundary. The test drug is considered highly permeable when its permeability value is equal to or greater than that of the selected internal standard with high permeability.

Information to support high permeability of a test drug (mean, standard deviation, coefficient of variation) should include permeability data on the test API, the internal standards, in vitro gastrointestinal stability information, and data supporting passive transport mechanism.

Appendix 2

Further information on the assessment of excipient differences

Fig. 1
Biopharmaceutics Classification System class I active pharmaceutical ingredients

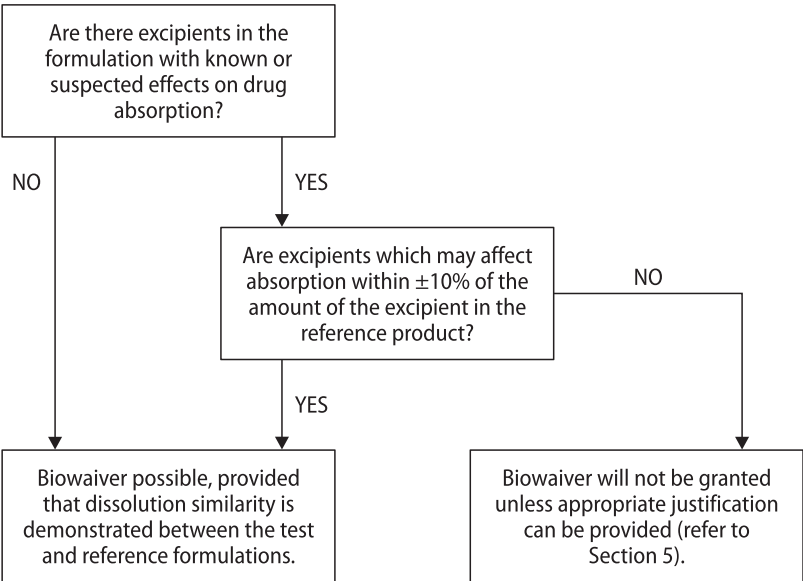
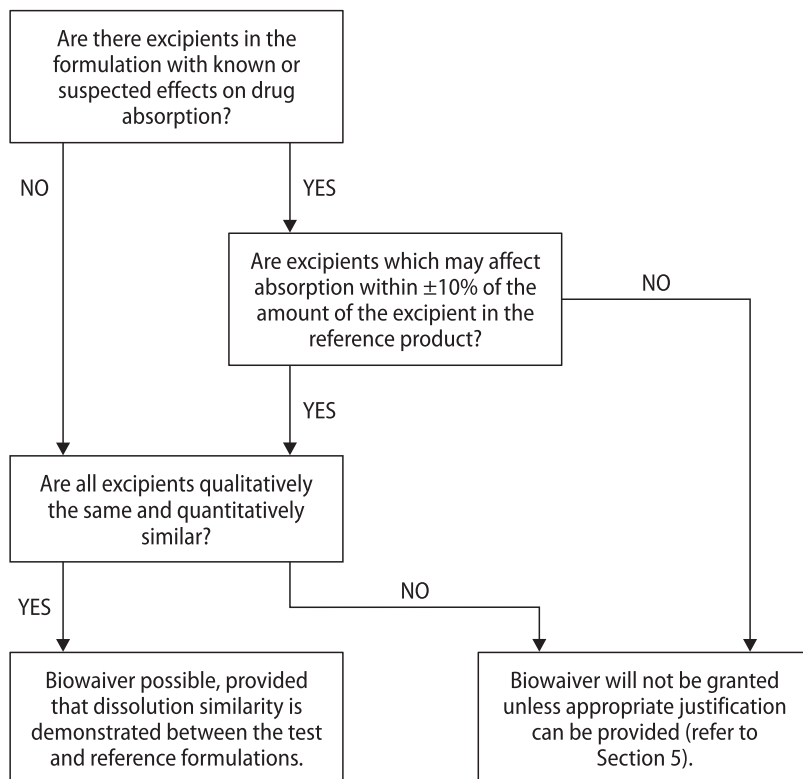


Fig. 2

Biopharmaceuticals Classification System class III active pharmaceutical ingredients**Examples of differences in excipients****Example 1. BCS class I biowaiver**

The formulation of the test product is qualitatively the same as that of the comparator product. Additionally, it contains sorbitol, an excipient with known or suspected effects on API absorption. The amount of sorbitol in the test formulation is within the permitted range of 45 milligrams (mg) to 55 mg based on the amount of sorbitol in the comparator formulation (that is, 50 mg $\pm$ 10%).

Component	Amount (mg) comparator	Amount (mg) test
API	100	100
Microcrystalline cellulose (filler)	100	95

Table continued

Component	Amount (mg) comparator	Amount (mg) test
Sorbitol (filler)	50	55
HPMC (binder)	10	10
Talc (glidant)	5	5
Total	265	265

Example 2. BCS class III biowaiver

The test formulation is qualitatively the same as the comparator formulation. Additionally, it contains sorbitol, an excipient with known or suspected effects on API absorption. The amount of sorbitol in the test formulation is within the permitted range of 9 mg to 11 mg based on the amount of sorbitol in the comparator formulation (that is, 10 mg $\pm$ 10%). Any differences in the amount of other excipients are within the criteria outlined in Table A7.1, subsection 5.1.

Component	Comparator product		Test product		Absolute % difference relative to core weights
	Composition (mg)	Proportion relative to core weight (%w/w)	Composition (mg)	Proportion relative to core weight (%w/w)	
API	100	49.3%	100	46.5%	–
Lactose monohydrate (filler)	85	41.9%	97	45.1%	3.2%
Sorbitol (filler)	10	4.9%	9	4.2%	0.7%
Croscarmellose sodium (disintegrant)	6	3.0%	7	3.3%	0.3%
Magnesium stearate (lubricant)	2	1.0%	2	0.9%	0.1%
Total	203	100%	215	100%	
Total change					4.3%

Example 3. Ineligible BCS class III biowaiver

The formulation of the test product is qualitatively the same as that of the comparator product. Further, the quantitative differences in excipient content between the products, based on percentage of core weight, satisfy the limits expressed in Table A7.1, subsection 5.1. However, the total core weight of the proposed product deviates by more than 20% from the total core weight of the comparator product, making the product ineligible for a biowaiver.

Component	Comparator product		Test product		Absolute % difference relative to core weights
	Composition (mg)	Proportion relative to core weight (%w/w)	Composition (mg)	Proportion relative to core weight (%w/w)	
API	8	8.0%	8	0.8%	–
Lactose monohydrate (filler)	75	75.0%	802	80.2%	5.2%
Silicon dioxide (glidant)	2	2.0%	20	2.0%	0.0%
Croscarmellose sodium (disintegrant)	13	13.0%	150	15.0%	2.0%
Magnesium stearate (lubricant)	2	2.0%	20	2.0%	0.0%
Total	100	100%	1000	100%	
Total change					7.2%

Appendix 3

Equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the Biopharmaceutics Classification System

Introduction

The Biopharmaceutics Classification System (BCS) was proposed in 1995 by Amidon et al. (1). It is a scientific framework that divides active pharmaceutical ingredients (APIs) into four groups according to their solubility and permeability. The recommended method for determination of the solubility is described below. If a defect can be expected to affect the performance, safety or acceptability of the condom, it should be classified as a critical defect.

Recommendations for conducting experiments for assessing solubility of APIs

Prior to the experiment, a solubility study protocol should be prepared describing the equipment and procedures in detail. The protocol should include, for example, methods of sample preparation, experimental conditions such as temperature, method and rate of agitation, method of solid/solution separation of the API, and method of sample analysis. The source and purity of the API to be used in the study should also be recorded in the protocol, as well as the methods that will be used to characterize the material.

Characterization of the solid API should be completed prior to the investigation. The depth of the characterization will depend on the existing knowledge of the solid-state properties of the API in question. For example, if it has been established that the API exists as a single polymorphic form, then less solid-state characterization is needed. In some cases, it may be necessary to characterize the solid starting material as well as the solid residue remaining after equilibrium has been reached and sampling has been completed. For a discussion of the factors that should be considered when planning the solid-state characterization studies, see Avdeef et al. (2).

Solubility experiments should preferably be carried out with the shake flask method, which is used to determine equilibrium solubility, although other methods are possible if justified. A discussion of the factors that should be considered when designing the study can be found in Avdeef et al. (2). The conditions employed should be fully described in the study protocol.

The pH solubility profile of the API should be determined over the pH range of 1.2–6.8 at 37 ($\pm$ 1) °C. Measurements should be made in triplicate under at least

three pH conditions, pH 1.2, 4.5 and 6.8, as well as at the pH of any known solubility minima in aqueous media within that pH range. Pharmacopoeial buffer solutions are recommended for use in solubility experiments – see, for example, Chapter 5.5 “Dissolution test for solid oral dosage forms” in *The International Pharmacopoeia* (3). Factors such as common ion effects and ionic strength should be considered when selecting buffers for the study. The pH should be verified after addition of the API and at the end of the experiment with a calibrated pH meter. Samples should be taken at several time points to ensure that the equilibrium solubility has been reached. Strong agitation followed by a period of sedimentation is suggested, to achieve solubility equilibrium.

A description of the methods of solid/solution separation employed, including details such as filter type and pore size or centrifugation speed, should be provided in the study protocol. Sedimentation, centrifugation and filtration are the standard methods of separation. The factors described by Avdeef et al. (2) should be considered when selecting the most appropriate approach for the API under study.

A validated, stability-indicating analytical method should be employed for determination of the solubility of APIs, for example, chromatography– see Chapter 1.14.1 “Chromatography” in *The International Pharmacopoeia* (3) – or an alternative, validated stability-indicating assay.

A study report should be created after the experiment detailing the actual experimental conditions, results (raw data plus mean values with standard deviations), and any observations, for example, the degradation of an API as a result of pH or buffer composition. The section describing the experimental conditions should include initial and equilibrium pH of solutions and de facto buffer concentrations. If applicable, filter adsorption studies should be documented. Any deviations from the protocol should be noted and justified.

The dose–solubility ratio is calculated as follows: highest single therapeutic dose (mg) divided by solubility (mg/mL). An API is considered highly soluble when the highest single therapeutic dose is soluble in 250 mL or less of aqueous media over the pH range 1.2–6.8, that is, the dose–solubility ratio is ≤ 250 .

References

1. Amidon GL, Lennemas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutical drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm Res.* 1995;12:413–20.
2. Avdeef A, Fuguet E, Llinàs A, Ràfols C, Bosch E, Völgyi G et al. Equilibrium solubility measurement of ionizable drugs: consensus recommendations for improving data quality. *ADMET & DMPK.* 2016;4:117–78.
3. Health products policy and standards. In: *The International Pharmacopoeia*, 11th edition. Geneva: World Health Organization; 2023 (<https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/international-pharmacopoeia> accessed 5 February 2024).

**3.4 WHO Biowaiver List: proposal to waive
in vivo bioequivalence requirements for
WHO Model List of Essential Medicines
immediate-release, solid oral dosage forms**
Annex 6, WHO Technical Report Series, 1052,
2024

1. Introduction and background	346
2. WHO solubility classification for biowaiver	346
3. Scope	347
4. Methodology	347
5. Results	348
References	355

1. Introduction and background

The World Health Organization (WHO) recognizes the possibility of waiving in vivo bioequivalence studies for immediate-release, solid oral dosage forms with active pharmaceutical ingredients (APIs) belonging to classes I and III according to the Biopharmaceutical Classification System (BCS), using comparative dissolution studies as surrogate proof of bioequivalence (1).

The WHO solubility classification, also referred to as the WHO Biowaiver List, is a tool for national regulatory authorities and pharmaceutical manufacturing companies, suggesting medical products that are eligible for a waiver from in vivo bioequivalence studies, which are usually necessary to establish the therapeutic equivalence with the originator (comparator). For exemption from an in vivo bioequivalence study, an immediate-release, multisource (generic) product should exhibit very rapid or rapid in vitro dissolution characteristics that are comparable to those of the reference product. A risk-based evaluation should also account for the excipients used in the formulation of the finished pharmaceutical product.

In addition, the present list replaces the existing literature-based compilation published in 2006 that is reported in the *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms* (2) based on data extracted from the public domain (that is, solubility data published by different authors using inconsistent experimental conditions).

The WHO Biowaiver Project is organized into study cycles. Previous and current cycles are summarized below in order to provide an outline of the project development:

- 2018: cycle I, also referred to as the pilot phase
- 2019: cycle II
- 2020: cycle III
- 2021: cycle IV
- 2022/2023: cycle V – The new results presented in this updated document (in Table A6.1, highlighted in bold) originate from cycle V.

2. WHO solubility classification for biowaiver

In 2017, the Fifty-second Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) recommended that the WHO Secretariat revise the existing list using verifiable laboratory data that are generated according to consistent WHO criteria. Acting on this directive from the ECSPP, the WHO Secretariat initiated a multicentre research project, the Biowaiver Project, aimed at experimentally determining the equilibrium solubility profile of medicines listed in the WHO Model List of Essential Medicines, using a harmonized approach (3).

To classify APIs according to the BCS framework, two critical properties are usually evaluated: (a) an API's aqueous solubility; and (b) its absorption or permeability. The initial phase of the WHO Biowaiver Project centres on unambiguous experimental assessment of the solubility parameter, as only highly soluble APIs are eligible for biowaiver. Once experimental solubility data are available, the exact BCS class assignment can be determined by utilizing quantitative absorption and permeability data. However, since high solubility within an aqueous environment is a necessary prerequisite for an API to be eligible for a waiver from bioequivalence studies, the current focus on solubility is justified to guide the regulatory decision.

The WHO classification should be considered a living document and is meant to be regularly updated in accordance with new quality requirements and progress in scientific development.

3. Scope

The aim of the WHO Biowaiver List is to enable an informed decision as to whether or not a waiver from in vivo bioequivalence studies could be granted safely according to the WHO guidance *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (1).

The WHO Biowaiver List is expected to promote access to standard-quality essential medicines by shortening the time required to develop a multisource (generic) product, thereby supporting optimized pharmaceutical development.

The WHO Biowaiver List has been recognized by WHO regional and country offices as a “global good” – a normative work essential to strengthening global health in WHO Member States.

4. Methodology

The WHO *Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver* (4) is a tool available to all participants in this research. It was developed with the purpose of providing a harmonized methodology for equilibrium solubility experiments, thereby minimizing a potential source of variability among centres and studies.

APIs studied in cycles I, II, III, IV and V were received primarily as in-kind donations from pharmaceutical manufacturers supporting WHO in this scientific work. Equilibrium solubility experiments were conducted by universities, official national control laboratories and WHO collaborating centres.

5. Results

Table A6.1 provides an overview of the APIs studied by WHO during cycles I, II, III, IV and V. The new APIs studied in cycle V are reported in bold. Fixed dose combination products, where all APIs contained in the combination drug product were studied as monocomponents (Table A6.1), are also reported in Table A6.2.

Table A6.1

WHO solubility classification of active pharmaceutical ingredients prioritized from the WHO Model List of Essential Medicines

Medicine ^a	Therapeutic area	Indication	Highest therapeutic dose (mg)	API PQ, EOI-PQ	WHO classification ^b
abacavir (sulfate)	Antiretrovirals	Antiretrovirals (HIV)	600	Yes	I/III
aciclovir	Antiviral medicines	Antiherpes medicines	800	No	II/IV*
amlodipine (besylate)	Cardiovascular medicines	Antihypertensive medicines	10	No	I/III
amoxicillin (trihydrate)	Antibacterials	Antibiotics	3000	Yes	II/IV*
azithromycin (dihydrate)	Antibacterials	Antibiotics	2000	Yes	II/IV
bisoprolol (fumarate)	Cardiovascular medicines	Antihypertensive medicines	20	No	I/III**
cefixime (trihydrate)	Antibacterials	Antibiotics	400	No	II/IV
chloroquine phosphate	Antiprotozoal medicines	Antimalarial medicines	1000 mg salt (= 600 mg base)	No	I/III
clindamycin (hydrochloride)	Antibacterials	Access group antibiotics	450	Yes	I/III
codeine (phosphate hemihydrate)	Medicines for pain and palliative care	Opioid analgesics	60	No	I/III
cycloserine	Antibacterials	Antituberculosis medicines	1000	Yes	I/III

Table A6.1 *continued*

Medicine ^a	Therapeutic area	Indication	Highest therapeutic dose (mg)	API PQ, EOI-PQ	WHO classification ^b
daclatasvir (dihydrochloride)	Antiviral medicines	Medicines for hepatitis C	60	Yes	II/IV**
darunavir (ethanolate)	Antiviral medicines	Antiretrovirals (HIV)	800	Yes	II/IV**
dexamethasone	1. Gastrointestinal medicines 2. Immunomodulators and antineoplastics 3. Medicines for pain and palliative care	1. Antiemetic medicines 2. Acute lymphoblastic leukaemia, multiple myeloma 3. Medicines for other common symptoms in palliative care	1, 3: 0.5 to 10 mg a day, depending on the disease being treated 2: 40 mg	Yes	I/III**
dolutegravir	Antiviral medicines	Antiretrovirals (HIV)	50	Yes	II/IV**
doxycycline (hyclate)	1. Antiprotozoals 2. Antibacterials	1. Antimalarial medicines 2. Antibiotics (access group)	100	No	I/III**
efavirenz	Antiviral medicines	Antiretrovirals (HIV)	600	Yes	II/IV
emtricitabine	Antiviral medicines	Antiretrovirals (HIV)	200	Yes	I/III**
entecavir	Antiviral medicines	Antihepatitis medicines	1	Yes	I/III**
ethambutol (hydrochloride)	Antibacterials	Antituberculosis medicines	2000	Yes	I/III
ethionamide	Antibacterials	Antituberculosis medicines	500–1000	Yes	II/IV*

Table A6.1 *continued*

Medicine ^a	Therapeutic area	Indication	Highest therapeutic dose (mg)	API PQ, EOI-PQ	WHO classification ^b
fluconazole (form III)	Antifungal medicines	Cryptococcosis and candidosis	800	Yes	I/III
furosemide	Cardiovascular medicines	Medicines used in heart failure	80	No	II/IV
hydralazine (hydrochloride)	Cardiovascular medicines	Antihypertensive medicines (pregnancy-induced hypertension)	100	No	I/III
hydroxychloroquine (sulfate)	Disease-modifying antirheumatic drugs (DMARDs)	Lupus erythematosus	600	No	I/III**
isoniazid	Antibacterials	Antituberculosis medicines	300	Yes	I/III
lamivudine	Antiviral medicines	Antiretrovirals (HIV)	300	Yes	I/III
levonorgestrel	Medicines for reproductive health and perinatal care	Oral hormonal contraceptives	1.5	Yes	II/IV*
mefloquine (hydrochloride)	Antiprotozoal medicines	Antimalarial medicines	1250 (as hydrochloride)	Yes	II/IV
methyldopa (sesquidrate)	Cardiovascular medicines	Pregnancy-induced hypertension	500	No	I/III
oseltamivir (phosphate)	Antiviral medicines	Influenza virus	75 (as phosphate)	Yes	I/III**

Table A6.1 *continued*

Medicine ^a	Therapeutic area	Indication	Highest therapeutic dose (mg)	API PQ, EOI-PQ	WHO classification ^b
paracetamol	Medicines for pain and palliative care, antimigraine medicines	Non-opioids and nonsteroidal antiinflammatory medicines, treatment of acute attack	1000	No	I/III
primaquine (phosphate)	Antiprotozoal medicines	Antimalarial medicines (curative treatment of <i>Plasmodium vivax</i> and <i>P. ovale</i> infections)	15	Yes	I/III
proguanil (hydrochloride)	Antiprotozoal medicines	Antimalarial medicines	200	No	I/III
pyrimethamine	Antiprotozoal medicines	Antimalarial medicines	75	Yes	II/IV
quinine (sulfate)	Antiprotozoal medicines	Antimalarial medicines	648	No	II/IV*
raltegravir (potassium)	Antiviral medicines	Antiretrovirals (HIV in pregnant women and in second line)	400	Yes	II/IV**
ribavirin	Antiviral medicines	Viral haemorrhagic fevers	600	Yes	I/III**
rifampicin	Antibacterials	Antituberculosis, antileprosy medicines	750	Yes	II/IV
sofosbuvir	Antiviral medicines	Medicines for hepatitis C	400	Yes	II/IV**
tenofovir disoproxil (fumarate)	Antiviral medicines	Antiretrovirals (HIV)	300	Yes	I/III**

Table A6.1 *continued*

Medicine ^a	Therapeutic area	Indication	Highest therapeutic dose (mg)	API PQ, EOI-PQ	WHO classification ^b
valganciclovir	Antiviral medicines	Cytomegalovirus retinitis (CMVr)	900	Yes	I/III**

API: active pharmaceutical ingredient; PQ: prequalification; EOI-PQ: expression of interest for prequalification.

Note: In the table, the new APIs studied in cycle V are reported in bold text.

^a 23rd WHO Model List of Essential Medicines (2023) (3).

^b According to the WHO *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (1), APIs belonging to classes I and III are eligible for biowaiver. Once experimental permeability data are available, the exact class attribution will be possible (that is, either class I or class III). The present solubility characterization is already sufficient to provide an indication as to whether or not an API is eligible for biowaiver.

* Change in solubility class with respect to WHO 2006 classification.

** APIs characterized for the first time within the WHO Biowaiver Project.

Table A6.2

WHO solubility classification of fixed-dose combination products prioritized from the WHO Model List of Essential Medicines

Medicine ^a	Therapeutic area	Indication	Highest therapeutic dose (mg)	API PQ, EOI-PQ	WHO classification ^b
efavirenz + emtricitabine + tenofovir disoproxil (fumarate)	Antiviral medicines	Antiretrovirals (HIV)	600 + 200 + 300	Yes	II/IV**
efavirenz + lamivudine + tenofovir disoproxil (fumarate)	Antiviral medicines	Antiretrovirals (HIV)	600 + 300 + 300	Yes	II/IV**
emtricitabine + tenofovir disoproxil (fumarate)	Antiviral medicines	Antiretrovirals (HIV)	200 + 300	Yes	I/III**

API: active pharmaceutical ingredient; PQ: prequalification; EOI-PQ: expression of interest for prequalification.

^a 23rd WHO Model List of Essential Medicines (2023) (3).

^b According to the WHO *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (1), APIs belonging to classes I and III are eligible for biowaiver. Once experimental permeability data are available, the exact class attribution will be possible (that is, either class I or class III). The present solubility characterization is already sufficient to provide an indication as to whether or not an API is eligible for biowaiver.

* Change in solubility class with respect to WHO 2006 classification.

** APIs characterized for the first time within the WHO Biowaiver Project.

Establishing a new WHO Biowaiver List that is based on unambiguous verifiable experimental solubility data is a critical project with tremendous public health implications for patients, procurers, United Nations agencies, national and regional regulatory authorities, payers, ethics committees and manufacturers worldwide. The involvement and support of WHO stakeholders and partners is highly encouraged and appreciated.

References

1. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-seventh report. WHO Technical Report Series No. 1052, Annex 8. Geneva: World Health Organization; 2023.
2. Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fortieth report. WHO Technical Report Series No. 937, Annex 8. Geneva: World Health Organization; 2006.
3. WHO Model List of Essential Medicines, 23rd list. Geneva: World Health Organization; 2023.
4. Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. WHO Technical Report Series No. 1019, Annex 4. Geneva: World Health Organization; 2019.

Further reading

- Guidance for organizations performing in vivo bioequivalence studies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. WHO Technical Report Series No. 996, Annex 9. Geneva: World Health Organization; 2016.
- General background notes on the list of international comparator pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. WHO Technical Report Series No. 1003, Annex 5. Geneva: World Health Organization; 2017.
- Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. WHO Technical Report Series No. 992, Annex 8. Geneva: World Health Organization; 2015.
- List of international comparator products (March 2024). Geneva: World Health Organization; 2024.

3.5 Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver

Annex 4, WHO Technical Report Series, 1019, 2019 (under revision)

1. Scope	357
2. Experimental considerations	357
3. Buffers for determination of equilibrium solubility	359
4. Experimental design	360
5. Preliminary assessment of the time to equilibrium and expected solubility	360
6. Stability	361
7. Recommendations for the analytical method	361
8. Pivotal experiment	362
9. Reporting of results	362
References	363
Further reading	364
Appendix 1	
Report template for equilibrium solubility experiments for Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver	365

1. Scope

The objective of this document is to provide guidance on the design and conduct of equilibrium solubility studies undertaken for the purpose of active pharmaceutical ingredient (API) classification within the Biopharmaceutics Classification System (BCS) (1, 2).

Notably, the definition and guidance given in this document for performing solubility studies apply to APIs and there might be differences in requirement with respect to the conditions for dissolution studies that are applicable to solid finished pharmaceutical products (FPPs).

A study protocol has been developed to provide a harmonized approach when performing solubility studies; however, alternative approaches to determining the solubility of an API, such as phase solubility analysis (3), can also be valid if the appropriate test conditions are employed.

The aim of the WHO biowaiver guidance is to reduce the risk of bioinequivalence to an acceptable level when granting biowaivers supporting pharmaceutical development. In this context, the solubility, the release from the drug product, and the subsequent absorption phase are considered critical processes underlying the equivalence of the test and reference product.

Equilibrium solubility profiles of APIs contained in medicines in the *WHO Model List of Essential Medicines* (EML) (4) can be used in conjunction with absorption/permeability data, FPP dissolution studies, and comparative consideration of FPP excipient content, to enable an informed decision on whether a biowaiver could be granted safely.

2. Experimental considerations

Overall, the API sample should be dissolved/suspended in buffer, then separated by appropriate methods, and the solubilized API concentration measured using a suitable analytical method.

According to the World Health Organization (WHO) definition given in the guidance document *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (5), an API is considered highly soluble when the highest single therapeutic dose (e.g. the total amount of API administered orally at once), as determined by the relevant regulatory authority, typically defined by the labelling for the innovator product, is soluble in 250 mL or less of aqueous media over the pH range of 1.2–6.8. The pH solubility profile of the API should be determined at 37 ± 1 °C in aqueous media. A minimum of three replicate determinations of solubility at each pH condition is recommended (5).

In general, equilibrium solubility experiments should be employed. However, in exceptional cases, for example, where the API is not available in sufficient quantities; it

is prohibitively expensive; or when it is not possible to maintain the pH of the medium with pharmacopoeial buffers, experiments where the highest therapeutic single dose as recommended by the approved label/summary of product characteristics (SmPC) is examined in a 250 mL volume, or a proportionally smaller amount examined in a proportionally smaller volume of buffer, can be considered. As these are equilibrium solubility experiments, small volumes of solubility media may be employed without issue if the available experimental apparatus will permit it.

The source and purity of the API should be reported according to the *Report template for equilibrium solubility experiments for Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver* (Appendix 1). Additional characterization of the solid API used in the solubility experiments may be necessary; for example, the solid form of the drug should be confirmed (the crystallinity and polymorphic form). The depth of the characterization will depend on existing knowledge of the solid-state properties of the API in question. For example, if it has been established that the API exists as a single polymorphic form, then less solid-state characterization is necessary.

The “shake flask” method for solubility determination is recommended; a mechanical agitation device should be used (e.g. orbital shaker) and an appropriately validated analytical assay method should also be employed. The device used should be capable of maintaining a temperature of 37 ± 1 °C and an appropriate agitation speed that ensures particle contact with the buffer solution. The agitation speed should be optimized based on the shape of the flask or tube and volume of the liquid, in order to prevent particle agglomeration and ensure particle contact with the diluent. Vortex formation should be avoided. With an optimized agitation rate, it is expected that samples will generally reach equilibrium within 24 hours (6). Samples should be collected and analysed at several time points, until equilibrium has been reached.

To address issues such as poor wettability and the tendency of the API to float on the surface of the solubility medium, it may be necessary to include tools such as glass microspheres to aid de-aggregation of the particles with agitation or sonication (6). Surfactant should be avoided in equilibrium solubility studies because they would produce biased results. Once wetting is successfully achieved, that is, there are no visible particles floating on the surface or sticking to the container, the solubility experiment should proceed toward equilibrium.

In some circumstances, it can be difficult to obtain true equilibrium solubility, for example, due to excessive material requirements (i.e. very high-solubility, micelle-forming API etc.), long equilibrium times (e.g. slow conversion to a salt form), or poor chemical stability. In these cases, particularly when the compound solubility is very high, it may be appropriate to report a lower solubility limit; that is, the actual solubility is greater than the reported value, which is still higher than the solubility required to dissolve the highest single therapeutic dose in 250 mL of medium.

3. Buffers for determination of equilibrium solubility

The pH–solubility profile of the API should be determined over the pH range of 1.2–6.8, with the API's solubility classification being based on the lowest solubility measured over this pH range. Measurements should be made in triplicate or more, according to the observed variability, under at least three pH conditions, pH 1.2, 4.5 and 6.8, using for example, 0.1 N HCl test solution or simulated gastric fluid without enzymes – pH 1.2; acetate buffer – pH 4.5; and phosphate buffer – pH 6.8 solution. If there are any known solubility minima for the API in aqueous media within that pH range (for example the pKa of the API is within the tested pH range of 1.2–6.8), data should also be collected at that pH. Pharmacopoeial buffer solutions are recommended for use in solubility experiments, as reported in Section 3.1. The pH of the buffers should be adjusted at the same temperature as that at which the equilibrium solubility experiments are performed, that is, at 37 ± 1 °C. The pH should be verified after addition of the API and at the end of the experiment, with a calibrated pH meter. If the pH of the buffer changes upon combination with the solute, adjustment of the pH with an appropriate acid or base solution may be sufficient to address the issue, or a buffer with a stronger buffering capacity may be employed. After adjustment of the pH, the solution should be allowed to re-equilibrate for at least one hour before a sample is taken.

3.1 Composition of buffers

Solution pH 1.2, TS (test solution)

Dissolve 2.52 g of sodium chloride R (reagent) in 900 mL of water R, adjust the pH to 1.2 with hydrochloric acid (~70 g/L) TS and dilute to 1000 mL with water R.

Buffer pH 4.5, TS

Dissolve 2.99 g of sodium acetate R in 900 mL of water R, adjust the pH to 4.5 by adding about 14 mL of acetic acid (~120 g/L) TS and dilute to 1000 mL with water R.

Buffer pH 6.8, TS

Dissolve 6.9 g of sodium dihydrogen phosphate R and 0.9 g of sodium hydroxide R in 800 mL of water R, adjust the pH to 6.8 with sodium hydroxide (~80 g/L) TS and dilute to 1000 mL with water R.

Information on the reagents to be used can be found by consulting *The International Pharmacopoeia section on Reagents, test solutions and volumetric solutions* (7).

4. Experimental design

The details of the solubility experiment's design should be based on the characteristics of the API under investigation. It is recommended that preliminary testing be conducted to assess the amount of API required and the length of time required for the pivotal solubility experiment.

5. Preliminary assessment of the time to equilibrium and expected solubility

Preliminary estimation of solubility from chemical structure may be used as a starting point, using an open-source tool (e.g. ChemSpider (8); Virtual Computational Chemistry Laboratory (9); Swiss ADME (10)) or by estimating the data.

From this calculation, the amount of solid needed to have approximately 30–40% excess of undissolved solid in 5 mL (or the selected working volume) of buffer solutions at pH 1.2, 4.5 and 6.8 can be determined. This amount of solid should be weighed in a glass or non-leaching vial of suitable material and of appropriate volume, for instance a 10 mL tube, if 5 mL of the buffer will be used (corresponding to the expected minimum solubility condition).

If the solubility is greater than expected, the working volume should be reduced to 3 mL, while if the expected solubility is low and the API is available in sufficient quantity, higher volumes should be used.

Alternatively, the volume can be kept at 5 mL and the mass can be increased or reduced as appropriate.

The presence of undissolved solid should be checked; if the entire solid dissolves when adding the buffer, additional solid should be added until such time that some solid remains undissolved in the tube. To solve any potential issues related to solid wettability or agglomeration, the tubes should be put in the agitation system, such as shaker or magnetic stirrer, adding glass beads.

When the amount of solute and volume of buffer has been determined to obtain a saturated solution, a minimum of three replicate samples for each pH should be prepared to allow measurements at multiple time points for identification of the equilibration time. The pH of the solution should be measured at the time intervals. pH adjustments may be made, if necessary and scientifically justified.

Filtration is normally recommended to remove undissolved API from collected samples, although centrifugation is a valid alternative method, particularly if the medium volume is small.

Either approach is acceptable, and should be scientifically justified.

The samples should be filtered (using, for example, a filter pore size of 0.45 μm) during or immediately after withdrawal, or dissolved API separated from undissolved API by centrifugation as appropriate.

Solubility experiments are performed at $37 \pm 1^\circ\text{C}$; therefore, if samples are to be left at room temperature until analysis, they should be diluted immediately after centrifugation or filtration, in order to avoid precipitation of the solute. This should be taken into account for back calculations.

To determine equilibrium solubility, the concentration of the solution should be measured at different time points, for example 2 h, 4 h, 8 h, 24 h, 48 h and 72 h, until it does not deviate significantly (e.g. 10%) between sequential measurement. The shortest time needed for reaching the plateau of drug concentration against time could be considered a suitable equilibration time.

Samples should be collected over time, to establish a plateau for the amount of solute dissolved and also to monitor the stability of the API at each pH (see Section 6).

The pH value of the buffer solutions should be measured after establishing the time to obtain equilibrium.

6. Stability

The API's stability across the pH range should be monitored, in order to measure true solubility (11, 12),

To distinguish the drug substance from its degradation products, a validated, stability-indicating analytical method should be employed for solubility determination of APIs such as those indicated in *The International Pharmacopoeia* (13) or other pharmacopoeias adapted as appropriate, if available, for example, high-performance liquid chromatographic (HPLC) analysis (see chapter 1.14.4 *High-performance liquid chromatography* in *The International Pharmacopoeia* (14)) or an alternative, validated stability-indicating assay. An advantage of an HPLC method over a spectrophotometric one is that the HPLC method can also be employed to detect impurities and instability (11, 12). If degradation of the drug substance is observed as a function of buffer composition and/or pH, it should be reported. If a stability-indicating analytical method is not available, separate stability experiments will be necessary to demonstrate that the API is stable in the buffer medium employed.

7. Recommendations for the analytical method

Calibration curves should be constructed, ideally with 5–6 standards for regression and estimation of intercept, slope, and correlation coefficient, and three additional control standards independently prepared for estimation of precision and accuracy.

If necessary, samples should be diluted to be on the range of the calibration curve, recording the dilution factor for back calculations.

Each sample should be run in duplicate and a calibration curve established. It is anticipated that at least 3–4 analytical runs are expected (e.g. the first for the samples of 2 h, 4 h, 8 h and then possibly another three for 24 h, 48 h and 72 h), depending on the stability

of the samples. In the end, data for intra- and inter-day accuracy and precision estimation should be available. In general, the control standards are intercalated with the samples.

To check filter influence, control standards could be injected without and after filtration. Recovery should be between 98% and 102% (if less than this value, there is some adsorption happening; if more, some filter component is affecting the analysis). If necessary, a change of filter type or switch to centrifugation is recommended.

The specificity, linearity, range, accuracy, repeatability and intermediate precision should be determined (12), which should meet the minimum acceptance limits.

8. Pivotal experiment

Pivotal experiments should be designed considering the results of the preliminary experiments. The following steps are presented as a general example of a pivotal solubility experiment:

1. In triplicate, for each pH condition to be evaluated, weigh approximately a 10% excess amount of API (as determined during the preliminary test) and combine with an appropriate volume of the necessary buffer solutions (at least pH 1.2, 4.5 and 6.8 buffers) in a flask. Sufficient API and volume should be used to allow for collection of residual API following the experiment.
2. Mix and measure the pH value.
3. Stop and secure the flask to the orbital shaker, with controlled temperature and shaker speed.
4. Collect an aliquot of the supernatant solution at the time equilibrium was established in the preliminary experiment.
5. Immediately separate dissolved from undissolved API by filtration or centrifugation.
6. Record the pH value of the solution at the end of the experiment.
7. Dilute the sample to avoid precipitation before quantifying.
8. Determine the concentration of the API.

9. Reporting of results

Test results should be reported in the *Report template for equilibrium solubility experiments for Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver* appended to this protocol as Appendix 1. The report should include information on the API (chemical structure, molecular weight, known dissociation constants, etc.), the actual experimental conditions, including information on buffer composition and the analytical method, results (raw data plus mean values with standard deviations), and any observations such as, for example, the degradation

of an API due to pH or buffer composition. The section describing the experimental conditions should include the initial and equilibrium pH of solutions and de facto buffer concentrations. If samples are filtered, the type and pore size of the filter should be recorded, along with data from filter adsorption studies. If samples are centrifuged, the conditions of centrifugation should be recorded. A graphic representation of the mean pH–solubility profile should be provided.

Any deviations from the protocol should be noted and duly justified.

The solubility should be reported in mg/mL. The relative standard deviation of the obtained solubility results should not be more than 10% between the replicates of each test condition.

The dose:solubility volume (DSV) represents the volume of liquid necessary to completely dissolve the highest single therapeutic dose of the API (as recommended by the approved label/SmPC) at the pH where the lowest solubility was observed. Based on the lowest solubility calculated in mg/mL, the DSV can be calculated by dividing the highest therapeutic dose (in milligrams) by the solubility (in milligrams per millilitre) obtained in the study. An API is considered highly soluble when the DSV is ≤ 250 mL over the entire pH range 1.2–6.8.

References

1. Amidon GL, Lennemas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutical drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm Res.* 1995;12:413–20. doi:10.1208/s12248-014-9620-9.
2. Proposal to waive in vivo bioequivalence requirements for *WHO Model List of Essential Medicines* immediate-release, solid oral dosage forms. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Geneva: World Health Organization; 2006: Annex 8 (WHO Technical Report Series, No. 937; https://apps.who.int/iris/bitstream/handle/10665/43443/WHO_TRS_937_eng.pdf?sequence=1, accessed 13 February 2019).
3. Methods of analysis: 1. Physical and physicochemical methods: 1.16 Phase solubility analysis. In: *The International Pharmacopoeia*, 8th ed. Geneva: World Health Organization; 2018 (<http://apps.who.int/phint/en/p/docf/>, accessed 14 February 2019).
4. WHO Model List of Essential Medicines, 20th list. Geneva: World Health Organization; 2017 (<https://apps.who.int/iris/bitstream/handle/10665/273826/EML-20-eng.pdf?ua=1>, accessed 6 February 2019).
5. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-first report. Geneva: World Health Organization; 2017: Annex 6 (WHO Technical Report Series, No. 1003; <http://apps.who.int/medicinedocs/documents/s23245en/s23245en.pdf>, accessed 14 February 2019).
6. Apley M, Crist GB, Fellner V, Gonzalez MA, Hunter RP, Martinez MN et al. 2015. Determination of thermodynamic solubility of active pharmaceutical ingredients for veterinary species: a new USP general chapter. *Dissolution Technologies.* 2017; February:36–9. doi:10.14227/DT240117P36.

7. Reagents, test solutions and volumetric solutions. In: The International Pharmacopoeia, 8th ed. Geneva: World Health Organization; 2018 (<http://apps.who.int/phint/en/p/docf/>, accessed 14 February 2019).
8. ChemSpider. Search and share chemistry (www.chemspider.com, accessed 14 February 2019).
9. Virtual Computational Chemistry Laboratory (<http://www.vcclab.org>, accessed 14 February 2019).
10. Swiss Institute of Bioinformatics. Swiss ADME (<http://www.swissadme.ch>, accessed 14 February 2019).
11. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization; 2018: Annex 10 (WHO Technical Report Series, No. 1010; <https://iris.who.int/bitstream/handle/10665/272452/9789241210195-eng.pdf?sequence=1&isAllowed=y>, accessed 12 February 2019).
12. Supplementary guidelines on good manufacturing practices: validation. Appendix 4: Analytical method validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937; https://apps.who.int/iris/bitstream/handle/10665/43443/WHO_TRS_937_eng.pdf?sequence=1, accessed 9 February 2019).
13. The International Pharmacopoeia, 8th ed. Geneva: World Health Organization; 2018 (<http://apps.who.int/phint/2018/index.html#d/b.1>, accessed 14 February 2019).
14. Methods of analysis: 1. Physical and physicochemical methods: 1.14 Chromatography: 1.14.4 High-performance liquid chromatography. In: The International Pharmacopoeia, 8th ed. Geneva: World Health Organization; 2018 (<http://apps.who.int/phint/en/p/docf/>, accessed 14 February 2019).

Further reading

- Guidance for organizations performing in vivo bioequivalence studies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fiftieth report. Geneva: World Health Organization; 2016: Annex 9 (WHO Technical Report Series, No. 996; <https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>, accessed 14 February 2019).
- Model certificate of analysis. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization; 2018: Annex 4 (WHO Technical Report Series, No. 1010; <https://iris.who.int/bitstream/handle/10665/272452/9789241210195-eng.pdf?sequence=1&isAllowed=y>, accessed 14 February 2019).
- Good practices for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-fourth report. Geneva: World Health Organization; 2010: Annex 1 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y, accessed 14 February 2019).
- WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-eighth report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986; https://iris.who.int/bitstream/handle/10665/112733/WHO_TRS_986_eng.pdf?sequence=1&isAllowed=y, accessed 14 February 2019).

Appendix 1

Report template for equilibrium solubility experiments for Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver

Header:

Logo of the laboratory/company issuing the certificate (if applicable)

Identification No. of the study:

page X of Y

Name and address of the laboratory issuing the study report: _____

Name of the active pharmaceutical ingredient (API) (international nonproprietary name [INN], brand name, etc.): _____

Certificates of analysis (CoAs) from manufactures provided:
assay within specifications <Yes/No> _____

Batch number: _____

Date received: _____ Quantity received: _____

Date of manufacture (if available): _____

Expiry date/retest date: _____

Details of original manufacturer

Name and address: _____

Telephone: _____

Email: _____

Information about the API

Chemical structure (please report here): _____

Nature of the drug (i.e. acid, basic, neutral, amphoteric): _____

Dissociation constants [i.e. $pK_a(s)$]: _____

Molecular weight (g/mol): _____

Equilibrium solubility experiment

Apparatus: _____

Highest therapeutic dose: _____

Recorded temperature (target 37 ± 1 °C): _____

Volume of the buffer: _____

Sampling times: _____

Time to equilibrium: _____

Buffer composition (*please indicate if different buffers from those recommended in the Protocol to conduct equilibrium solubility experiments for the purpose of BCS-based classification of APIs for biowaiver were used*): _____

Separations of samples (*please indicate how and when samples were filtered, filter type and pore size. If samples are centrifuged, the conditions of centrifugation should be recorded. If separated through different methods, this should be justified*):

Stability (*report and discuss any problems with pH-related stability of samples*):

Solubility method and conditions: _____

Brief summary of analytical methods, including validation: _____

Result of the *preliminary* solubility experiment

Theoretical pH	Individual pH measurement	Final pH before correction	Adjusted with (mL of 0.1 M HCL or NaOH) ^a	Final pH corrected	API equilibrium concentration (mg/mL) ^b	Concentration mean (mg/mL) ^c	CV %	Concentration (mg/mL)						
								2 h	4 h	6 h	12 h	24 h	48 h	72 h
pH 1.2	1													
	2													
	3													
pH 4.5	1													
	2													
	3													
pH 6.8	1													
	2													
	3													
Potential additional pH	1													
	2													
	3													

CV: coefficient of variation; HCL: hydrochloric acid; NaOH: sodium hydroxide.

^a Amount of acid or base needed to adjust the measured pH. The measurement should be conducted in triplicate and, per each measurement, the corresponding pH values should be reported.

^b Report here the three measurements registered at each pH.

^c Report here only the mean of the individual values reported in the previous column.

Result of the *pivotal* solubility experiment

Theoretical pH	Individual pH measurement	Final pH before correction	Adjusted with (mL of 0.1 M HCL or NaOH) ^a	Final pH corrected	Time to equilibrium	APIs weight	Buffer volume	API equilibrium concentration (mg/mL) ^b	API equilibrium concentration mean (mg/mL) ^c	CV %
pH 1.2	1 2 3									
pH 4.5	1 2 3									
pH 6.8	1 2 3									
Potential additional pH	1 2 3									

CV: coefficient of variation; HCL: hydrochloric acid; NaOH: sodium hydroxide.

^a Amount of acid or base needed to adjust the measured pH. The measurement should be conducted in triplicates and, per each measurement, the corresponding pH values should be reported.

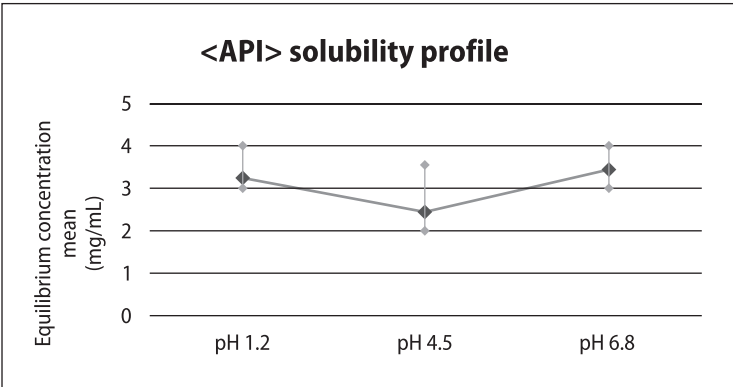
^b Report here the three measurements registered at each pH.

^c Report here only the mean of the individual values reported in the previous column. It is the mean solubility value for each pH.

Plot of solubility

To identify the pH of minimum solubility: plot concentration at saturation versus pH and provide a graphical representation of the results. Include error bars on the mean.

Example chart



Please report here the intermediate calculation for the dose:solubility volume (DSV) at (add additional pHs tested as appropriate):

- pH 1.2 Highest therapeutic dose (mg)/Solubility (mg/mL) [concentration mean] =
- pH 4.5 Highest therapeutic dose(mg)/Solubility (mg/mL) [concentration mean] =
- pH 6.8 Highest therapeutic dose(mg)/Solubility (mg/mL) [concentration mean] =

Conclusion: is the highest single therapeutic dose (according to the approved originator product labelling) soluble in 250 mL of buffer over the pH range of 1.2–6.8 at 37 ± 1 °C, i.e. in all buffers tested including buffers at pH 1.2, 4.5 and 6.8?

<Yes>/<No>

Solubility classification (*please refer to Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability*):¹

<High>/<Low>

¹ Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-first report. Geneva: World Health Organization; 2017: Annex 6 (WHO Technical Report Series, No. 1003; <http://apps.who.int/medicinedocs/documents/s23245en/s23245en.pdf>).

Name of the head of laboratory or person authorized to approve the certificate:

Telephone:

Email:

Signature:

Date:

4. Regulatory standards: general guidance

4.1 Good regulatory practices in the regulation of medical products

Annex 11, WHO Technical Report Series, 1033, 2021

Background

A fundamental role of government is to protect and promote the health and safety of the public, including by delivering health care. A well-functioning health care system requires available, affordable medical products that are safe, effective and of assured quality. As medical products are essential in the prevention, diagnosis and treatment of disease, the consequences of substandard and falsified medical products can be life threatening. This is a concern, as users of medical products are not usually in a position to judge their quality. The interests and safety of the public must therefore be entrusted to a regulatory body or bodies that ensure that only products in legal trade are available and that marketed products are safe, perform as claimed and are of assured quality.

The regulation of medical products has become increasingly complex with the globalization of product development, production and supply and the rapid pace of technological and social change in the context of limited financial and human resources. The importance of robust regulatory systems was recognized by the Sixty-Seventh World Health Assembly when it endorsed resolution WHA 67.20, Regulatory system strengthening for medical products. The resolution notes that “effective regulatory systems are an essential component of health system strengthening and contribute to better public health outcomes”, that “regulators are an essential part of the health workforce” and that “inefficient regulatory systems themselves can be a barrier to access to safe, effective and quality medical products” (23).

A sound system of oversight requires that regulatory authorities be supported by an effective framework of laws, regulations and guidelines and that they have the competence, capacity, resources and scientific knowledge to deliver their mandate in an efficient and transparent manner. The extent to which a regulatory framework fulfils its policy objectives depends on the quality of its development and implementation. GRP are critical to efficient performance of a regulatory system and, consequently, to the public’s confidence in the system, while also setting clear requirements for regulated entities. A sound regulatory framework, including international norms and standards, and the recruitment and development of competent staff are necessary but not sufficient conditions to ensure “good

oversight”. All individuals in regulatory authorities should be guided by GRP in setting appropriate requirements and formulating decisions that are clear, transparent, consistent, impartial, proportionate, timely and based on sound science. Regulated parties and other stakeholders also play important roles in ensuring a clear, efficient regulatory environment so that quality-assured medical products are available to patients.

Acknowledgements	373
Abbreviations to Annex 11	373
Executive summary	373
1. Introduction	374
2. Purpose	375
3. Scope	375
4. Glossary	375
5. Objectives	377
6. Key considerations	378
7. Overview of a regulatory system for medical products	379
7.1 Components of the regulatory framework	379
7.2 Components of a regulatory system	380
8. Principles of good regulatory practices	383
8.1 Legality	384
8.2 Consistency	385
8.3 Independence	387
8.4 Impartiality	388
8.5 Proportionality	389
8.6 Flexibility	390
8.7 Clarity	392
8.8 Efficiency	394
8.9 Transparency	397
9. Enablers of good regulatory practices	399
9.1 Political and government-wide support	399
9.2 Effective organization and good governance supported by leadership	399
9.4 A robust, well-functioning quality management system	400
9.5 Sufficient, sustainable financial resources	400
9.6 Competent human resources	400
9.7 Organizational ethics and values	401
9.8 Science- and data-driven decision-making process	401
10. Implementing good regulatory practices	401
References	401

Acknowledgements

WHO acknowledges all the authors, stakeholders and organizations who contributed to the preparation of this document.

Abbreviations to Annex 11

APEC	Asia–Pacific Economic Cooperation
ASEAN	Association of Southeast Asian Nations
GRP	Good regulatory practices
OECD	Organisation for Economic Co-operation and Development

Executive summary

A fundamental role of government is to protect and promote the health and safety of the public, including providing health care. A well-functioning health care system requires available, affordable medical products that are safe, effective and of consistently assured quality.

The medical products sector is one of the most regulated of all industries, because of the impact of the diverse range of medical products on health, the difficulty in assessing their quality, safety and efficacy or performance¹ and the complexity of their development, production, supply and surveillance. It is therefore essential that the interests and safety of the public be entrusted to a regulatory body responsible for ensuring that only products in legal trade are available and that marketed products are safe, perform as claimed and are of assured quality.

Regulatory authorities have a duty to ensure that they regulate in a manner that achieves public policy objectives. A coherent legal framework should be established and implemented that provides the required level of oversight while facilitating innovation and access to safe, effective and good-quality medical products. The framework should also have the necessary flexibility and responsiveness, particularly for managing public health emergencies, addressing new technologies and practices and promoting international regulatory cooperation.

Governments incur costs by establishing and maintaining regulatory systems to protect and promote the health of their citizens. Regulated parties incur costs in complying with regulations. Inefficient regulatory systems, however, have impacts on the health system, with potentially significant implications for morbidity and mortality, health care costs and the economy.

¹ Medicines and vaccines: efficacy; medical devices including in-vitro diagnostics: performance

A sound legal framework, adoption of international norms and standards and recruitment and development of competent staff are necessary but not sufficient conditions to ensure “good regulatory oversight”. These measures must be combined with good regulatory practices (GRP) that guide all individuals in organizations entrusted with regulating medical products in formulating decisions that are clear, transparent, consistent, impartial, proportionate, timely and based on sound science and legislation.

GRP can be defined as a set of principles and practices applied to the development, implementation and review of regulatory instruments – laws, regulations and guidelines – to achieve public health policy objectives in the most efficient way. Successful application of GRP is the hallmark of a modern, science-based, responsive regulatory system in which regulations are translated into desired outcomes. GRP provide a means of establishing and implementing sound, affordable, efficient regulation of medical products as an important part of health system performance and sustainability.

This document is intended to present Member States with widely recognized principles of GRP derived from an extensive review of public documents issued by governments and multilateral organizations as well as many consultative workshops, benchmarking exercises and interactions with Member States. The nine principles presented in this document – legality, consistency, independence, impartiality, proportionality, flexibility, clarity, efficiency and transparency – are relevant to all authorities responsible for the regulation of medical products, irrespective of their resources, sophistication or regulatory model. Regulated parties and other stakeholders also have important roles to play in achieving an efficient regulatory environment.

GRP serve as a basis for guidance documents on best regulatory practices. The body of WHO guidance documents is intended to provide regulatory authorities with comprehensive guidance for improving their performance. This document will be supplemented by practical guides and tools designed to facilitate implementation of GRP.

1. Introduction

This document responds to requests from national authorities responsible for regulation of medical products (see 4. Glossary) for guidance in addressing common gaps in regulatory practices identified during benchmarking exercises. The document draws on documents published by multilateral bodies such as the Asia-Pacific Economic Cooperation (APEC) (10), the Organisation for Economic Co-operation and Development (OECD) (11, 12), the World Bank (13) and the Association of Southeast Asian Nations (ASEAN) (14), as well as guides published by a number of governments. The document also takes account of earlier WHO documents that touch on aspects of GRP (15–22) and of WHO experience in applying the WHO Global Benchmarking Tool (GBT) and promoting the principles of good regulatory practices (GRP). Proper implementation of

GRP through GRP enablers across the regulatory system (see 4. Glossary) can result in desired regulatory outcomes and impact.

2. Purpose

This document presents the high-level principles of GRP. They are intended to serve as benchmarks and thereby guide Member States in applying good practices in regulation of medical products. This document is also meant to guide Member States in prioritizing the functions of their regulatory system according to their resources, national goals, public health policies, medical products policies and the medical product environment. This “principles-based” document will be supplemented by practical guides and tools to facilitate implementation of GRP by organizations responsible for the regulation of medical products. This basic document is complemented by related guidance on best regulatory practices, including good governance practices (24), good reliance practices (25), good review practices (26) and quality management systems (see 4. Glossary) for national regulatory authorities (NRAs) (27). The group of documents is intended to provide regulatory authorities with comprehensive guidance on improving performance.

3. Scope

This document presents principles and considerations in the development and use of the regulatory instruments that underpin regulatory activities. Broader practices and attributes are presented that define well-performing regulatory systems for medical products.

The document is relevant to all regulatory authorities, irrespective of their resources, maturity or regulatory model. High-level GRP principles are equally applicable to supranational (e.g. regional), national and subnational regulatory systems, and systems in which several institutions are charged with regulating certain products or activities in a country or jurisdiction. The document is also intended for a number of related audiences: institutions and policy-makers responsible for formulating health policies, laws, regulations and guidelines; institutions that, together, form national or supranational systems for regulation of medical products; and regulatory networks and parties affected by or otherwise interested in regulatory frameworks, such as industry or other developers of medical products.

4. Glossary

The definitions given below apply to the terms as used in this document. They may have different meanings in other contexts. Readers are also encouraged to consult related WHO guidance for more complete definitions relevant to best regulatory practices (see References).

Co-regulation. A system of shared regulatory responsibilities in which an industry association or professional group assumes some regulatory functions, such as surveillance and enforcement or setting regulatory standards.

International standards and guidelines. For the purpose of this document, the term includes relevant WHO standards and guidelines and any other relevant, internationally recognized standards (e.g. International Organization for Standardization or pharmacopoeial standards) and guidelines (e.g. the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use or guidelines of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme).

Medical product. For the purpose of this document, the term includes medicines, vaccines, blood and blood products and medical devices, including in-vitro diagnostics.

Public health emergency. The condition that requires a governor to declare a state of public health emergency, defined as

an occurrence or imminent threat of an illness or health condition, caused by bioterrorism, epidemic or pandemic disease, or (a) novel and highly fatal infectious agent or biological toxin that poses a substantial risk of a significant number of human fatalities or incidents or permanent or long-term disability.

The declaration of a state of public health emergency permits a governor to suspend state regulations and change the functions of state agencies (1).

Quality management system. An appropriate infrastructure comprising the organizational structure, procedures, processes, resources and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

Recognition. Acceptance of the regulatory decision of another regulator or other trusted institution. Recognition should be based on evidence that the regulatory requirements of the reference regulatory authority are sufficient to meet the regulatory requirements of the relying authority. Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement.

Regulatory convergence. A voluntary process whereby the regulatory requirements in different countries or regions become more similar or “aligned” over time. Convergence results from gradual adoption of internationally recognized technical guideline documents, standards and scientific principles, common or similar practices and procedures or the establishment of appropriate domestic regulatory mechanisms that align with shared principles to achieve a common public health goal (2).

Regulatory cooperation. A practice among regulatory authorities for efficient and effective regulation of medical products. May be practised by an agency, an institution or a government. The formal mechanisms include creation of joint institutions, treaties and conventions such as mutual recognition agreements, while less formal mechanisms include sharing information, scientific collaboration, common risk assessment, joint reviews and inspections and joint development of standards. May also include work with international counterparts to build regulatory capacity or provide technical assistance, thus contributing to improvement of international regulatory governance practices (3–6).

Regulatory harmonization. A process whereby the technical guidelines of participating authorities in several countries are made uniform (7).

Regulatory impact analysis. Process of examining the probable impacts of a proposed regulation and of alternative policies to assist the policy development process (8).

Regulatory stock. Collection or inventory of accumulated regulations.

Regulatory system. The combination of institutions, processes and the regulatory framework with which a government controls particular aspects of an activity (9).

Reliance. The act whereby a regulatory authority in one jurisdiction takes into account and gives significant weight to assessments by another regulatory authority or trusted institution or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others.

5. Objectives

GRP ensure sound, effective regulation of medical products as an important part of health system performance and sustainability. If they are implemented consistently and effectively, they can result in higher-quality regulation, better regulatory decision-making and compliance, more efficient regulatory systems and better public health outcomes. They help to ensure that regulatory systems remain up to date as the technologies and systems in which they are used continue to evolve. In an increasingly complex, interconnected regulatory environment, GRP also promote trust among regulatory authorities and other stakeholders, such as industry, academia, research centres and health care professionals and thereby facilitate international cooperation and the adoption of more effective and efficient approaches to ensuring the quality, safety and efficacy or performance of medical products in the global regulatory community. The ultimate aim of GRP is to serve and protect public health and patients' interests, with respect for all applicable ethical principles.

6. Key considerations

The medical products sector is one of the most regulated of all industries because of the impact that the diverse range of medical products can have on health and society, the difficulty in assessing their quality, efficacy or performance and safety, lessons learnt from public health tragedies and the complexity of developing, producing, supplying and monitoring medical products to ensure that they consistently perform as intended. Many countries therefore have increasingly sophisticated sets of laws, regulations and guidelines to control all aspects of the life cycle of medical products.

In providing the necessary regulations and tools for fulfilling publicly entrusted mandates, regulatory authorities have a duty to ensure that they regulate in a manner that achieves public policy objectives. They must therefore establish and implement a coherent regulatory framework to provide the required level of oversight and control while facilitating innovation and access to safe, effective and high-quality medical products. They must also build the necessary flexibility and responsiveness into the regulatory framework, particularly for managing public health emergencies (see 4. Glossary), addressing new technologies and best practices and promoting international regulatory cooperation (see 4. Glossary).

Increasingly, policy-makers and regulatory authorities are adopting modern models of regulation that are responsive to resource constraints while meeting the challenges posed by scientific development, globalization, rising public expectations and public health emergencies. Weak or inefficient regulatory systems can limit access to safe, effective and, high quality medical products and pose a threat to public health. As countries strengthen their regulatory capacity, they must ensure that their regulatory systems are science-based, that they adhere to international standards and guidelines and that their approach leverages the work of other, trusted regulatory authorities and institutions when possible. To this end, countries are encouraged to formulate and implement policies and strategies that promote international collaboration (23), convergence, harmonization, information- and work-sharing and reliance (see 4. Glossary) as part of GRP (25). WHO is establishing a framework for evaluating NRAs and regional regulatory systems and for designating those that meet the requirements of WHO listed authorities (28).

Regulatory control of medical products to protect public health is fully acknowledged, as noted above. The issue is how to regulate effectively, efficiently and transparently, such that the interests of the health care system are served. Consistent application of GRP in all aspects of oversight is essential in ensuring that those interests are served and in providing the foundation for a well-performing, respected regulatory system. GRP are principles and practices applied to the development, implementation and review of regulatory instruments – laws, regulations and guidelines – in order to achieve public health policy objectives in the most efficient way. GRP instil a culture of best practices among institutions responsible for regulatory oversight to ensure that regulation is fairly, consistently and effectively applied.

7. Overview of a regulatory system for medical products

Definitions are essential for a common understanding of concepts. While more terms are defined in the Glossary, the terms “regulatory framework”, “legal framework”, “regulatory authority”, “regulatory system” and “regulatory outputs” are explained below to ensure proper understanding of their use in this document.

7.1 Components of the regulatory framework

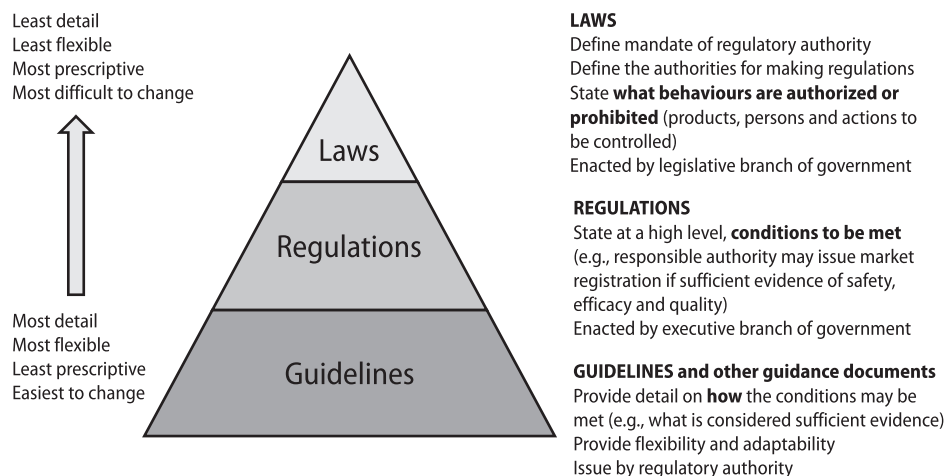
In this document, the terms “law” and “regulation” are used to describe the components of the legal framework (binding legislation). Other terms may be used in some jurisdictions, such as “act” instead of “law” or “ordinance” instead of “regulation”.

Laws generally define the roles and responsibilities of institutions, in this case, a regulatory authority, ministry of health or other relevant organizations. They define the products, persons and activities that are to be regulated and state what is permitted and what is not. More importantly, laws authorize an institution to make lower-level (or subordinate) regulations.

Regulations are a diverse set of instruments by which governments place requirements on enterprises and citizens. Regulations usually state at high level the conditions to be met and the requirements defined in laws. For instance, a law may prohibit the manufacture, importation or sale of a medical product in the absence of specific authorization, while regulations would set out the conditions for obtaining authorization, such as the provision of certain types of information (the results of non clinical testing and clinical trials, data on manufacturing and control) that allow the regulatory authority to establish the quality, safety and efficacy or performance of a medical product.

Guidelines (and other guidance documents) provide further detail on how the regulated stakeholders can comply with laws and regulations. Guidelines may also provide details of the processes of enforcement of the respective legislation (laws and regulations). Within a regulatory framework for medical products, such documents are usually non-binding and are generally more detailed and scientific in nature. They are thus appropriate for describing the approaches that are generally considered suitable for satisfying regulatory requirements but unsuitable for inclusion in legislation.

Fig. 1
Applied PDCA cycle



7.2 Components of a regulatory system

A *regulatory authority* is a public institution(s) or governmental body or bodies authorized by law to exercise independent regulatory oversight over the development, production, marketing and surveillance of medical products. Although the term implies that a single organization is responsible for all regulatory functions, these functions may be undertaken by one or more institutions that report to the same or a different senior official. The regulatory authority plays a critical role in ensuring the quality, safety, efficacy and performance of medical products and also the relevance and accuracy of product information.

The *regulatory framework* is the collection of laws, regulations, guidelines, guidance documents and other regulatory instruments through which a government and a regulatory authority control particular aspects of a specific activity.

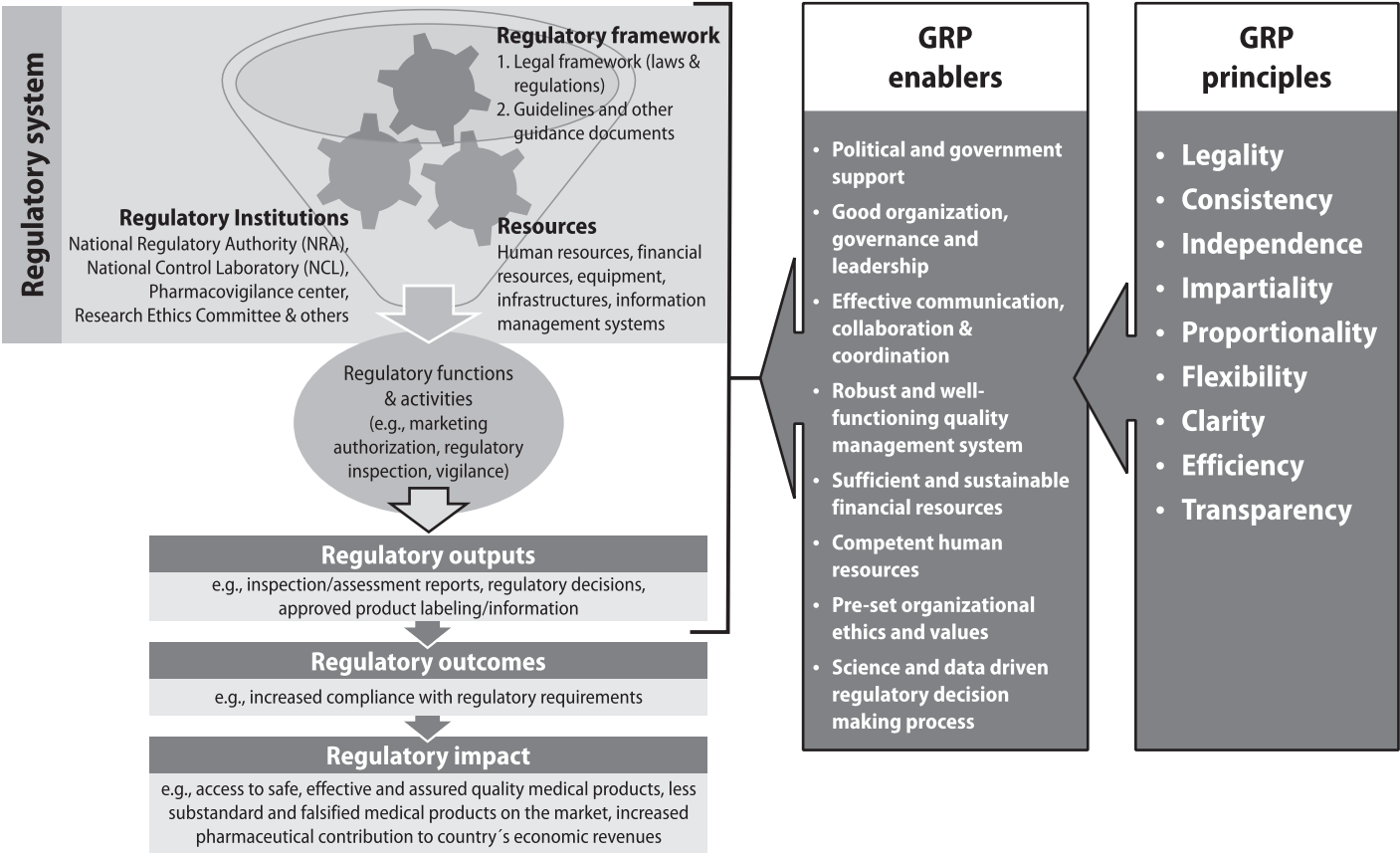
The *legal framework* is the part of the regulatory framework that contains binding pieces of legislation, such as laws and regulations.

Regulatory outputs are the results or products of the regulatory authority, such as reports of inspections and assessments, decisions and product labels.

The term *regulatory system* is used to describe the combination of institutions, processes, regulatory framework and resources which, taken together, are integral to effective regulation of medical products in a country or multi country jurisdiction. GRP should be considered and applied to the whole regulatory system.

Fig. 2 illustrates the principles and enablers of GRP and the components of a regulatory system.

Fig. 2
Principles and enablers of good regulatory practices (GRP) and components of a regulatory system



In the overall regulatory system, three components (inputs) contribute most to regulatory functions and activities: (i) the regulatory framework, composed of the legal framework (laws and regulations), guidelines and other guidance documents; (ii) regulatory institutions, which may be represented by one or more entities, including the NRA, the national control laboratory, pharmacovigilance centres and research ethics committees; and (iii) all types of resources, including human and financial, infrastructure and equipment and information management systems. The regulatory outputs depend on the functions and activities concerned (e.g. regulatory and marketing authorization, inspection and assessment reports). The concepts and principles of GRP apply to the overall regulatory system, as explained above. For application and implementation of GRP, several enablers are essential (see section 9. Enablers for Good Regulatory Practices). When the principles of GRP are properly implemented through the enablers, the desired regulatory outcome and impact can be achieved.

WHO classifies the spectrum of regulatory activities for medical products into seven common regulatory functions, which are applicable to all medical products: clinical trials oversight, marketing authorization, vigilance, market surveillance and control, licensing of establishments, regulatory inspection and laboratory testing (29). In addition, a number of non common functions apply to certain medical products, such as official lot release of vaccines and other biologicals.

The term *regulatory authority* implies that a single organization is mandated to perform all regulatory functions. This is not always the case. For example, different organizations may be legally responsible for regulating medicines and vaccines and for medical devices. Even when one body is responsible for all regulatory functions, aspects critical to certain functions may lie outside its authority, such as those performed by surveillance or vigilance centres that have formal relations with the authority; these include activities such as collecting reports on adverse events, surveillance for substandard and falsified medical products and monitoring advertising. Certain regulatory functions may be undertaken by third parties, as in the case of auditing organizations for medical devices. In order to ensure a comprehensive and efficient regulatory system, clear roles, responsibilities, processes and communication channels must be established among the different organizations responsible for performing regulatory functions.

Regulatory activities may also be undertaken at supranational (e.g. regional), national or subnational level. Examples include supranational evaluation of certain products for the purpose of granting marketing authorization that is valid for several countries or inspections of certain manufacturing sites for medical products for good manufacturing practices at national level.

8. Principles of good regulatory practices

There is no universal model for regulation of medical products. Each approach reflects national health policies and priorities, national socioeconomic development, the availability of resources and infrastructure, the health system, the national legal system, research and development capacity and local production capacity. Nonetheless, as in other regulated sectors, there is growing international consensus on best practices to be applied in regulation of medical products.

A review of public documents on GRP (10, 13, 14, 30) reveals common practices that should be adopted by all institutions responsible for or involved in regulation of medical products. These principles apply equally to the development and implementation of regulatory oversight and to daily regulatory business. GRP are guided by overarching principles. Nine principles are listed in Table 1 and described below, with considerations relevant to regulation of medical products. The principles, practices and examples will be further elaborated in supplementary guidance that will complement this document.

Table 1
Principles of good regulatory practices

Legality	Regulatory systems and the decisions that flow from them must have a sound legal basis.
Consistency	Regulatory oversight of medical products should be consistent with existing government policies and legislation and be applied in a consistent and predictable manner.
Independence	Institutions that execute regulation of medical products should be independent.
Impartiality	All regulated parties should be treated equitably, fairly and without bias.
Proportionality	Regulation and regulatory decisions should be proportional to risk and to the regulator's capacity to implement and enforce them.
Flexibility	Regulatory oversight should not be prescriptive but rather be flexible in responding to a changing environment and unforeseen circumstances. Timely responsiveness to a specific need and in particular to public health emergencies should be built into the regulatory system.
Clarity	Regulatory requirements should be accessible to and understood by users.
Efficiency	Regulatory systems should achieve their goals within the required time and at reasonable effort and cost. International collaboration promotes efficiency by ensuring the best use of resources.
Transparency	Regulatory systems should be transparent; requirements and decisions should be made known, and input should be sought on regulatory proposals.

8.1 Legality

Regulatory systems and the decisions that flow from them must have a sound legal basis.

Key elements:

- The regulatory framework should provide the necessary authority, scope and flexibility to safeguard and promote health.
- Delegation of power and responsibilities to various levels of the regulatory system should be clear and explicit.
- Regulatory frameworks should support and empower regulatory authorities to contribute to and benefit from international cooperation.
- Systems should be in place to ensure that regulatory decisions and sanctions can be reviewed.
- The regulatory framework should clearly define the scope and lines of authority of the institutions that form the regulatory system to ensure its integrity.
- The regulatory authority must be held accountable for its actions and decisions to the public, those regulated and the government within a legal framework.

The principle of legality requires that a regulatory system be structured such that all regulatory actions and decisions are based on clear legal authority, thus respecting the “rule of law”.

A regulatory body exists to achieve objectives deemed by the government to be in the public interest. It must operate within and in accordance with the powers conferred by the legal framework (31). The law or act that establishes the regulatory authority should clearly state the objectives of the enabling legislation, the powers of the authority, the scope of the products and general activities that the authority is mandated to regulate and the provisions for making regulations.

Delegation of power and responsibilities to different levels of the regulatory system should be explicit and clear. When more than one institution or level of government is involved in regulating medical products, the functions and responsibilities of each should be clear and complementary, and the processes for communication and coordination among them should be defined (see section 8.2 Consistency).

As cooperation among regulatory authorities is essential to manage increasingly complex and cross jurisdictional issues, a modern legal framework for medical products must support and encourage all forms of cooperation, including convergence, harmonization, information- and work-sharing, reliance and recognition (see 4. Glossary). Ideally, this is stated explicitly in provisions of laws and/or regulations, with operational detail provided in policies and procedural guidance. A legal framework

should at least not prohibit all forms of regulatory cooperation, such as the use of assessments and decisions of other trusted regulatory authorities and institutions in conducting its own work. Cooperation does not alter the sovereign responsibility and accountability of each regulatory authority to protect the health and safety of its citizens but allows the exchange of good practices and may save resources and avoid duplication.

Legislation must be in place to control and perform all the required regulatory activities under common and non-common regulatory functions. Policies, guidelines and procedures cannot compensate for the absence of legislation. A legal framework should ensure the integrity of the regulatory system by providing clear authority, scope, power, roles and responsibilities to the institutions that form the system. Conflict in organizational authority or responsibilities should be avoided.

All regulatory authorities must be accountable to the public, the bodies they regulate and the government for their actions and decisions as part of good governance and accountability. In the context of GRP, regulatory authorities are accountable when they are: (i) responsible for acting according to certain standards and commitments, (ii) answerable for their actions and (iii) willing to face the consequences when standards or commitments are not met.

Regulatory actions and decisions should be consistent with the authority and controls provided for by the legal framework. Processes should therefore be in place for review of regulatory decisions, including internal appeals and judicial appeal of the decisions of regulators, such as on the grounds of procedural fairness and due process, in addition to scientific and administrative grounds.

8.2 Consistency

Regulation of medical products should be consistent with government policies and legislation and be applied consistently and predictably.

Key elements:

- The regulatory framework for medical products should fit coherently into the national legal and policy framework.
- New regulations should complement, and not conflict with, existing regulatory instruments.
- Regulatory requirements should be implemented and enforced consistently for all medical product sectors and stakeholders.

Regulation of medical products must be performed in the context of and in ways coherent with the national legal framework, general government policies and public health policy objectives. It should also be coherent with any treaties, conventions

and regional or international agreements to which the country is a party as well as any supranational legislation that affects constituent member states.

Any overlap or conflict with existing laws and regulations should be avoided, as this causes confusion, duplication of mandates and unnecessary regulatory work and increases the likelihood of noncompliance. Manufacturers (for the purpose of this document, manufacturers also means marketing authorization holders), importers, distributors and other stakeholders should be able consistently to identify the responsible authority in laws and regulations. Consistency is particularly important when regulation of medical products is decentralized, for instance, with central and state or provincial authorities. Effective systems should be in place for consultation, cooperation and coordination among the different levels of government to promote national uniformity of regulatory requirements while respecting local responsibilities. All regulatory functions and activities should be efficiently integrated to ensure the uniformity of the regulatory system. Similar considerations apply when more than one institution or department at the same level of government is responsible for different, or the same, regulatory functions and products – a situation that is not uncommon. Unclear or conflicting mandates and requirements create complex regulatory systems and challenge effective communication and coordination. In all instances, formal mechanisms for proper coordination should be established during the drafting and execution of regulatory instruments and the operations of bodies charged with the regulation of medical products.

Consistency in regulatory actions and decisions is ensured when the same or similar circumstances lead to the same or a similar outcome. It is therefore important that the regulatory system build an institutional memory, by recording decisions, to ensure similar, fair treatment in future situations. Regardless of differences in technology, the level of regulatory oversight in relation to the risk posed by different types of medical products and regulated entities (manufacturers, importers and distributors) must be consistent. Consistency is upheld when the regulatory framework provides for impartial appeal of regulatory decisions. The enforcement of such appeals and corrective measures should also be consistent among sectors.

Consistency is also ensured by sufficient, clear regulatory guidance, based, when possible, on international guidelines; orientation and training programmes for staff; and regular, transparent interactions with regulated parties and other stakeholders (e.g. industry associations, patients, health care professionals associations and other relevant government institutions). These are mechanisms for improving process and for the identification and resolution of issues.

Application of a well-functioning quality management system that covers all regulatory activities (33) is critical for regulatory consistency. This includes adoption of a process approach, involving systematic definition and management of regulatory processes and their interactions to achieve the intended results in accordance with the quality policy and strategic direction of the organization.

Performance-based indicators, internal reviews and external audits may also be important in ensuring consistency in the application of regulations and regulatory operations.

8.3 Independence

Institutions responsible for regulation of medical products should be independent.

Key elements:

- The regulatory system must operate, and be seen to operate, in an independent and authoritative manner, discharging its duties independently from politicians, government and regulated entities.
- Regulatory activities and decisions should be free of improper and undue influence of stakeholders.
- Appropriate funding and clear funding processes are essential.
- The independence of the leadership should be established to ensure independent behaviour during and after employment.

According to an OECD publication entitled *Creating a culture of independence* (32):

Regulatory agencies (authorities) often find themselves under various pressures from different stakeholders and interest groups which can subject them to different forms of influence. To ensure they conduct their activities correctly and achieve the right policy outcomes they must take on board legitimate interests and protect themselves from inappropriate or undue influence.

Good governance and anti-corruption measures (24) should be built into the regulatory framework to obviate actual or perceived conflicts of interest, unfounded bias or improper influence by stakeholders (also known as “regulatory capture”). To maintain public confidence, the regulatory authority must operate, and be seen to operate, independently, authoritatively and impartially and to discharge its duties independently of the regulated entities (e.g. researchers and industries).

When regulators are funded by fees, an appropriate cost-recovery mechanism is essential to set the “right” fee and to avoid a regulator that is under-funded, captured by industry or undermined by the executive. It may be easy to influence a regulator that is funded from general government revenues by reducing its resources. Annual appropriations make it easier to influence a regulator than multi annual appropriations, which are less susceptible to short-term shocks, such as political or electoral imperatives.

Adequate safeguards can protect the budget from being used to unduly direct the regulator.

The nomination and appointment of the regulator's leadership should be based on transparent and accountable processes. Clear rules to avoid conflicts of interest should be in place to ensure independent behaviour during and after employment.

8.4 Impartiality

All regulated parties should be treated equitably, fairly and without bias.

Key elements:

- Regulatory activities and decisions should be free of conflicts of interest or unfounded bias.
- The regulatory system must operate impartially.
- The regulatory authority should not be engaged in the activities it regulates nor be hierarchically subordinate to the institutions that perform the regulated activities.
- Regulatory decisions should be based on science and evidence, and the decision-making process should be robust, according to defined criteria.

Regulatory instruments must be written such that the regulatory activities and decisions made on the basis of such instruments are legitimate, evidence-based and ethical. Public and private bodies and domestic and foreign entities should be regulated equitably, with the same principles and framework, to ensure competitive neutrality.

The regulatory authority must operate impartially, discharging its duties independently of the regulated entities (see section 8.3 Independence). This principle extends to researchers and other experts sitting on scientific and advisory committees that make recommendations to the regulatory authority on regulatory policy or the authorization of medical products. Declarations of interest must be completed and reviewed, and rules for withdrawal should be defined before discussions in order to maintain the integrity and impartiality of the committee and its recommendations.

The regulatory authority should not be engaged in the activities it regulates nor be hierarchically subordinate to the institutions that perform the regulated activities, including the procurement of medical products by a ministry of health or other government institution.

Regulatory activities and decisions should be based on science and evidence and be predictable. While good regulatory judgement and discretion are necessary in enforcement, actions and decisions should be based on regulatory requirements and on the evidence for or the circumstances of the situation (see also sections 8.2 Consistency and 8.6 Flexibility).

Regulators should avoid actual or perceived influence and be open and transparent about their decisions and decision-making process. The scientific and technical basis for regulatory oversight should be objective and accessible. Public consultation and transparency throughout decision making should ensure impartiality, better regulatory outcomes and greater public confidence in the use of regulated products.

8.5 Proportionality

Regulatory oversight and regulatory decisions should be proportional to the risk and to the regulator's capacity to implement and enforce the decisions.

Key elements:

- Regulatory oversight should be adequate to achieve the objectives without being excessive.
- Regulatory measures should be proportionate to the risk of the product or activity or service.
- Regulations should not exceed the national capacity to implement and enforce them.
- Assessment of medical products should be based on a benefit–risk evaluation and continuous monitoring of the benefit–risk profile in a robust vigilance system.

The principle of proportionality demands that an action not exceed what is necessary to achieve the intended objective. This principle should be applied to all elements of a regulatory system. Regulation should be created only when necessary and should be adequate for the aim and not excessive. The content and form of regulation should be appropriate to both the issue being addressed and the risk it poses. For instance, extensive pre-clinical and clinical studies are necessary to ensure the safety and efficacy of a new medicine for marketing authorization, whereas studies such as of in-vivo bioequivalence or, when appropriate, in-vitro studies are sufficient for generic medicines.

Regulatory enforcement and inspection regimes should also be proportionate to the risk and severity of an infraction in order to reduce or mitigate the health risk posed by the infraction. A proportionate, risk-based approach allows the regulator to allocate resources where the need is greater. It also ensures that the cost of complying with a regulation is proportionate to the nature of the risk. For instance, the frequency of inspections could be determined in part by a manufacturer's history of compliance.

The principle of proportionality also applies to the policies and processes by which regulations are made. Regulation-making should be flexible and proportionate to the complexity and/or impact of the problem that it is to address. For instance, a

rigorous cost–impact analysis may be required for a new, complex regulatory framework, whereas a more pragmatic approach could be used for simple regulations or when the policy alternatives are limited.

Regulation should not exceed national capacity to implement and enforce it.

If there are no strategies, facilities and resources for implementation and enforcement, legislation on its own will achieve nothing. A law with modest aims and objectives that is properly enforced is preferable to a more comprehensive one that cannot be implemented (21).

Furthermore, lack of resources or ability to implement and enforce represent a liability for governments.

Assessment of medical products should be based on a benefit–risk evaluation based on the evidence submitted on the quality, safety and efficacy or performance of the product. All the demonstrated benefits of the medical products should be weighed against the identified risks. Regulatory systems should include appropriate surveillance or vigilance to monitor the benefit–risk profile and to take any actions required.

8.6 Flexibility

Regulatory oversight should be flexible in order to respond to a changing environment and unforeseen circumstances.

Key elements:

- The regulatory system, including its frameworks, should provide sufficient flexibility to reflect or respond to changes in the regulated environment, such as evolving science and technology.
- The regulatory system should be prepared to provide timely responses to urgent situations such as public health emergencies and shortages of medical products.
- The language of regulation should reflect performance when possible, allowing for alternative approaches to achieve the same result.
- The regulatory system should provide the flexibility for applying good judgement.

Flexibility is essential to ensure that regulatory frameworks and regulatory systems remain “fit for purpose”. The design and use of regulatory instruments must therefore be appropriate. A meaningful, understandable, enforceable regulatory framework should contain sufficient detail to ensure clarity. It should also allow flexibility to respond to new technologies and innovation and to changes in the regulated environment and to ensure a timely response to unforeseen public health threats.

Flexibility in regulatory oversight should be risk-based and should not compromise the quality, safety, efficacy or performance of a product (28).

Responsiveness is an extended principle of flexibility. It represents the possibility of responding more rapidly than usual in certain circumstances. For example, an expedited response or review might be necessary in a public health emergency.

Responsiveness is time-bound and temporary, as it is necessary in urgent situations such as a public health emergency, serious shortages of a medical product with no alternative, an unmet medical need or rare disorder and medical products for compassionate use or donation. Regulatory systems should be well prepared and have the necessary regulatory instruments to respond to and manage such situations. The NRA should have flexible and expedited development programmes or review processes to accelerate the access to patients by approval of innovative products for serious, life threatening and rare diseases and to address unmet medical needs. Flexible and responsive provisions are critical for ensuring that the authority can make decisions based on the best available science and on benefit–risk considerations, often in the face of less than complete information (e.g. compassionate use, emergency use authorization or listing). Lack of the necessary regulatory tools and flexibility can be a real, significant impediment to ensuring public safety, particularly during public health emergencies.

When regulatory responsiveness is essential, a regulatory authority should consider prioritizing its activities through a risk-based approach. The involvement of policy- and decision makers and regulatory collaboration and coordination within the international regulatory community significantly contribute to regulatory responsiveness.

The aim of flexibility and responsiveness in regulatory frameworks should be to accommodate the evolution of science and technology. The language of the regulations that support laws is usually based on performance rather than being prescriptive (15), thus allowing regulated parties to use alternative approaches to achieve the same outcome.

Guidelines and other guidance documents are the most detailed, most flexible and most amendable regulatory instruments. These attributes ensure that the regulatory framework can respond to new risks in a timely manner and allow for possible use of advances in regulatory science and technology for a future medical product. Unlike laws and regulations, guidelines in themselves usually do not have the force of law; however, guidelines are very effective if appropriately anchored in the regulation and used to describe how compliance with the regulation may be achieved. They should also allow for other, justified approaches to compliance. Alternative approaches to the principles and practices described in guidance may be acceptable, provided they are adequately justified. The flexibility and amendable attributes of guidelines are lost if such detailed texts become part of regulation.

For science that is evolving rapidly but not sufficiently mature to justify regulatory guidelines, lists of “points to consider” can provide useful principles-

based guidance and definitions for promoting best practices, a common regulatory understanding and international convergence and prepare the ground for eventual guidelines. International guidelines and standards should always be considered in developing new guidance documents, and regulators should support international harmonization and convergence. National requirements beyond international standards should be well justified.

The regulation of medical products is complex and evolving. New technologies and practices will continue to pose challenges to regulatory systems and redefine the boundaries of what can and should be regulated. Before developing regulations to address new technologies or address certain practices, regulators should have the necessary regulatory flexibility to interpret existing legislation and regulations appropriately. It should be possible to revise or withdraw a regulation or guideline when it is no longer required.

8.7 Clarity

Regulatory requirements should be accessible to and understood by users.

Key elements:

- Regulatory instruments should be written in language that is understood by users.
- The terminology should be defined and consistent with international norms when possible.
- Consultation, education and training in new requirements contribute to clarification and compliance.
- Guidelines and good guidance practices are instrumental to proper interpretation of regulations.
- The process and basis for taking regulatory decisions and enforcement actions should be clear.

Compliance with and consistent application of regulatory requirements and processes require a clear understanding of what is expected. Both the regulator and the regulated party should understand the conduct that is expected and the consequences of non-compliance.

Proposed regulatory instruments should be written in language that can be understood by the intended users. This will require collaboration with legal personnel in considering the objectives of the legal instrument, the intended audience, other stakeholders who may be impacted and feedback from internal and external consultations, including subject matter experts. Drafting of instruments in clear, unambiguous, precise

language in a form consistent with other laws and regulations reduces possible disputes or misinterpretation and promotes compliance. Meetings between NRAs and regulated entities can be helpful in clarifying the application of guidance and cases in which there is no guidance.

As an initial step, an authority that is drafting medical product regulations should conduct a review to identify unclear areas and resolve any inconsistencies in the regulation itself or with other regulations. This step also provides an opportunity to review the “regulatory stock” – the accumulated body of applicable regulations (see 4. Glossary) – to identify whether updating and better integration of regulatory requirements are necessary to eliminate inconsistencies, redundancy and complexity or to adapt to new requirements.

Interested parties, including the public, should be informed of and contribute to regulatory development and regulatory impact analysis (see 4. Glossary) in order to improve the quality and language of a regulatory instrument, ensuring clear understanding of what is intended and increasing the likelihood of buy-in and future compliance. The means by which interested parties can contribute should be made clear.

Regulatory impact analysis is valuable for systematic assessment of the expected effects of regulatory proposals. It is usually undertaken by policy analysts in the regulatory departments, agencies or ministries that are sponsoring the proposal, primarily to assist decision-makers in considering a proposal. The product of a regulatory impact analysis is a document that summarizes the regulatory proposal, possible alternatives and the aspects and impacts of implementing the proposal.

Terms should be defined in order to avoid ambiguity or misinterpretation. When possible, they should be consistent with established international norms, standards and harmonized guidelines. As noted previously, international standards and guidelines (see 4. Glossary) are particularly important vehicles for promoting common regulatory language, convergence and international cooperation.

The principle of clarity is also applicable to regulatory and administrative guidelines, which are instrumental for interpreting and providing operational clarity to regulations. Guidelines should be developed according to good guidance practice to ensure that they are written clearly and concisely and are consistent with other guidelines and the underlying regulations. Standard templates and formats, style guides, editors, experts in the regulatory framework and users’ feedback obtained with established tools (e.g. forms, webinars, institutional polls) should be used.

Draft guidelines, like regulations, should be submitted for internal and external consultation to confirm that the language is clear or requires revision to improve comprehension. Plain language and simple sentence structure should be the goals, with illustrative examples when possible. Education, awareness sessions and training, with clear timelines for adoption of new regulations and guidelines, should be considered for ensuring clarity and compliance when introducing or amending regulations and guidelines, particularly when they are complex.

Regulations and supporting guidelines should be reviewed periodically to ensure that they reflect the authority's current practices and expectations, are adapted to scientific and technological developments and are aligned with current international standards and guidelines, when applicable. Review and revision of a guideline should include consideration of the consequential changes in other guidelines, which should be revised simultaneously.

The process and basis for taking regulatory decisions and enforcing them should be clear and accessible to those directly impacted or otherwise affected (see section 8.9 Transparency).

In summary, clarity is essential in all aspects of regulatory oversight (requirements, procedures, decisions and communications) if regulatory programmes are to have the desired effect.

8.8 Efficiency

Regulatory systems should achieve the intended results within the required time and at reasonable effort and cost.

Key elements:

- Efficient regulatory systems achieve the intended public health goals.
- A sound regulatory framework, competent staff and effective use of resources and information from other authorities are the key elements of an efficient regulatory system.
- Policy-makers should seek the most efficient, least burdensome means of achieving their regulatory purposes and confirm effectiveness after implementation.
- The total burden and resources required for cumulative regulation should be evaluated.
- Regulatory authorities should continually explore ways of improving efficiency in fulfilling their mandate.
- Alignment of regulatory requirements with those of other countries and international collaboration promote efficiency.
- Regulated entities contribute critically to the efficiency of regulatory systems.
- The efficiency of regulatory instruments and regulatory operations should be assessed with performance-based indicators.

An efficient regulatory system must be based on science and evidence and the principles of risk assessment and management and embed a strategy of international regulatory cooperation into daily business. A regulatory system in which sound decisions cannot be made in a timely, consistent fashion is not effective. Its efficiency depends not

only on sufficient resources but also on the type of resources and their effective use, irrespective of size. In this context, lack of integrity in the overall regulatory system is a barrier to regulatory efficiency.

Regulatory systems with fewer resources can be as effective as those with more resources if they use a risk-based approach, take advantage of the work and decisions of other regulatory authorities and focus their resources on essential, value-added activities that can be provided only by the regulatory authority (26).

Regulatory oversight cannot be considered efficient if it creates unjustified barriers to access, trade or international regulatory cooperation. Successful establishment of effective regulatory control on medical products depends on a number of factors, as previously described, including:

- analysis of options, including the results of consultations with stakeholders, as regulations are more likely to be effective if those who are impacted have provided input;
- regulations that are proportional to the perceived risk, encourage innovation and pose no unnecessary barriers to trade (e.g. sample testing at import); and
- early planning for implementation and for the practicalities of future enforcement. Application and enforcement should not be after-thoughts.

In developing new regulatory instruments and analysing their impact, the regulatory authority should develop “strategies for education, assistance, persuasion, promotion, economic incentives, monitoring, enforcement, and sanctions” (34). The authority should decide which compliance strategies to establish and whether consumer awareness and market forces can reasonably be used, in addition to the threat of penalties. The role of civil society in monitoring adherence to regulation should also be considered. Co-regulation (see 4. Glossary) may be considered in certain circumstances. In such situations, a government issues regulations and enters into a non-statutory agreement with a body (e.g. industry or professional health care association) to develop and administer a compliance programme. When a government works with and through such a body in regulating the activity, it does not delegate its oversight of the activity.

Regulatory authorities may also consider use of third parties to conduct their activities. This model is prevalent in the regulation of medical devices, such as use of recognized auditing organizations to audit manufacturers’ quality management systems to ensure that they are of an international standard and respect applicable regulatory requirements. Regulatory resources are used to establish and maintain oversight of audit organizations, resulting in more effective use of limited resources (35).

A government incurs costs by establishing and maintaining regulatory systems. Industry and other regulated parties incur costs in complying with regulations, such as undertaking studies, preparing application dossiers, maintaining records and paying

fees – the cost of doing business. Additional costs accrue in inefficient regulatory systems. If the cost of complying with a regulation is disproportionately high, companies may decide not to develop a product and/or commercialize it in a particular market. For instance, a mandatory requirement to conduct local clinical trials as a condition for marketing authorization could be a disincentive to entering that market, particularly if trials conducted elsewhere reflect the patient profiles of the intended market and demonstrate the safety and efficacy of the product. Similarly, long and/or unpredictable times for product review result in lost revenue and unnecessary delays in the availability of products for patients, with potentially significant negative implications for morbidity, mortality, health care costs and the economy. Healthy economies require healthy people.

Inefficiency also results in a negative impact on a regulatory authority's resources, reputation and job satisfaction and increases the time spent addressing complaints about performance. Regulatory frameworks that reflect the principles of proportionality, flexibility and consistency are more likely to be efficient, as they allow resources to be allocated to the regulatory activities that most need them.

International collaboration. Regulatory frameworks that are consistent and aligned with those of other countries and regions encourage the necessary investment to bring appropriate, affordable products to that market. Internationally consistent frameworks also enable the regulatory authority to participate in work sharing networks and other forms of regulatory cooperation (including convergence, harmonization, information- and work-sharing, reliance and recognition). When properly anchored in the regulatory framework, reliance on the work of other authorities eliminates or reduces inefficient duplication of regulatory evaluations of medical products and inspection or audit of facilities. International collaboration thus facilitates access to medical products for all.

Regulatory authorities should continually explore means of improving their efficiency while maintaining standards for evaluating the quality, safety and efficacy or performance of medical products. This could include introduction or refinement of good review practices (28) and a quality management system (28); greater, more effective use of information technology; consultations with industry, health care professionals and patients on common deficiencies and how best to address them; risk-based criteria for scheduling and conducting inspections; addressing gaps in guidance; performance measurement; and – as noted above – regulatory cooperation and reliance (26).

Industry also contributes critically to the efficiency of regulatory systems. For example, high-quality applications for marketing authorization reduce the overall review time by reducing the number of review cycles. Similarly, a manufacturer with a good compliance record should not require the same frequency or depth of inspection as a poorly performing manufacturer. Consultations and training can effectively complement enforcement in achieving the desired level of compliance.

In a regulatory impact analysis, policy-makers should seek the most efficient, least burdensome means of achieving their regulatory purposes at a minimum reasonable cost. A regulatory approach should include consideration of the total burden and resources required for cumulative regulation.

Periodic performance assessments should be conducted to evaluate the actual efficiency of regulatory instruments to ensure that the foreseen benefits are realized and, if so, the direct and indirect costs.

8.9 Transparency

Transparency is the hallmark of a well-functioning regulatory system and is essential for building public trust and enabling international cooperation.

Key elements:

- Transparency requires investment and a culture of openness, supported by government policy, commitment and action.
- Stakeholders should be consulted in the development of new or revised regulatory instruments.
- Regulatory requirements, processes, fees, assessments, decisions and actions should be as accessible as possible.
- The policies of the regulatory authority with respect to disclosure should be consistent with national laws on access to information.

The WHO Constitution states “Informed opinion and active co-operation on the part of the public are of the utmost importance in the improvement of the health of the people.” Transparency is in the interests of patients, consumers, governments, health care workers and manufacturers, as it increases public trust and confidence in the regulation of medical products. Transparency in regulatory requirements and actions results in better informed decisions about investment in the public and private sectors and discourages discriminatory, corrupt or abusive practices.

With transparency, all affected and potentially interested parties – domestic, foreign, public and private – have a meaningful opportunity to be informed of new or amended regulations and guidelines and to make their views known before they are enacted. With transparency, once medical product regulations and guidelines are adopted, they are readily available and accessible to stakeholders and the general public. Relevant laws, regulations and guideline documents should be posted on the authority’s website. Additionally, national industry and professional associations often work with regulatory authorities to disseminate new regulatory texts or to provide opportunities for exchanges of relevant information.

The assessments (positive and, when possible, negative), decisions and actions of the regulatory authority should be documented and made publicly available, with the rationale for the decisions, ideally by issuing a public assessment report. This information is important to a range of stakeholders, including industry, researchers, health professionals, patients and consumers, who use the information for various purposes. It is also essential for building trust and confidence in the regulatory system.

Regulated parties should be able to access the full reports of a product assessment or site inspection that pertains to them. This not only provides insight into the basis for comments and decisions but is also educational, helping to improve regulatory compliance and the quality of future submissions. This practice can also be beneficial to the regulatory authority by fostering a culture of transparency and accountability at operational and management levels. Furthermore, it can lead to higher-quality reports by ensuring that they clearly explain how such assessments led to decisions. The manufacturer should be given the opportunity to redact any trade secret or confidential personal or commercial information before publication.

Transparency requires investment and a culture of openness, which, in turn, should be supported by government policy, commitment and action. While not all regulatory authorities may be able to implement the full range of measures for an optimally transparent regulatory system, a step wise approach can be adopted. Given the prevalence of smart devices and the Internet, an up-to-date, searchable public website could be established and maintained that contains basic information such as:

- the roles, responsibilities, organization and contact information of the regulatory authority;
- access to the laws, regulations, guidelines and procedures necessary to satisfy regulatory requirements and improve the efficacy, safety and quality of medical products;
- a searchable registry of approved, suspended and withdrawn products;
- product information for health care professionals and patients;
- the licensing status of manufacturing sites;
- health advisories, safety information, alerts on quality or on substandard or falsified medical products, advisory notices, recalls and other time-sensitive information of public health interest;
- performance targets and results and annual reports;
- proposed new regulatory instruments, including periods for comment and how to provide input; and
- public assessment reports and reports of facility audits or inspections.

The findings of all audits or oversight reviews of the performance and functioning of the regulatory authority should be made public. Such reviews are important elements of public accountability, as are reports of performance against targets and annual reports.

In fulfilling their responsibilities, regulatory authorities will create or access proprietary or confidential information. Examples include identifiable personal information from clinical trials or reports of adverse events, trade secrets or confidential commercial information such as specifications of medical product compounds or materials or manufacturing processes. Measures should be established to prevent the disclosure of such information, with a mechanism to address disputes about the proprietary nature or confidentiality of information.

In general, national laws and regulations should favour transparency and public access to both the process and the criteria of regulatory decision-making. The disclosure policies of a regulatory authority should be consistent with national laws on public access to government information or “freedom of information”. Procedures and contact points for obtaining information held by a regulatory authority should be accessible and clear.

Transparency enables adoption of new, more efficient ways of conducting regulatory operations. It is incumbent upon regulators to practise transparency in regulatory operations and decisions, not only as a fundamental principle of GRP but also to build trust and maximize opportunities for cooperation and reliance as part of the shared responsibility of the regulatory community.

9. Enablers of good regulatory practices

An enabling environment facilitates successful implementation of GRP. Some elements are described below.

9.1 Political and government-wide support

Sustained support at the highest political and government levels, including policy-makers, is essential for proper implementation of the concept and principles of GRP. GRP should form an integral part of all government policies on regulatory systems and be backed by strong political support.

9.2 Effective organization and good governance supported by leadership

The structure and line of authority among and within all institutions in the regulatory system should be well defined. The integrity of the overall regulatory system is critical to the efficient performance of each of its constituent institutions. If more than one institution is involved in the regulatory system, the legislation or institutional regulation should provide for clear coordination and no overlap of regulatory activities. Leadership is critical for setting and realizing the organizational vision, mission, policies and strategies, which in turn significantly contribute to organizational efficiency.

9.3 Inter- and intra-organizational communication, collaboration and coordination

Adequate, effective communication plays a fundamental role in the exchange of information within and outside the institutions that form the regulatory system. When regulatory authorities communicate regularly, both internally and externally, they remain more transparent and accountable. Communication of correct information prevents potential misunderstandings and dissemination of misleading information to patients and the public. Communication is a powerful tool for collaboration and coordination with relevant national and international stakeholders, which leads in turn to efficient use of resources and better regulatory outcomes.

In view of their responsibilities, regulatory authorities should have the personnel, infrastructure and technical tools adequate for the performance of their tasks. Coordination may be facilitated by communication technologies and efficient, rapid information-sharing, which will result in fewer gaps and less duplication of effort.

9.4 A robust, well-functioning quality management system

A quality management system (28), which includes application of quality risk management principles, makes the decisions of regulatory authorities more credible and their operations more stable and consistent. A quality management system contributes to systematic planning, control and improved quality in all processes in regulatory functions and ensures a comprehensive approach.

9.5 Sufficient, sustainable financial resources

Investment in a regulatory system is critical to a well-functioning health care system. Adequate financial resources to fulfil its regulatory mandate effectively and to improve the performance of regulatory activities continuously are essential for the independence, impartiality, consistency and efficiency of a regulatory system. The financial resources of all institutions of the regulatory system should be sustainable, apart from donations from donors or philanthropic entities.

9.6 Competent human resources

An array of technical and scientific knowledge and skills of regulatory staff contribute to the development, implementation and maintenance of an effective regulatory system for medical products. Policies and measures for personal and career development (e.g. training programmes, competitive remuneration schemes) are critical for regulatory authorities to attract competent staff and retain them in the service.

9.7 Organizational ethics and values

Regulatory personnel should abide by organizational ethical principles and values and show professionalism. All regulatory staff should be made aware of and be trained in the ethical principles and values of the regulatory authority (e.g. a code of conduct). A system should be established, within or outside the regulatory system, for managing departures from organizational ethics and values.

9.8 Science- and data-driven decision-making process

Regulatory decisions and decision-making should be based on scientific foundations and accurate data rather than intuition or arbitrariness. Science-based decisions provide for consistent, predictable regulatory outcomes. Adherence to international standards and guidelines is a key enabler of science based regulatory decision-making.

The enablers listed above are not effective when present individually. Rather, they work in harmony in the application and implementation of GRP. For example, sufficient, sustainable financial resources contribute to the recruitment, development and maintenance of competent human resources. Similarly, financial resources should be managed according to good governance practices.

10. Implementing good regulatory practices

WHO Member States are encouraged to implement GRP in their regulatory systems with due consideration of the realities of their legal and regulatory systems. Transparent, predictable processes should be used to ensure high-quality regulatory oversight that achieves the intended objectives while minimizing negative impacts and costs. At the same time, regulatory systems should be sufficiently flexible for the processes to be applied proportionately to the scope, magnitude and complexity of the issue. Sustained support at the highest levels, with adequate resources, is essential.

Further guidance will be issued to assist Member States both in establishing new regulatory systems for medical products and in updating existing ones.

References

1. WHO definitions: emergencies. Geneva: World Health Organization; 2020.
2. Regulatory harmonization. Geneva: World Health Organization; 2014. WHO Drug Inf. 2014;28(1):3–10. (<https://iris.who.int/bitstream/handle/10665/331132/DI281-3-10-eng.pdf>, accessed 29 January 2021).
3. International regulatory co-operation: addressing global challenges. Paris: Organisation for Economic Co-operation and Development; 2013 (<http://dx.doi.org/10.1787/9789264200463-en>, accessed 29 January 2021).

4. Guidelines on international regulatory obligations and cooperation. Ottawa: Treasury Board of Canada Secretariat; 2007 (<http://www.tbs-sct.gc.ca/hgw-cgf/priorities-priorites/rtrap-parfa/guides/iroc-cori/iroc-cori-eng.pdf>, accessed 29 January 2021).
5. International regulatory cooperation – better rules for globalization. Paris: Organisation for Economic Co-operation and Development; 2013 (<http://www.oecd.org/gov/regulatory-policy/irc.htm>, accessed 29 January 2021).
6. Recommendation of the Council on Regulatory Policy and Governance. Paris: Organisation for Economic Co-operation and Development; 2012 (<http://www.oecd.org/gov/regulatory-policy/2012-recommendation.htm>, accessed 29 January 2021).
7. Regulatory harmonization and convergence. Silver Spring (MD): US Food and Drug Administration; 2015. (<http://www.fda.gov/BiologicsBloodVaccines/InternationalActivities/ucm271079.htm>, accessed 29 January 2021).
8. Best practice regulation handbook. Canberra: Australian Government; 2007 (http://regulationbodyofknowledge.org/wp-content/uploads/2013/03/AustralianGovernment_Best_Practice_Regulation.pdf, accessed 29 January 2021).
9. Evaluating the effectiveness of infrastructure regulatory systems. Washington DC: The World Bank; 2006:17 (https://ppp.worldbank.org/public-private-partnership/sites/ppp.worldbank.org/files/documents/world_bank-_ppiaf-_handbook_for_evaluating_infrastructure_regulatory_systems_2006_english.pdf, accessed 29 January 2021).
10. APEC–OECD Co-operative Initiative on Regulatory Reform. APEC–OECD integrated checklist on regulatory reform. Paris: Organisation for Economic Co-operation and Development; 2005 (<http://www.oecd.org/regreform/34989455.pdf>, accessed 29 January 2021).
11. The OECD report on regulatory reform. Paris: Organisation for Economic Co-operation and Development; 1997 (<https://doi.org/10.1787/9789264189751-en>, accessed 29 January 2021).
12. OECD guiding principles for regulatory quality and performance. Paris: Organisation for Economic Co-operation and Development; 2005 (www.oecd.org/fr/reformereg/34976533.pdf, accessed 29 January 2021).
13. Better regulation for growth. Governance frameworks and tools for effective regulatory reform. Washington DC: The World Bank; 2007 (<http://documents1.worldbank.org/curated/en/955811468330978599/pdf/556350WP0Box0310Governance01PUBLIC1.pdf>, accessed 29 January 2021).
14. ASEAN good regulatory practice (GRP) guide. Bangkok: Association of Southeast Asian Nations; 2009 (<http://regulatoryreform.com/wp-content/uploads/2015/08/ASEAN-Good-Regulatory-Practice-GRP-Guide-2009.pdf>, accessed 29 January 2021).
15. The “blue book”. Marketing authorization of pharmaceutical products with special reference to multisource (generic) products, a manual for national medicines regulatory authorities (NMRAs). Second edition. Geneva: World Health Organization; 2011 (https://apps.who.int/iris/bitstream/handle/10665/44576/9789241501453_eng.pdf;jsessionid=52D37F5BD27B9BB5055CF9DA79453B5B?sequence=1, accessed 29 January 2021).
16. National drug regulatory legislation: guiding principles for small drug regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-fifth report (WHO Technical Report Series, No. 885). Geneva: World Health Organization; 1999: Annex 8 (https://iris.who.int/bitstream/handle/10665/42145/WHO_TRS_885.pdf?sequence=1&isAllowed=y, accessed 29 January 2021).

17. Regulation of vaccines: building on existing drug regulatory authorities. Geneva: World Health Organization; 1999 (document WHO/V&B/99.10) (http://apps.who.int/iris/bitstream/10665/65968/1/WHO_V-B_99.10_eng.pdf, accessed 29 January 2021).
18. Effective drug regulation: a multi-country study. Geneva: World Health Organization; 2002 (<https://apps.who.int/iris/bitstream/handle/10665/42470/9241562064.pdf?sequence=1&isAllowed=y>, accessed 29 January 2021).
19. Medical device regulations: global overview and guiding principles. Geneva: World Health Organization; 2003 (<https://iris.who.int/bitstream/10665/42744/1/9241546182.pdf>, accessed 29 January 2021).
20. A model regulatory programme for medical devices: an international guide. Washington DC: Pan American Health Organization; 2001 (http://new.paho.org/hq/dmdocuments/2009/AmodeRegulatoryProgramforMedicalDevices_AnInternalGuide.pdf?ua=1, accessed 29 January 2021).
21. How to develop and implement a national drug policy, second edition. Geneva: World Health Organization; 2001 (<https://iris.who.int/bitstream/handle/10665/42423/924154547X.pdf?sequence=1>, accessed 29 January 2021).
22. Global model regulatory framework for medical devices including IVDs. Geneva: World Health Organization; 2017 (<https://apps.who.int/iris/bitstream/handle/10665/255177/9789241512350-eng.pdf?sequence=1>, accessed 29 January 2021).
23. Resolution WHA67.20. Regulatory system strengthening for medical products. In: Sixty-seventh World Health Assembly, Geneva, 19–24 May 2014. Resolutions and decisions: resolutions. Geneva: World Health Organization; 2014 (http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R20-en.pdf, accessed 29 January 2021).
24. Good Governance for Medicines: Model Framework, Geneva: World Health Organization; 2014 (http://www.who.int/medicines/areas/governance/ggm_modelframe_updated/en/, accessed 29 January 2021).
25. Good Reliance Practices: Good reliance practices in regulatory decision-making: 6 high-level principles and recommendations 8 Draft. Geneva: World Health Organization; 2020 (working document QAS/20.851).
26. Good review practices: guidelines for national and regional regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2015: Annex 9 (WHO Technical Report Series, No. 992; https://iris.who.int/bitstream/handle/10665/176954/9789240693968_eng.pdf?sequence=1&isAllowed=y, accessed 29 January 2021).
27. WHO guideline on the implementation of quality management systems for national regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty fourth report. Geneva: World Health Organization; 2020: Annex 13 (WHO Technical Report Series, No. 1025, <https://iris.who.int/bitstream/handle/10665/331814/9789240001824-eng.pdf?sequence=1&isAllowed=y>, accessed 29 January 2021).
28. Policy evaluating and publicly designating regulatory authorities as WHO-listed authorities. Draft. Geneva: World Health Organization; 2019 (working document QAS/19.828).
29. WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems (<https://iris.who.int/bitstream/handle/10665/341243/9789240020245-eng.pdf?sequence=1>, accessed 29 January 2021).

30. APEC Sub-committee on Standards and Conformance. Information notes on good practice for technical regulation. Singapore: Asia-Pacific Economic Cooperation; 2000 (<http://www.inmetro.gov.br/qualidade/comites/pdf/docAPEC.pdf>, accessed 29 January 2021).
31. Improving regulation and regulatory review. Executive Order 13563. Executive Office of the President. Federal Register: the Daily Journal of the United States Government, 21 January 2011 (<https://federalregister.gov/a/2011-1385>, accessed 29 January 2021).
32. The governance of regulators. Creating a culture of independence. Practical guidance against undue influence. Paris: Organisation for Economic Co-operation and Development; 2017 (<https://www.oecd.org/gov/creating-a-culture-of-independence-9789264274198-en.htm>, accessed 29 January 2021).
33. Recommendation of the Council of the OECD on improving the quality of government regulation, including the OECD reference checklist for regulatory decision-making and background note. Paris: Organisation for Economic Co-operation and Development; 1995 (<https://legalinstruments.oecd.org/public/doc/128/128.en.pdf>, accessed 29 January 2021).
34. Medical device single audit program (MDSAP). Silver Spring (MD): Food and Drug Administration; 2020 (<https://www.fda.gov/medical-devices/cdrh-international-programs/medical-device-single-audit-program-mdsap>, accessed 29 January 2021).

4.2 Good review practices: guidelines for national and regional regulatory authorities¹

Annex 9, WHO Technical Report Series, 992, 2015

Background

The good review practices (GRevP) guidelines for regulatory authorities emanate from a partnership between the Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC) and the World Health Organization (WHO). This is the first set of guidelines of its kind globally and addresses an important gap identified at the 2012 International Conference of Drug Regulatory Authorities (ICDRA). Although the RHSC does not directly produce guidelines, contributing to WHO guidelines is in line with the RHSC's principle of working with appropriate partners to achieve common objectives.

In June 2013 the RHSC convened an expert working group with WHO representation to develop a draft GRevP document, intended to cover both medicines and medical devices, for submission to WHO in early 2014. The draft document subsequently underwent the required WHO consultation process with a view to its further development into WHO guidelines for adoption by the Expert Committee on Specifications for Pharmaceutical Preparations and the Expert Committee on Biological Standardization. This led to these new GRevP guidelines for regulatory authorities adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its forty-ninth meeting.

¹ Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC) good review practices (GRevP) with the participation of Working Group Members representing the regulatory authorities (RAs) from the economies of Australia, Canada, Taipei (China), Japan, Republic of Korea, Saudi Arabia, Singapore, United States of America; and representatives of the Centre for Innovation in Regulatory Science (CIRS); and the Food and Drug Administration Alumni Association International (FDAAA).

1. Introduction	407
1.1 Document objective	407
1.2 Context	407
1.4 Scope	408
2. Glossary	408
3. Principles of a good review	409
4. Managing the review	411
4.1 Project management	411
4.2 Quality management	411
4.2.1 Say what you do	413
4.2.2 Do what you say	413
4.2.3 Prove it	413
4.2.4 Improve it	413
4.3 Standard operating procedures	414
4.4 Review process stages	415
5. Communications	415
5.1 Intra-agency	415
5.2 Interagency	416
5.3 With applicants	416
5.4 With external experts	417
5.5 With the public	417
6. Review personnel	418
6.1 Reviewer expertise, competencies and training	418
6.2 Critical thinking	419
7. Conducting the review	420
7.1 Key elements in defining a review strategy	420
7.1.1 Public health priority of the medical product application	420
7.1.2 Understanding other RAs' action on the application	420
7.1.3 Understanding specific intrinsic and extrinsic factors	421
7.1.4 Identification of major scientific questions and their possible resolution	421
7.2 Applying the review strategy	422
Bibliography	423

1. Introduction

1.1 Document objective

The objective of this document is to provide high-level guidance on the principles and processes of good review practice (GRevP) for use across a range of regulatory authority (RA) maturities. It is not intended to provide detailed instruction on how to conduct a scientific review.

This document is envisioned as one building block in a set of tools and is sufficiently expandable to accommodate additional annexes or ancillary documents in the future.

1.2 Context

RAs are increasingly seeking ways to improve their performance and ensure the quality of their regulatory systems. GRevPs are an integral part of overall good regulatory practices and focus on the medical product review aspect of regulatory work. Review is a highly complex, multidisciplinary assessment of the medical product applications to ensure that they meet the scientific and evidentiary standards for safety, efficacy² and quality. It forms the scientific foundation for regulatory decisions.

The extent to which an RA can achieve timeliness of the review (i.e. completion within a specified time frame), as well as predictability, consistency, transparency, clarity, efficiency and high quality, can have a significant impact on public health (for example, in relation to patients' access to important medical products, and costs to both government and applicants). Implementation of GRevPs helps to achieve these outcomes by ensuring that those involved in the review process have the critical thinking skills and tools needed to optimize scientifically sound, evidence-based decisions. It also facilitates progress towards regulatory convergence through the exchange of review reports and the enhancement of mutual understanding among RAs.

Several RAs have introduced ways of monitoring and improving their review process through structured approaches or by moving towards stepwise implementation of GRevPs. RAs should consider review models and best practices within the context of available resources and legal requirements. The GRevP principles and elements described in this document can be adapted to meet the continuous needs for improvement of a diverse range of RAs.

1.3 Definition of good review practices

GRevPs are documented best practices for any aspect related to the process, format, content and management of a medical product review. The objective of GRevPs is to

² Although effectiveness is the term often used for medical devices, efficacy is used throughout this document.

help achieve timeliness, predictability, consistency, transparency, clarity, efficiency and high quality in both the content and management of reviews. This is done through the development of review tools (for example, standard operating procedures (SOPs) and templates) and reviewer learning activities (for example, training courses, mentoring, orientation packages and discussion sessions). To promote continuous improvement, all aspects of GRevPs should be continuously evaluated and updated.

1.4 Scope

This document applies to the review of safety, efficacy and quality data in medical product applications filed with RAs for marketing authorization.

Although this document was written to provide guidance on pharmaceutical products and biologicals and higher-risk medical devices used in humans, the concepts may be applied to other types of medical products. Similarly, the concepts could also be applied to the entire product life cycle from investigational testing to new product applications, updates or variations to existing marketing authorizations and maintenance of the product.

2. Glossary

The definitions given below apply to the terms used in this document. They may have different meanings in other contexts.

applicant. The person or company who submits an application for marketing authorization of a new medical product, an update to an existing marketing authorization or a variation to an existing marketing authorization.

application. The information provided by the applicant to the RA for evidence-based review and marketing authorization decision.

good regulatory practices (GRP). Reference definition in WHO GRP guidelines (currently under development)

good review practices (GRevP). Documented best practices for any aspect related to the process, format, content and management of a medical product review.

marketing authorization. Also referred to as product licence or registration certificate. A legal document issued by the competent medicines RA that authorizes the marketing or free distribution of a medical product in the respective country after evaluation of safety, efficacy and quality. In terms of quality it establishes inter alia the detailed composition and formulation of the medical product and the quality requirements for the product and its ingredients. It also includes details of the packaging, labelling, storage conditions, shelf-life and approved conditions of use.

principles (of a good review). The important GRevP elements for RAs to implement in order to achieve successful review outcomes.

project management (for the review process). The planning, organization and resources to achieve a complete and high quality review of an application within a specified time frame.

quality management (QM). The coordinated activities that direct and control an organization with regard to quality.

quality management (QM) system. An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

regulatory authority (RA). The agency responsible for the registration of and other regulatory activities concerning medical products.

regulatory convergence. The process whereby regulatory requirements, approaches and systems become more similar or aligned over time as a result of the adoption of internationally recognized technical guidance, standards and best practices.

review. A highly complex, multidisciplinary assessment of medical product applications to assess whether they meet scientific and evidentiary standards for safety, efficacy and quality. It forms the scientific foundation for regulatory decisions. The first stage of the review process, validation (sometimes referred to as screening), occurs before the scientific review with the aim of ensuring completeness of the application in order to subsequently facilitate the scientific review.

review strategy. The approach or plan of action that a reviewer or review team uses to review a medical product application.

standard operating procedure (SOP). An authorized written procedure giving instructions for performing operations (both general and specific).

transparency. Defining policies and procedures in writing and publishing the written documentation, and giving reasons for decisions to the public.

3. Principles of a good review

As noted in the definition of GRevP, the objective of GRevPs is to help achieve successful review outcomes. The principles of a good review describe the GRevP elements that are important for RAs to implement in order to achieve successful review outcomes. Listed in alphabetical order in Box A9.1, the 10 key principles of a good review are provided as a general guide for RAs. Although not prescriptive in nature, they can serve as a solid GRevP foundation upon which RAs can continue to build.

Box A9.1

10 key principles of a good review

Balanced

A good review is objective and unbiased.

Considers context

A good review considers the data and the conclusions of the applicant in the context of the proposed conditions of use and storage, and may include perspectives from patients, health-care professionals and other RAs' analyses and decisions.

Evidence-based

A good review is evidence-based and reflects both the scientific and regulatory state of the art. It integrates legislative, regulatory and policy frameworks with emerging science.

Identifies signals

A good review comprehensively highlights potential areas of concern identified by the applicant and the reviewers.

Investigates and solves problems

A good review provides both the applicant's and the reviewers' in-depth analyses and findings of key scientific data and uses problem-solving, regulatory flexibility, risk-based analyses and synthesis skills to devise and recommend solutions and alternatives where needed.

Makes linkages

A good review provides integrated analysis across all aspects of the application: preclinical; nonclinical; clinical; chemistry/biocompatibility; manufacturing; and risk management plan. It includes timely communication and consultation with applicants, internal stakeholders and, as needed, with external stakeholders who have expertise relevant to the various aspects of the application.

Thorough

A good review reflects adequate follow-through of all the issues by the reviewers.

Utilizes critical analyses

A good review assesses the scientific integrity, relevance and completeness of the data and proposed labelling, as well as the interpretation thereof, presented in the application.

Well-documented

A good review provides a well-written and thorough report of the evidence-based findings and conclusions provided by the applicant in the dossier, and the reviewers' assessment of the conclusions and rationale for reaching a decision. It contains clear, succinct recommendations that can stand up to scrutiny by all the parties involved and could be leveraged by others.

Well-managed

A good review applies project and quality management processes, including clearly defined steps with specific activities and targets.

4. Managing the review

RAs actively manage the process of reviewing medical product applications in order to maximize both the potential for a positive public health impact and the effective and efficient use of review resources. RAs should clearly define the separate steps in the process, each with specific activities and targets.

The principles of project management and quality management are critical to well-functioning RAs. The practices of planning and monitoring review activities coupled with timely, informative communications within the RA and clearly-defined work instructions for the reviewers, can maximize the efficiency and effectiveness of the review.

4.1 Project management

Project management for the review process refers to the planning, organizing and resourcing necessary to achieve a complete and high-quality review of an application within a specified time frame.

Techniques to monitor the progress of applications under review will be specific to each RA. For example, an individual reviewer can use a simple table or spreadsheet, or a project manager may use computer software to monitor many applications at one time. Data should be periodically collected and interpreted to assess the effectiveness of the review strategy (see section 7) for completing reviews within the specified time frame.

The technique most suitable for the RA will be one that enables:

- interpretation of the data to show the progress of one application as well as that of many applications under review at any one time;
- interpretation of the data to help in decision-making with respect to balancing workload against resources;
- monitoring that can be performed and/or interpreted by the relevant people.

As the conditions, resources and workload for the RA evolve, the techniques and complexity of project management should also be adapted.

4.2 Quality management

Quality management (QM) is defined as the coordinated activities that direct and control an organization with regard to quality. A QM system refers to the appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

In an RA, QM includes standardized procedures to ensure that GRevPs are in place, regularly monitored and subject to continuous improvement. Beyond

standardized processes and procedures that provide consistency and predictability, QM has the ultimate goal of supporting robust regulatory decisions and actions.

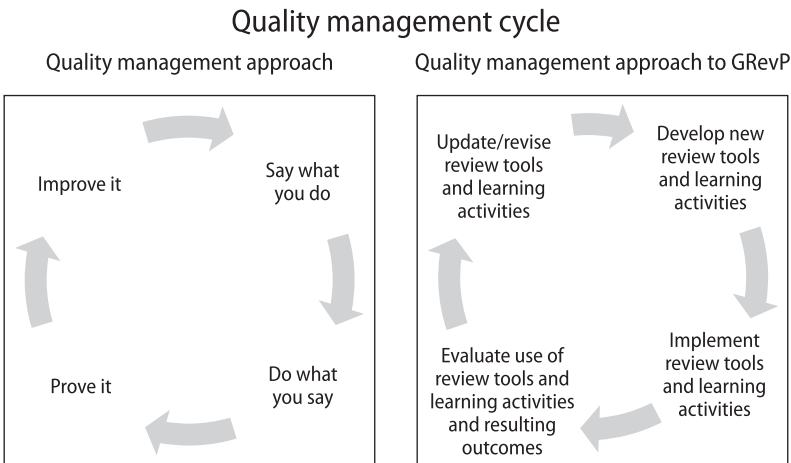
An RA's QM system will be influenced by a number of factors including size and resources of the RA, competencies, its particular objectives, the processes it employs, and its organizational structure. However, even RAs with limited resources can institute the key elements of QM. Successful QM implementation requires the commitment of senior management but is ultimately the responsibility of everyone in the organization.

The quality cycle is made up of four key components:

- say what you do
- do what you say
- prove it
- improve it.

This cycle ensures that GRevPs are not just esoteric guidelines (say what you do) but become embedded in the daily practice of an agency (do what you say). Quality management is also important as it can help an agency review its practice (prove it) and evolve where necessary, either in response to evolving regulatory science or through the adoption of a new review process and procedures (improve it) (Figure A9.1).

Figure A9.1
Quality management cycle



Source: Based on United States of America Food and Drug Administration figure.

4.2.1 Say what you do

- Provide key documents, such as SOPs and assessment templates.
- Define processes for decision-making, such as decision frameworks, time frames for completion and communication of reviews, use of external experts, public meetings and peer-review.

4.2.2 Do what you say

- Implement processes defined in key documents and adhere to specified time frames.
- Offer professional development, mentoring and regular on-the-job training.
- Record and collect key documents, such as minutes of meetings and teleconferences, memoranda, letters and reports.

4.2.3 Prove it

- Ensure that review procedures and templates are being consistently interpreted and applied through the assessment of various inputs, such as internal and external feedback and periodic evaluation of practices by internal and external experts.
- Assess public health impacts of regulatory decisions, such as through a lessons-learned session that could include assessing the impact on disease, the health-care system and any unintended consequences.

4.2.4 Improve it

- Review documentation and decision-making processes regularly.
- Consider introducing improvements to the review and decision-making process, such as: internal assessment of a review; peer review; internal quality audits; self-assessments; analyses of feedback from stakeholders; post-approval analysis of the decision in collaboration with other authorities; the public and applicants; and analysis of impact on public health.
- Implement new and improved work practices, the latest evaluation techniques, and scientific and technological advancements.

Implementing QM is an iterative process that incorporates lessons learned with regard to improved processes and decision-making.

4.3 Standard operating procedures

Creating and adopting a set of SOPs enables the RA to:

- outline the workflow processes that facilitate project management when multiple reviewers assess different parts of the same application and when there are multiple applications to review;
- handle and review product applications in a consistent manner;
- facilitate staff training.

SOPs are authorized written procedures giving instructions for performing operations (both general and specific). They describe procedures (or processes) in a step-by-step manner. They may be detailed or brief, but should describe the overall procedure from start to finish. SOPs should be written clearly to provide both instruction and consistency related to the work being performed.

SOPs may be structured to contain additional tools that will assist in performing the procedure. Alternatively, companion documents can be created to give more detailed instruction and structure in support of an SOP. These companion documents (for example, guidelines for reviewers, templates and checklists) can describe in detail how a particular procedure is performed or give advice on handling a specific situation when performing the procedure.

Templates and checklists present information in a structured manner to facilitate understanding of the information submitted for review. Templates prompt the user to provide specific information, while checklists prompt the user to ensure either that information has been provided or that a particular task has been completed. Templates and checklists have the added benefit of training reviewers and review teams on how to provide information in a structured, consistent manner.

While SOPs have often been kept internal within an RA, making templates and checklists available to applicants can be beneficial in ensuring mutual understanding of the information to be submitted for review. SOPs can be further complemented by guidelines for applicants, in order to promote transparency and guide applicants on how to submit high-quality marketing authorization applications. Guidelines for applicants can be made available using a step-wise approach, usually involving informing applicants of the guidelines before making them publicly accessible.

SOPs, guidelines, templates and checklists will require updating (or in some cases even cancellation) as technological advances occur or scientific and regulatory thinking evolves. This evolution could be related to influences including scientific progress, international harmonization of guidelines, changes in review strategy, available resources, increased volume of applications, collaborative work-sharing and national laws and regulations, among others.

4.4 Review process stages

Two key stages in the process of reviewing medical product applications are validation³ and scientific review. The validation stage occurs first, with the aim of ensuring completeness of the application in order to facilitate the subsequent scientific review.

Validation involves an examination of the application to ensure that it is well-organized and that all the required forms and relevant documents have been submitted. Identifying missing information in the application prior to scientific review enables the RA to avoid spending time and review resources on an application that does not allow critical analysis, signal identification or regulatory decision-making. Scientific review will be discussed further in section 7.

It is essential that applicants are made aware of the RA's expectations at both stages, including the target time frames, guidelines, requirements, templates and checklists. This results in a more predictable and clear process for applicants. In turn the RA benefits when applicants submit complete applications at the outset.

5. Communications

Good communication is critical and has many advantages for RAs, applicants and the public. It can improve the efficiency of the development and review process, allowing patients faster access to important medical products. It can also improve the quality of the review by providing access to additional expertise.

Communications can take many active forms, from providing information on RAs' websites to engaging with the international community on RA projects. In turn, these active forms of RA communications can be used to the advantage of others, including other RAs.

5.1 Intra-agency

Product reviews are conducted in a collaborative environment. They often require expertise from and coordination with different organizational units within the RA, such as pre- and postmarketing scientific disciplines, pharmacovigilance, inspection and others.

Therefore, good communication will improve efficiency. Open, clear, constructive and timely communications regarding the progress of the review, review findings, differing data interpretations and discussion of possible solutions and actions within the RA are desirable. In addition to establishing meetings, forums and other vehicles for exchange of ideas among reviewers, a checklist of personnel or departments involved on specific issues or actions may be helpful. Information management systems should be process-centric rather than organizational structure-centric to ensure appropriate and efficient information flow.

³ Although screening is a term that is also sometimes used, validation is used throughout this document.

5.2 Interagency

RA to RA communications have become more frequent and in many cases normative. As a means of peer collaboration and cooperation, interagency communications can facilitate greater regulatory convergence. This, in turn, can increase the efficiency and quality of medical product development and RA review processes and improve patient access. Types of interagency communication include:

- accessing information from other RAs' public websites, such as guidelines, application decisions and product recalls;
- using information from other RAs, such as review reports and certificates of pharmaceutical product;
- actively sharing information between RAs, such as nonclinical, clinical and inspection findings during an application review;
- actively working with other RAs, for example, on joint reviews of applications and development of new guidelines.

Interagency communication may evolve from sharing and awareness of information, to consideration of findings from one RA by another in its decision-making, to using and relying on those findings to make the best use of resources.

Information-sharing arrangements and procedures, such as memoranda of understanding, confidentiality arrangements, consent from the applicant, redaction and non-disclosure of specific information, as well as other arrangements and actions, have been used to ensure confidentiality of commercial data, trade secrets and personal information.

5.3 With applicants

Public availability of RA guidelines, notices, questions and answers and presentations, as well as finalized RA review reports and decision summaries (redacted as needed), provide insight into the RA's current thinking and expectations. These communications allow applicants to provide better quality applications.

Communication between the RA and individual applicants on specific applications before, during and after the review process is also important as it can:

- foster efficient medical product development through the provision of scientific advice;
- increase applicants' understanding of evolving regulatory expectations in a changing medical and scientific environment;
- increase the RA's understanding of challenges and trade-offs with various requirements;

- foster applicants' compliance with requirements (although it is also important for RAs to be open to proposals from applicants for alternative approaches that address the same requirements);
- inform applicants about the progress and status of the review of their applications.

Procedures allowing applicants and the RA to engage with each other can facilitate the development, review and availability of medical products. Topics for dialogue can relate to product development requirements (including feedback on guideline development and implementation), as well as issues identified during the application review or postmarketing.

5.4 With external experts

Expertise in the scientific assessment of the safety, efficacy and quality of medical products is not limited to applicants and RAs. Academic institutions, industry associations, patient organizations and medical and scientific organizations all have extensive expertise that may be useful to the review.

Asking for the input of external experts into RA decision-making improves public confidence, provides additional perspectives for the RA to consider and provides expertise that otherwise may be lacking. RAs have used advisory panels, both in public and closed sessions, to ensure that expertise and health-care contexts are addressed. RAs may also use a system whereby external experts conduct the review of all or part(s) of the application. Ensuring both confidentiality and absence of conflict of interest is important and can be achieved through transparent processes for management of confidential information and screening for potential conflicts.

5.5 With the public

Communication with the public about the mission and accomplishments of the RA can foster greater public awareness, understanding of and confidence in the RA. Transparency refers to defining policies and procedures in writing, publishing the written documentation, and giving reasons for decisions to the public. For the RA, transparency initiatives usually involve web-based information about how it is organized and operates, its decision-making processes and criteria, and its actions, such as application approvals and product recalls. Additionally, there may be mechanisms whereby the public can provide input on medical needs, efficacy expectations and risk tolerances, such as through public meetings and RA advisory boards. Providing the public with the opportunity to comment permits enhanced content and feasibility of proposed guidelines and regulations. Use of plain language will ensure RA communications are properly understood.

The public may also be consulted on specific applications under review by the RA. There are various mechanisms by which this can be achieved, such as surveys, focus groups, public meetings, workshops and appointment to advisory boards.

6. Review personnel

The quality, timeliness and success of medical product application reviews are dependent on adequate RA review capacity. In addition to having a sufficient number of reviewers, capacity relates to many personnel factors including the knowledge, skills, abilities and attitudes of reviewers. Together, these considerations define the core competencies for personnel involved in the various aspects of managing and conducting reviews.

Reviewers may be RA staff, external experts or both. To ensure the integrity of product reviews and recommendations, reviewers should be free of actual or perceived conflicts of interests. To be free of any conflict of interest means the review decision or recommendation is not likely to be influenced by personal, family, financial or professional motives, including those of employers when an external expert is also a consultant to the regulated industry.

6.1 Reviewer expertise, competencies and training

The use of core competencies can contribute to improved application review by encouraging evidence-based, population-focused, ethical decision-making.

Core competency starts with reviewers who are scientifically trained. Reviewers should have professional qualifications, training and expertise in scientific or medical fields that relate to the assessment of medical product safety, efficacy and/or quality. Both practical and theoretical knowledge is desirable in order to achieve a good understanding of the issues likely to be associated with the product under review.

Reviewer competencies depend on the duties and scope of review work. Scientific writing, presentation of data, data analysis, inferential and deductive reasoning, risk-based analyses and problem-solving are important skills for reviewing a medical product application. Review staff should also follow sound ethical practices.

General competencies required to conduct review work include:

- knowledge of statutes, regulations, guidelines and precedents, including international guidelines and precedents, and their applicability;
- knowledge of the process of medical product development from early development phases to postmarketing surveillance and risk management;
- scientific communication skills for written evaluations, public presentations and negotiation and consensus building with applicants and stakeholders.

Reviewers should keep their scientific expertise up to date. Increasingly, regulatory science curricula from universities and international regulatory initiatives and organizations are available. Reviewers should have the opportunity to attend relevant conferences, courses and international meetings. Reviewers should also be encouraged to read scientific journals and to be members of professional societies or relevant organizations.

For on-the-job training, a site visit programme that allows reviewers to visit sites such as laboratories, manufacturing facilities and clinical settings may be considered. In addition, experienced reviewers should be encouraged to mentor and train junior reviewers. The establishment of structured training programmes within RAs to facilitate the professional development of review staff should also be considered, whenever feasible.

6.2 Critical thinking

Critical thinking requires an objective and systematic approach to analysing information and to problem-solving. It relies on the collection of data and evidence-based decision-making instead of generalizing from one's own experience, intuition or trial and error. Decisions should be reproducible and clearly understood by others.

Nevertheless, every regulatory decision involves judgement. Therefore, core competence in public health and bioethics, and the ability to integrate up-to-date scientific knowledge with an understanding of the evidentiary standards for regulatory action (including the flexibility inherent in those standards and regulations), can guide decisions.

Beyond their professional qualifications, reviewers should have the ability to critically appraise the information presented in an application and not just accept it as presented. This skill may often be developed or strengthened during the training process, for instance, by evaluating the responses to questions raised by a senior reviewer so that the questioning process becomes a learning tool. Discussion among reviewers and external experts on application-specific issues can promote critical regulatory thinking and problem-solving.

Good judgement is required to come to a balanced decision. This involves focusing on the important issues in the application, rather than on data that provide more information, but will not ultimately affect the outcome of an application. Good judgement includes, where applicable, using international harmonized regulatory requirements and adopting regulatory approaches that show flexibility to maximize public health benefits while minimizing adverse, unintended consequences.

Regulatory decision-making or recommendations from reviewers should be based on the best current science. The public health needs of the country and its health-care system provide context for this decision-making. In decisions to grant authorization the benefits must, on balance, outweigh the risks, based on sound scientific evidence. Documentation of scientific rationale for decision-making, taking into account regulatory requirements, provides a record to ensure the integrity of the review process. The decision-making document should address dissenting, evidence-based views and clearly identify the information that was considered. Decision-making by an RA should be independent of influences beyond public health.

7. Conducting the review

Defining and then following an application-specific review strategy that is amended only as needed when new information comes to light, ensures soundness of the review process, the quality of the report and the efficient use of resources.

7.1 Key elements in defining a review strategy

A review strategy is the approach or plan of action that a reviewer or review team uses to review a medical product application. The strategy employed may be shaped by the following.

7.1.1 Public health priority of the medical product application

Each medical product application poses unique and varied scientific questions, challenges and opportunities for the public health of a nation and these, in turn, determine the public health priorities of the application. Given the limitations of resources within RAs, prioritization based on public health needs may be helpful in setting and communicating review time frames, the extent of involvement of management and other RAs, resources assigned to the review team (which helps determine who may review what portions of the application), need for public input and other plans.

7.1.2 Understanding other RAs' action on the application

The use of reviews and decisions reached by other RAs is expected to become increasingly important in making the review process more efficient in the face of pressures on resources. To implement optimal and consistent use of other RAs' reviews and decisions, development of a policy framework and review strategy is critical. Such strategies should consider both the use of publicly available information (for example, decisions, review reports and summaries) and of confidential information obtained directly from applicants or other RAs (for example, review packages which include responses to questions posed by RAs). Clear direction and support from senior management on the use of regulatory outputs from other RAs is also essential. The goal is to consider how to achieve efficiencies and improve the quality of the review through use of other RAs' reviews and/or decisions in appropriate situations. When considering another RA's action, it is important to understand whether there are differences in the product reviewed (for example, formulation or final container presentation) and any differences in the proposed indications or conditions of use in the local population.

GRevPs are important in promoting the use of information from other RAs, by:

- encouraging greater transparency and public availability of non-confidential regulatory information (for example, decisions, review reports and/or summaries and review processes);

- promoting confidence and trust in the regulatory system that produced the review report and the regulatory decision;
- applying the same GRevP principles to the consistent integration of the scientific reviews and decisions of other RAs into the domestic review process.

As previously noted, the implementation of GRevPs also facilitates opportunities for work-sharing between RAs.

7.1.3 Understanding specific intrinsic and extrinsic factors

Whether or not a medical product is authorized by another RA, the review should focus on available information that may be clinically relevant to the population of the country where the product is being authorized. Such information could include: identification of potential differences in genotypes and phenotypes; disease manifestation; and comparison of available alternatives and medical practice in both the study population relevant to the application and the population of another RA that has already rendered a decision on the application under review.

7.1.4 Identification of major scientific questions and their possible resolution

Early identification of complex, precedence-setting or high uncertainty issues in the application is important and can lead to faster and more efficient resolution. Major scientific application-specific questions would be likely to relate to product safety, efficacy or quality. Examples may include:

- identification of possible cases of organ toxicity in a patient population with a high background incidence of the same organ disease;
- use of a new end-point for regulatory approval that may not be a direct measure of clinical benefit;
- use of conditions for stability testing that are not appropriate for the RA's regional climate.

If problems are identified early on, reviewers can formulate a plan to first review the data in the application that are of greatest relevance to these problems, the RA can develop a plan to seek external advice if desirable, or if the application does not permit a conclusion about benefits and risks, the RA can avoid spending time and resources altogether.

Understanding what information is needed to reach an acceptable level of certainty to resolve scientific questions and meet regulatory standards for marketing authorization, versus what information can be collected in the postmarketing period, is an important aspect of regulatory decision-making.

7.2 Applying the review strategy

The way a review is conducted will depend on the resources available. While a multidisciplinary team will provide broader expertise, in some cases an application may be assigned to a single reviewer. In this case, input from external experts and/or the information and decisions of other RAs may be necessary to ensure that scientific and evidentiary standards for safety, efficacy and quality are adequately met.

The review should be evidence-based, taking into account national laws and regulations, regional and international guidelines, and, where applicable, monographs and standards. The reviewer should determine the information necessary to approve the product application and consider whether further information can be obtained in post-approval studies without compromising safety.

The model adopted for review may allow for questions to be asked during the review to supplement or clarify information supplied, until the reviewer is satisfied that enough information has been provided to allow a conclusion to be reached. In other models, the review is completed on the basis of the information submitted, and a list of questions is then sent to the applicant setting a specified time-limit for response, and one further round of assessment of the responses takes place before a decision is made.

There are a number of internal processes that may be implemented to help ensure an efficient, consistent and effective review process. These include:

- periodic meetings to allow consideration of the views of different reviewers;
- peer review, in the context of a co-rapporteur, or a team meeting;
- an internal panel review;
- an external panel review;
- the involvement of senior management.

The review strategy should ultimately enable the reviewer or review team to understand the benefit–risk profile of the medical product, given the indication and context of use. The nature of the benefits and types of risks should be described as part of the review. Benefits and risks can be quantified or qualitatively characterized, and the levels of certainty surrounding the benefits and risks should be stated. The review should address generalizability of the data, the clinical significance of findings and what (if any) additional information may be needed to clarify benefits and risks.

Various methodologies can be used to quantify benefits and risks. The choice depends on circumstances such as complexity of issues and utility to the RA. The acceptability of benefits and risks will depend on public health priorities, presence of available alternative therapies, size and certainty of the treatment effect versus that of the adverse reactions and possible risk mitigation or benefit enhancement that can be implemented (such as conducting responder analyses to identify a population more

likely to experience benefits). It is important to note that the benefit–risk profile may vary depending on intrinsic and extrinsic factors that may differ among countries and regions. Moreover, judgement may vary from within and among RAs. Evidence-based and public health-focused decision-making principles may serve to mitigate some of the variation.

The findings and conclusions of the review must be described in a well-documented review report (see section 3). Once the final decision is made it should be conveyed to the applicant. If an RA decides not to grant authorization, a statement of reasons should be provided, which details the documents, information and applicable regulatory requirements taken into account in reaching the decision. An appeal mechanism should be provided to ensure that applicants have an opportunity to present their case to an independent arbiter.

Some RAs may offer to hold a post-action discussion with the applicant to help improve the quality of future applications. The RA may also have mechanisms for communication with the public on the approval of the product and/or action taken in relation to the application. Publication of information on the approval of products increases transparency of regulatory actions.

Bibliography

- Guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-sixth report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 981; https://iris.who.int/bitstream/handle/10665/81144/WHO_TRS_981_eng.pdf?sequence=1, accessed 14 December 2014).
- Liu L-L et al. Characterizing Good Review Practices: A Survey Report Among Agencies of APEC Member Economies, Therapeutic Innovation & Regulatory Science, November 2013; vol. 47, 6: pp. 678-683. First published on July 19, 2013.
- Chen J-SS, Lin H-Y, Gau C-S, Liu L-L. APEC workshop report of good review practice on medical products (manuscript accepted for publication).

4.3 WHO guideline on the implementation of quality management systems for national regulatory authorities

Annex 13, WHO Technical Report Series, 1025, 2020

Abbreviations	425
1. Background	425
2. Objectives	426
3. Scope	427
4. Glossary	428
5. Quality management system requirements for national regulatory authorities	430
5.1 Quality management system concepts	430
5.2 Quality management system requirements	433
6. Quality management system implementation methodology	453
6.1 Supporting factors for quality management system implementation	453
6.2 Situational analysis of quality management system implementation status in the national regulatory authority	454
6.3 Gap analysis for developing a roadmap for quality management system implementation	455
6.4 Quality management system development and implementation roadmap	465
6.5 Activity plan for quality management system implementation	466
References	466
Appendix 1 References to the <i>WHO Global Benchmarking Tool</i> , revision VI	468
Appendix 2 Activity plan for quality management system implementation	471

Abbreviations

CREAM	clear, relevant, economic, adequate and monitorable
EDQM	European Directorate for the Quality of Medicines and HealthCare
GBT	<i>WHO Global Benchmarking Tool (4)</i>
GRP	good regulatory practices
ICT	information and communication technology
IT	information technology
ISO	International Organization for Standardization
M&E	monitoring and evaluation
NRA	national regulatory authority
PDCA	plan–do–check–act
QA	quality assurance
QMS	quality management system
RCA	root cause analysis
SMART	specific, measurable, attainable, realistic and time-bound
SWOT	strengths, weaknesses, opportunities and threats
WHO	World Health Organization

1. Background

Implementation of the Thirteenth World Health Organization (WHO) General Programme of Work (2019–2023) (1), as adopted by the Seventy-first World Health Assembly (2018), and the WHO Leadership priorities (2), has attracted much international public health attention to the theme of universal health coverage and to increased access to safe and effective medical products.

Several World Health Assembly resolutions, including WHA67.20 (2014) (3), mandate WHO to provide support to its Member States in strengthening national regulatory systems for medical products. It recognizes that “effective regulatory systems are an essential component of health system strengthening and contribute to better public health outcomes, that regulators are an essential part of the health workforce, and that inefficient regulatory systems themselves can be a barrier to access to safe, effective and quality medical products” (3). Accordingly, to facilitate access to these products, WHO’s vision is for all Member States to have an effective regulatory system that ensures

medical products and other health technologies in the market meet internationally recognized standards of quality, safety and efficacy.

National regulatory authorities (NRAs) are responsible for ensuring the safety, quality and efficacy of medical products within their respective Member States; demonstrating that the services they provide consistently meet legal and regulatory requirements; delivering effective and efficient services; evaluating performance; and making improvements. An effective quality management system (QMS) can help to ensure that the products or services an NRA provides consistently meet statutory and regulatory standards and meet customers' expectations. A QMS provides opportunities to enhance customer satisfaction; address context-associated risks and opportunities for continued improvement; demonstrate conformity to specific QMS requirements; and assure the quality, safety and efficacy of medical products.

In 2015, WHO developed and launched the *WHO Global Benchmarking Tool* (GBT) (4). This tool assists WHO and regulators worldwide in evaluating the maturity and performance of regulatory systems and related functions. The GBT includes one indicator that assesses the NRA's level of development with respect to a QMS (4). Benchmarking results of low- and middle-income countries indicate that the majority of NRAs need to establish and implement a QMS or, if already established, enhance and maintain the QMS.

QMS implementation is challenging for NRAs, owing to the diversity of NRA legal mandates and organizational structures; the different levels of NRA development; and the number of regulatory functions that need to be implemented. WHO has developed this guideline to respond to requests by Member States for an international guideline on implementation of QMSs by NRAs.

2. Objectives

The aim of this guideline is to assist NRAs to develop, implement and improve their QMSs, based on principles from International Organization for Standardization (ISO) document ISO 9001 standard requirements (5). It provides recommendations on what NRAs should implement and maintain under each QMS to effectively and efficiently support the execution of NRA functions as mandated by national laws and regulations. The guideline is expected to promote consistency in regulatory practices within and across NRAs, to facilitate harmonization, mutual reliance and recognition mechanisms among Member States.

Therefore, the objectives of the guideline are as listed next.

1. Describe principles for implementing a QMS to support planning, execution, monitoring and evaluation (M&E) of the performance of all applicable functions and activities of an NRA.
2. Provide requirements for the QMS to support and facilitate systematic linkages and integration of different processes and systems of the regulatory functions and activities within an NRA.

- c) Provide requirements that NRAs should consider for evaluating the performance of the QMS and measures that the NRA should implement for continually improving the QMS.

3. Scope

This is an overarching guideline that should be applied across all regulatory functions and activities, including registration and marketing authorization; vigilance; market surveillance and control; licensing establishments; regulatory inspections; laboratory access and testing; clinical trials oversight; national lot release; and others, as applicable to the implementing NRA. The guideline should be implemented to cover all types and categories of medical products and other health technologies under the responsibility of an implementing NRA. All other existing or future guidelines for QMSs for specific regulatory functions will complement this guideline.

The guideline can also be used for other regulatory activities that are mandated by the national laws and regulations to ensure public health safety, by assuring the quality, safety and effectiveness of medical products. This extends to areas of medical products such as pricing, professional training and regulation, as well as to other areas within the legislative mandates and functions of the NRA.

This guideline on QMS implementation can also be used for all models of NRA. NRAs can be legally, organizationally and operationally structured as follows:

- **discrete:** two or more institutions involved in partial or full enforcement of national laws and regulations for medical products in a country (e.g. one institution with legal mandates to enforce marketing authorizations and another one within the same country for licensing establishments' regulatory function);
- **decentralized:** one NRA with full legal mandates to enforce national laws and regulation of medical products within the country. A legally defined amount of enforcement, authority and operations is executed in localized zones or geopolitical zones of the country, while the rest is enforced at country level. This model exists in Member States with a federal governance system where laws and regulations are enforced at state/province and national levels; and
- **centralized:** one NRA with full legal mandates to enforce national laws and regulation of medical products within the country. The enforcement, authority and operations are executed, managed and controlled centrally for all applicable regulatory functions and activities.

The guideline is equally applicable to small, medium and large NRAs, as the principles and intended results of a QMS remain the same, regardless of the complexity of

NRA. Therefore, this guideline describes the requirements that should be implemented; the MS and respective NRAs reserve the right to decide on how to address these requirements within the existing contexts and provisions of the laws. The guideline can be utilized by institutions that are responsible for single or multiple specific regulatory functions related to medical products.

Although the use of this guideline is voluntary, NRAs are encouraged to use it to facilitate implementation of their QMS. The implemented QMS should be demonstrated by documented evidence to have systematic processes that are controlled, maintained and evaluated for continuous improvement. NRAs are free to use any appropriate national or international standard or guideline on QMSs as a basis for the implementation.

Where different units within the NRA have already implemented a QMS for specific regulatory functions (such as laboratory testing and/or regulatory inspection), this guideline could be used by the NRA for those functions and processes that have not been addressed by the management systems already implemented. This is to avoid duplications and overlaps of management systems. It is expected that NRAs will gradually integrate all existing management systems within the overall QMS of the NRA. The implementing NRA could determine the extent to which this guideline should be implemented, without omitting any of its processes and activities that are mandated by national laws and regulations.

Effective implementation of this guideline will not lead to any WHO certifications and WHO will not conduct any audits for verification of implementation of a QMS. However, as part of the regulatory systems strengthening programme, WHO will conduct the benchmarking of the Member State's regulatory system and functions, including QMS-related processes, using the GBT (4) to determine the strengths and gaps, if any, for capacity-building and continuous improvement. This guideline should be implemented to cover regulatory functions that are part of the GBT, and other functions and activities of the NRA that are addressed by national laws and regulations but that are not part of the GBT. References to GBT revision VI (4) provides a linkage between GBT indicators and the relevant sections of this guideline (see Appendix 1).

The QMS using this guideline should be implemented on the foundation of the principles and recommendations on *Good regulatory practices* (GRP) (6). The implementation of the QMS should ensure that the GRP are integrated to the extent possible without affecting the effectiveness and efficiency of the NRA to execute its functions.

4. Glossary

The definitions given below apply to the terms used in this guideline that are not defined in existing WHO terms and definitions databases. They may have different meanings in other contexts.

competence. Knowledge, skills and attitude required for successful work performance.

correction. Any action that is taken to eliminate a nonconformity. However, corrections do not address causes.

corrective actions. Steps that are taken to eliminate the causes of existing nonconformities in order to prevent recurrence. The corrective action process tries to ensure that existing nonconformities and potentially undesirable situations do not happen again.

customer. A person or organization that could or does receive a product or a service that is intended for or required by this person or organization. Customers of an NRA include individuals or parties who receive or could receive and use products and services that are provided and offered by the NRA. These parties include the general public, patients, manufacturers, distributors, health practitioners, researchers, the ministry of health and other individuals and institutions that rely on the NRA's products and services to make public health decisions.

customer satisfaction. A customer's perception of the degree to which the customer's expectations have been fulfilled. This relates to the expectations that different parties have of the NRA. The expectations include assurance that safe, efficacious and high-quality medical products will be available under the NRA mandate to regulate, and that the NRA will provide other products such as guidelines, public reports and related regulatory services that meet the expectations of different types of customers.

internal audit. An examination and assessment of all or part of a QMS with the specific purpose of improvement. An internal audit should be conducted by an independent (i.e. of the function to be audited) team of competent auditors as designated by the management for this purpose.

process. A set of interrelated or interacting activities that use inputs to deliver an intended result. In the context of NRAs, the production and service provision processes should coincide with basic regulatory functions.

product. Output of an organization that can be produced without any transaction taking place between the organization and the customer. They are also called regulatory products in this guideline. Products of NRAs relate to the tangible items that the NRA produces for its customers. These items include regulatory guidelines; public health notices; guidance notes; alerts; databases; mobile phone applications; reports; and other materials that are intended to provide regulatory information and communications to customers. Before their production, some of these products may require lengthy consultations for designing them.

quality. The total set of characteristics of an entity that affect its ability to satisfy stated and implied needs and to ensure the consistent and reliable performance of services or products in conformity with specified requirements.

quality management system. An appropriate infrastructure, encompassing the organizational structure, procedures, processes, resources and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

quality policy. A brief statement that describes the organization's purpose, overall intentions and strategic direction; provides a framework for quality objectives; and includes a commitment to meet applicable requirements.

senior (top) management. Person(s) who direct and control an organization at the highest levels and who have the authority and responsibility to mobilize resources within the organization. In NRAs, the terms “senior management” or “top management” can be used interchangeably.

services. Output of an organization with at least one activity necessarily performed between the organization and the customer. Services of NRAs are also called regulatory services in this guideline. This includes, for example, activities such as evaluation of applications for market authorizations, inspections of facilities, testing of health product samples, etc.

5. Quality management system requirements for national regulatory authorities

5.1 Quality management system concepts

NRAs should implement a QMS that is supported by the process approach concept, plan–do–check–act (PDCA) cycle and risk-based thinking. NRAs should ensure that the implemented QMS meets its needs without making it unnecessarily complex, to avoid a negative effect on the NRA's effectiveness and efficiency. The QMS should be simple, fit for purpose and understandable.

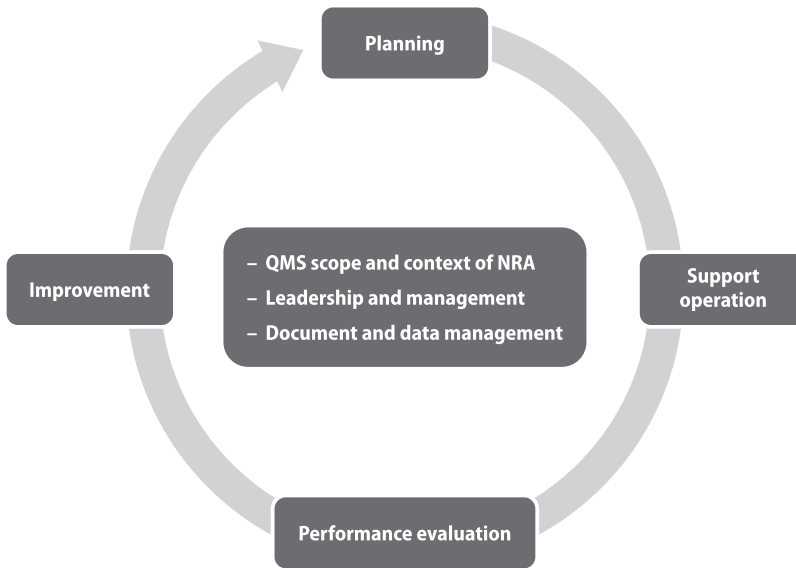
The PDCA cycle requires NRAs to carry out planning, performing (implementing), checking (evaluating) and acting (to improve) processes in the QMS. The applied PDCA cycle covering the chapters in this guideline is provided in Fig. A13.1. The ISO 9001 standard (5) provides a brief description of the PDCA as follows:

- **Plan:** establish the objectives of the system and its processes, obtain the resources needed to deliver results in accordance with customers' requirements and the NRA's policies, and identify and address risks and opportunities;
- **Do:** implement what was planned;
- **Check:** monitor and, where applicable, measure processes and the resulting products and services against policies, objectives, requirements and planned activities and report the results;
- **Act:** take actions to improve performance, as necessary.

Fig. 1

Applied PDCA cycle

NRA: national regulatory authority; PDCA: plan–do–check–act;
QMS: quality management system.



The scope of the QMS and context of the NRA are placed in the middle, to provide the limitations to which the QMS should be implemented.

Leadership and management are centrally indicated, as they are important requirements for effective QMS implementation. Top management should commit and support all QMS processes, from planning up to acting for continuous improvement.

Document and data management are centrally indicated, because they should be part of every step of the PDCA cycle, in the form of procedures, forms and records that facilitate the consistent implementation of QMS processes and record retention.

Applying risk-based approaches (included in planning stages) enables NRAs to identify factors that could cause QMS processes to deviate or that could prevent the planned results from being achieved; to put in place proactive measures and controls to minimize the impact of negative effects; and to leverage opportunities as they arise. Risk-based thinking is applicable and should be implemented throughout the PDCA cycle.

NRAs should implement a QMS that identifies and integrates other management system standards that are applicable to the processes. The management systems that are for specific areas and processes should be documented. The NRA should ensure that the management systems do not create duplications, overlaps or inconsistencies within the overall QMS. While other WHO guidelines have been implemented for management

systems of specific regulatory functions such as inspections and quality control testing, the overall QMS should be consistently implemented throughout the organization across different regulatory functions and other supporting areas.

QMSs are influenced by the different policies, objectives, diverse work methods, resource availability and administrative practices specific to each NRA. NRAs are free to decide the mode and routes to use when implementing this guideline, as long as the implemented QMS yields effective, consistent, transparent and reliable results in the regulation of medical products.

The QMS requirements that are described in this guideline are based upon the quality management principles presented next, as provided in ISO 9000 (7).

- **Customer focus:** the primary focus of a QMS is to meet customer requirements and to strive to exceed customer expectations. In this guideline, customer focus means meeting the needs and expectations of the public, patients, health-care practitioners, manufacturers, researchers and procurers, by providing regulatory products and services that assure access to high-quality, safe, effective and affordable medical products and health technologies.
- **Leadership:** leaders at all levels establish unity of purpose and direction and create conditions in which people are engaged in achieving the NRA's planned objectives.
- **Engagement (involvement) of people:** competent, motivated, empowered and engaged people at all levels throughout the organization are essential to enhance the organization's capability to create and deliver valued services.
- **Process approach:** consistent and predictable results are achieved more effectively and efficiently when activities are understood and managed as interrelated processes that function as a coherent system. This is critical, as it avoids having systems that are based on individuals within the NRA.
- **Improvement:** successful organizations have an ongoing focus on improvement. The NRA should ensure that it strives continuously to improve its processes, products and services and the QMS.
- **Evidence-based decision-making:** decisions based on the analysis and evaluation of data and information are more likely to produce the desired results. This requires NRAs to implement measures for monitoring, analysing and evaluating the collected data, to assess whether the processes are delivering the desired results.
- **Relationship management:** for sustained success, organizations should manage their relationships with relevant interested parties. Implementing an effective QMS requires the NRA to ensure that its relationships are managed strategically for continuous operations. The relationships include

management of contractual agreements for activities subcontracted to individuals and institutions. The areas with subcontract agreements would either be technical or administrative and, if not managed properly, may have negative effects on the effective implementation of the QMS.

5.2 Quality management system requirements

The QMS requirements described in the subsequent subsections describe what NRAs should implement as part of their overall QMS. Table A13.1 provides a summary and focus for each subsection.

Table A13.1

Summary of quality management system requirements for each subsection

Subsection	Summary of requirements for implementation of a quality management system
5.2.1 Introduction	The requirements of this subsection focus on the NRA describing and documenting the setup of its QMS. The setup includes: • legislative mandates and scope (functions) of the NRA; • standards and guidelines used in QMS implementation; • QMS implementation history; • integration (as applicable) with other management and software systems for personnel performance appraisals, finances and accounting, environment, occupational health and safety, workflow, customer relationship management, ministry of health policies and strategic action plans; • identification of the functions and processes that are already covered by other QMSs.
5.2.2 Scope of the quality management system	This subsection describes the requirements for NRAs to document the processes that are covered by the implemented QMS. All processes and activities that are done by the NRA as mandated by national laws and regulations should be included in the QMS. Implementation can be done at once or in phases.
5.2.3 Organizational context of the national regulatory authority	The focus of this subsection is to provide guidance regarding what should be indicated when describing and documenting the setup of the NRA with its regulatory system, functions and activities within the QMS. This extends to the model type (discrete, decentralized or centralized) and to the relationships with other institutions providing regulatory services for medical products and other health technologies. The context should also specify what to implement in the QMS to support the NRA in handling and managing internal and external issues within its regulatory mandates and functions, as well as meeting the needs and expectations of interested parties (i.e. customers and stakeholders).

Table A13.1 *continued*

Subsection	Summary of requirements for implementation of a quality management system
5.2.4 Leadership, management and organization	This subsection describes requirements for what should be expected from top management for effective implementation of the QMS. It also includes the roles, responsibilities and authorities that should be part of the implemented QMS.
5.2.5 Document and data management	This subsection provides requirements that should be applicable to internally generated documents and to those of external origins, including data. The requirements include development, review, approval, distribution, version and access control, storage, retrieval and disposition of documents.
5.2.6 Planning	This subsection focuses on planning requirements for achieving the set objectives, managing risks and opportunities across the NRA, and planning changes to the QMS for continuous improvement.
5.2.7 Support and resources	This subsection includes requirements for input resources (technical and non-technical), personnel and infrastructure needed for effective implementation of the QMS.
5.2.8 Operation	This subsection addresses the requirements for QMS implementation in core processes and activities that are within the mandates of the NRA. It also provides guidance on documenting operational linkages of processes and systems for effective and efficient QMS implementation.
5.2.9 Performance evaluation	This subsection provides methodologies and recommendations regarding what should be implemented by the NRA to facilitate accurate, objective and efficient performance monitoring, analysis and evaluation of operations indicators, QMS effectiveness, resources and customer satisfaction.
5.2.10 Improvement	This subsection presents requirements for NRAs to implement in the QMS to support continuous improvements based on collected, analysed and evaluated data.

5.2.1 Introduction

NRAs should have documented, available and accessible legislative laws and regulatory policies on medical products that describe the regulatory functions and activities that should be included in the QMS.

NRAs should list and maintain current versions and copies of national, regional and international management system standards and guidelines that are used for the QMS implementation.

NRAs should document the history and evolution of their QMS, to demonstrate the controls and management of changes in the system to ensure that it is effective for

the institution. The evolution and changes should be justified and related to any changes to the adopted national, regional and/or international management system standards and guidelines (e.g. the case of the *Compendium of quality management system (QMS) technical documents for harmonization of medicine regulation in the East African Community* (8)).

NRAs should ensure that all existing and already implemented management systems are integrated in the QMS. The integration should ensure that there are systematic, adequate and appropriate linkages between the overall QMS and the management systems for specific technical or administrative functions. The QMS should be integrated into the regulatory processes, to ensure that it helps the NRA to achieve its legal mandates and functions.

The NRA should identify the functions and processes that are already covered by other QMSs. This should be done to identify gaps and align specific management systems with the overall QMS of the NRA as much as possible, to ensure consistency and facilitate effective performance M&E. The management systems for specific technical and administrative functions and processes are described in the next subsections.

5.2.2 Scope of the quality management system

This guideline aims to provide guidance on implementing a sustainable and effective QMS based on adapted ISO 9001 standard (5) requirements, to address the needs of NRAs with respect to all regulatory functions, including administrative and supporting processes. The scope of the QMS should include functions, processes and the facilities where they are undertaken.

NRAs should ensure that the implemented QMS provides a clear statement of scope that specifies the functions and processes that are covered as mandated by the national legal framework. The scope should include all applicable regulatory functions that are provided in the current version of the GBT (4). In addition, the QMS should also cover all additional technical and administrative functions and processes that are part of the NRA's routine operations.

Where there is more than one institution that is partially or fully involved in the regulatory activities of medical products of a country, the QMS for each institution should support consistency, effectiveness, efficiency and systematic collaboration, to improve and strengthen coordination between institutions. The QMS should also include the technical and administrative functions and processes that are interrelated and interdependent for the effective undertaking of the affected regulatory function(s). The QMS should be clear on the scope for each involved institution, to ensure that there are neither gaps nor overlaps of the processes and activities.

When a specific unit of an NRA has implemented a QMS (e.g. a quality control laboratory, inspectorate or province/zone/state), the scope should be clear on the inclusions and exclusions (with justifications as applicable), without weakening operational linkages and interdependencies for timely and effective regulatory decision-making.

The scope statement of the implemented QMS should be documented and supported by a relevant national legal framework and by current best practices of the affected functions and processes.

5.2.3 Organizational context of the national regulatory authority

5.2.3.1 Understanding the national regulatory authority organization and its context

The NRA should demonstrate that it understands its organizational and operational context within the country's regulatory framework as part of national health system. The organization should understand the context under which it provides the regulatory products and services, which may be through using a discrete, decentralized or centralized type of organizational structure. This understanding facilitates the identification and management of internal and external issues relevant to its ability to achieve the objectives as defined in the NRA's strategic plans.

The NRA should document the context in which it exists and in which it has been given the legal mandate to perform regulatory functions that are within the scope of the QMS. The context should indicate the limitations of the NRA and the relationships with other institutions that are part of its routine operations.

The documented context of the NRA should clearly indicate the technical and administrative areas that are not exclusively under the control and management of the NRA. This could include areas such as personnel recruitment, management of finances, procurement, and management of equipment and infrastructure.

Determination and documentation of internal and external issues should be integrated in the regulatory processes of the NRA, based on the needs and expectations of customers and stakeholders. The determination of internal and external issues should also be linked to the development of a strategic plan to ensure that the implemented QMS helps the NRA achieve the objectives.

Internal and external issues can change (e.g. changes to laws or regulations, or procurement, changes in national labour laws, or changes to professional practice regulations), and therefore they should be monitored and reviewed. The NRA should conduct and document reviews of its organizational context at planned intervals, and whenever there are changes to the legal framework or when there are organizational or structural changes.

NRAs should understand the context, as well as the internal and external issues that provide the foundation and inputs for determining a strategic plan; scope of the QMS; quality policy; quality objectives; and related risks and opportunities.

NRAs may use national legal provisions to identify different types of interested parties (customers and other stakeholders) for the regulatory products and services that are provided. Where customers and other stakeholders are defined in the national laws and regulations, this would be sufficient, as long as all outputs and services provided by the NRA are addressed. This identification helps NRAs to separate other stakeholders

from customers who should also be the focus of the QMS. NRAs should focus on all interested parties that can affect its ability to achieve the quality objectives. In addition, these interested parties should be categorized, along with their respective needs and expectations of the NRA that the implemented QMS is designed to support.

NRAs should have a robust and defined system in place to monitor, review and document the relevant requirements of interested parties at planned intervals.

5.2.3.2 Quality management system processes

NRAs should ensure that inputs and resources that are required to perform the processes and functions covered in the QMS scope, with expected outputs, are determined, documented and provided. NRAs should document the sequences and interactions of regulatory processes, together with related measures and criteria for their control (e.g. key performance indicators). The level and type of controls that are applied to the regulatory processes should be determined and documented with a risk-based approach and should utilize the available opportunities. The QMS should provide procedures for evaluating the processes and allow for the implementation of corrective actions under a controlled and managed change process. This should facilitate continuous improvements of the processes and the entire QMS.

The QMS should be integrated in the regulatory functions and processes, to ensure that the personnel who are assigned with responsibilities and authorities in performing regulatory and administrative activities have the required competencies.

5.2.4 Leadership, management and organization

5.2.4.1 Commitment of top management

Top management of the NRA should demonstrate leadership and commitment towards the effective implementation and sustainability of the QMS within the national legal framework, through continual identification of the needs and expectations of its customers. The following are responsibilities of top management with respect to a QMS:

- providing needed resources for the implementation of an effective QMS that is consistently implemented across the NRA units, functions and processes;
- integrating QMS requirements into the regulatory processes and aligning the quality policy and quality objectives with the strategic plans of NRAs;
- implementing a QMS that incorporates a risk-based approach and that is based on functions and processes rather than being built around individual personnel or specific activities;
- communicating the importance of the QMS, to maintain consistency in NRA functions and to improve the effectiveness and efficiency of the QMS;

- engaging, supervising and supporting all NRA personnel to contribute to the implementation and effectiveness of the QMS and to ensure that the NRA achieves the intended expectations; and
- reviewing the performance of the QMS and promoting improvements.

Top management should ensure that the risks and opportunities that can affect the ability of the NRA to provide products and services of the quality expected by customers are determined and documented. Top management should also ensure that the NRA implements measures to enhance customer satisfaction. To increase customer satisfaction, innovation and best practices may be introduced into the NRA's processes, with the appropriate determination of related risks and practicality.

5.2.4.2 Quality policy

Top management of NRAs should establish, implement and maintain a documented quality policy that contains actionable and practical statements that:

- take into consideration the organizational context and strategic directions and plans and provide a framework for setting quality objectives;
- include a commitment to comply with applicable national legislation, as well as regional and global regulatory requirements and best practices;
- include a commitment to continual improvement of the QMS; and
- include a commitment to adopt and implement GRP, as provided in the *WHO good regulatory practices: guideline for national regulatory authorities for medical products* (6).

Top management should communicate the quality policy to all NRA personnel and ensure that the personnel have read, understood and applied it within their respective activities. Where applicable and appropriate, controlled copies of the quality policy should be available to customers and stakeholders, through established document control procedures as per QMS requirements.

5.2.4.3 Roles, responsibilities and authorities

To effectively implement the QMS, top management should assign and document roles, responsibilities and authorities, and should ensure that this information is communicated and understood within the NRA. Depending on the organizational context of the NRA and on the scope and complexity of the QMS, top management should assign the following responsibilities and authorities to one or more job function:

- ensuring that the QMS of the NRA conforms to the requirements of the adopted standards and guidelines;

- ensuring that the integrated QMS and regulatory processes are delivering their intended results as per action and strategic plans of the NRA;
- monitoring and reporting on the performance of the QMS and proposing opportunities for improvements to top management;
- ensuring the promotion of customer focus throughout the NRA, while assuring the quality, safety and efficacy/effectiveness of health products; and
- ensuring that the integrity of the QMS is maintained when changes (e.g. legislative, process, organizational or structural) to the QMS are planned and implemented.

Top management should ensure that the job function(s) to be assigned the above responsibilities and authorities have the necessary competencies and have direct access to and are accountable to top management.

5.2.5 Document and data management

NRAs should have the guidelines, policies and procedures that are necessary for the effective implementation of the QMS within the legislative provisions.

QMS documents should include, but are not limited to, internally and externally generated hard copy and/or soft copy formats of regulations, drawings, policies, guidelines, strategic plans, action/work plans, manuals, procedures, registers, logbooks, databases, spreadsheets, templates and forms, codes of ethics and professional conduct, inventories, checklists and all other documents that are used in the technical and administrative activities of NRAs.

QMS documents should include internally and externally generated evidential documents (e.g. records, files and reports) in hard copy and/or soft copy formats, which are retained by NRAs.

NRAs should consider all published materials, either on intranets or websites or in newsletters and other forms of publication, to be part of QMS documents and covered by the requirements of this guideline.

Within the QMS, NRAs should implement policies and procedures for identifying, describing, formatting, reviewing, approving, controlling (e.g. distribution, access and version control, retrieval and use), retaining and disposing of internally generated documents. QMS documents of external origin (e.g. regulations, standards, pharmacopoeia and WHO guidelines) should be subjected to the same requirements as for those that are internally generated, to the extent possible and practical, depending on the nature and intended use.

Where information technology (IT) is utilized to optimize regulatory processes for technical and administrative functions, NRAs should ensure that the system templates, forms and software that are used are identified, reviewed, approved,

controlled and maintained under the same QMS policies and procedures that apply for other documents.

NRAs should implement a data management, protection (i.e. confidentiality, loss and integrity) and retention policy/procedure, to define clearly the types and categories of collected, analysed, evaluated and retained data. The policy/procedure should provide clear requirements for the format, medium and duration of retention for data and documents. In addition, there should be a policy/procedure for NRAs covering the maintenance and retention of all documents and data.

5.2.6 Planning

5.2.6.1 Quality management system planning

NRAs should plan and document how they will meet the needs and expectations of their customers and stakeholders, as stipulated in the national laws and regulations. The plan should include all technical and administrative functions, processes and activities of the NRA and their respective objectives.

5.2.6.2 Action to address risks and opportunities

When planning for the QMS, the NRA should consider the issues (internal and external) and requirements of the stakeholders and determine the risks and opportunities that need to be addressed in the context of the organization. The NRA should plan actions to address these risks and opportunities, with assigned roles, responsibilities and authorities. The planned actions should include a framework for monitoring and evaluating the effectiveness of the actions taken. The NRA can choose the methods of risk management that suit its needs. Depending on the size, complexity and regulatory functions of the NRA, principles can be based on the WHO guidelines on quality risk management (9) and the ISO 31000 standard (10).

5.2.6.3 Quality objectives and planning to achieve them

NRAs should establish quality objectives for relevant regulatory and administrative functions, for all levels and sections of the NRA and for all processes needed for the QMS. Where quality objectives are established for multiple levels within the NRA (e.g. directorate, department, unit or zone), the objectives should be consistent, to ensure that all levels contribute towards achieving the overall expectations from legal mandates and of customers. The quality objectives should be integrated with regulatory objectives, to ensure that the QMS supports the consistency, effectiveness and efficiency of the NRA.

Quality objectives of the NRA should be consistent with its quality policy; should contribute to customer satisfaction; and should be relevant to the regulatory products and services as mandated by the national legal framework.

To the extent possible, quality objectives should be specific, measurable, attainable, realistic and time-bound (SMART). The QMS should provide the measures

for the NRA to communicate the objectives to designated audiences within the NRA and the means to monitor and update the objectives.

The QMS should include a plan to ensure that the set objectives will be met. The planning exercise includes determining the actions that will need to be taken; the resources that will be required (e.g. human and financial to purchase equipment and the required supplies); the responsibilities that will be assigned to staff for specific tasks; the timelines that will be defined for completion of each step; and the means that will be used for monitoring and evaluating whether or not the objectives have been achieved.

5.2.6.4 Planning of changes

The NRA should plan for changes to the QMS. The purpose of planning changes is to maintain the integrity of the QMS and ensure the NRA's ability to provide conforming regulatory products and services during any changes. For any change, the NRA should consider the availability of resources and necessary allocation or reallocation of responsibilities. This could be done by implementing an effective change management process within the QMS.

The need for changes can result from changing needs of customers and other relevant interested parties, for example, new products to be evaluated to grant market authorization; availability of new information and communication technologies (ICTs) for a service or process; a move to outsourcing of important processes; departure of persons in key roles (e.g. due to retirement or job change); or a move to online service provision.

5.2.7 Support and resources

5.2.7.1 Resources

NRAs should determine, document and provide the resources that are needed to establish, implement, maintain and continuously improve the QMS. The determination should be done within the organizational context of the NRA and the scope of the legal mandates on the functions and activities. NRAs should also determine and document those technical and administrative resources that need to be provided by external providers (companies and individual experts).

5.2.7.2 Personnel

NRAs should determine, provide and document the personnel and their required minimum competencies necessary for effective implementation of the QMS and for effective operation and control of its processes. A focal person or lead may be appointed to coordinate and monitor the implementation of the QMS at appropriate levels and functions.

The competencies of all personnel should include a combination of appropriate education, professional training, experience and behavioural attitude, as deemed

necessary by the NRA. Where the assigned personnel with defined responsibilities and authorities do not have all the competencies, training plans should be developed and implemented, with appropriate evaluation criteria for acquired competencies.

For the purposes of consistency of the QMS, NRA training plans for the rest of the technical and administrative personnel and functions should be based on the competency framework or matrix and/or performance appraisal system coordinated by human resources departments.

Records of evidence of an employee's competence, including educational diplomas or degrees; completion of training certificates; resumé; performance reviews; licences; and other documents should be retained.

The competency framework or matrix should be used in assigning official and non-official job function hierarchies and relationships (e.g. junior officer, senior officer or head of unit). The framework should also include the procedure for designation or qualification of technical officers (e.g. senior or lead assessor, senior or lead inspector, senior or lead analyst); these should be supported by requalification procedures.

5.2.7.3 Infrastructure and work environment

NRAs should determine, provide and maintain a documented list of infrastructures needed for technical and administrative processes in the execution of the legal mandates. Lists of the following should be maintained to allow for identification, location, type, quantities, versions, operational status (i.e. in use versus not in use) and plans for qualification, validation, calibration and maintenance (as applicable):

- buildings and associated utilities;
- technical (e.g. inspection and testing equipment) and administrative equipment (e.g. servers, computers, and printers), including hardware and software;
- transportation and logistical resources; and
- ICT.

NRAs should determine, provide and maintain the human and physical factors of the work environment necessary for the operation of technical and administrative processes and activities within the context of the organizational structure and national legislation. To the extent that it is practical, the environment should address social, psychological and physical (i.e. workspace) conditions to promote work–life balance. Depending on the activities of the NRA, applicable occupational, health and safety policies and procedures should be considered for implementation, as provided in ISO 45001 (11).

The NRA and its units should implement and document a policy and procedure on the management of waste that is generated. The waste management should be conducted within the recommendations and applicable requirements of the current version of ISO 14001 (12).

5.2.7.4 Monitoring and measuring resources and equipment

NRA should determine and document a list of monitoring and measuring resources and equipment used, to ensure that the regulatory products and services meet the expected requirements. The equipment should be suitable for the measurement activity to be undertaken, and maintained to ensure continued fitness.

For the equipment, including software, that is used in technical measurements (e.g. inspection and laboratory equipment), NRAs should ensure that the results obtained from such equipment are valid and that the calibration of equipment is traceable to national or international measurement standards. The calibrated equipment should be identified with its calibration status and safeguarded from adjustments, damage or deterioration.

In the event of measuring equipment being found to be out of calibration, NRAs should evaluate and document the validity of previous measurement results obtained from the equipment, and take appropriate actions.

5.2.7.5 Organizational knowledge management and awareness

The NRAs should consider how to determine and manage the organizational knowledge required to meet the NRA's present and future needs. Individuals and their experience are the foundation of organizational knowledge. Capturing their experience and knowledge can generate synergies leading to the creation of new or updated organizational knowledge. In determining, maintaining and making organizational knowledge available, NRAs can benefit by (i) learning from failures and successes; (ii) gathering knowledge from stakeholders, experts and partners; and (iii) capturing existing internal knowledge.

The tools for maintenance and distribution of organizational knowledge can include the intranet, libraries, awareness sessions, newsletters and others.

NRA should ensure that all personnel (both full-time and part-time) have read and understood the quality policy and the quality objectives that are relevant to their level in the organization. This should be documented to verify that personnel understood their contributions to the effectiveness of the QMS and the benefits of improved performance. NRA personnel should be aware of the implications of not following policies and procedures established under the QMS, for example, the release to customers of non-conforming regulatory products.

5.2.7.6 Internal and external communication

NRA should determine, implement and document internal and external communication policies and procedures within the QMS. The policy should clearly describe "what" to communicate, and define responsibilities and authorities for communication to the assigned competent personnel. Depending on the context, nature and intent of the communication, the policy should describe the level, audience and frequency of the

communication, including the format and medium (e.g. verbal, letter, mail, website or intranet). Social media and mobile applications are additional tools for communicating with interested parties.

The communication policy and procedure should be implemented within the legal framework of the NRA and related national (governmental) procedures and practices.

5.2.8 Operation

NRAs should ensure that planning of technical and administrative processes is done effectively, as provided under Section 5.2.6 for all operations within the scope of the QMS.

5.2.8.1 Customer communication and review of the regulatory products and services requirements

NRAs should ensure that there is a process of consistent communication with customers and stakeholders to collect their feedback, inputs and other inquiries that may be useful for reviewing the pertinence of the offered regulatory products and services. The details of the regulatory products and services offered, including contingency requirements (such as those applied during natural disasters or epidemics), should be publicised (e.g. through the NRA website, pre-submission meetings, or scientific advice), so that customers are aware of the requirements for submissions to the NRA relating to regulatory products and services.

NRAs should ensure that the requirements and expectations for the products and services are determined and defined within the applicable national laws and regulations. To promote public transparency and accountability, the product and service requirements may include fee schedules and delivery timelines for product market authorizations, licences, reference standards (e.g. pharmacopoeia), permits and certificates. This information may be included in the national guidelines and guidance notes and should be publicly available to customers and stakeholders.

NRAs should ensure through a review process that requests for services received from customers are complete and in conformity with service requirements. A checklist used for such reviews should be documented. When there is a difference between the requirements for products or services as requested by the customer and the requirements prescribed by the NRA, this should be communicated to the customer and resolved before processing the request. Any verbal request or change in the requirements, either by the NRA or by the customer, should be confirmed before services are processed.

When the requirements for products and services are changed for any reason, NRAs should take measures to inform all relevant interested parties. They should retain evidence of the results of the revisions to the requirements of products and services, and any new requirements for the products and services that are provided.

5.2.8.2 Design and development of new products and services

When NRAs plan on implementing new regulatory function(s) due to revision of the national legal framework, or wish to introduce new regulatory products and/or services (such as through mobile phone application), the following process steps should be followed:

1. Determine and document the process(es) that will form part of the new function, including the stages, steps and control measures needed through implementation roadmaps or projects. The determination should include expected reviews, verifications and validations that the processes are sufficiently robust for the intended function. NRAs should also determine and document the competencies, responsibilities and authorities of the project development team. Where the NRA would not be able to provide all the required resources, the NRA should document those resources that will be externally sourced. NRAs should determine the need to involve customers, stakeholders and internal personnel to ensure that key inputs are collected. NRAs should also assess whether any of the existing requirements (e.g. timelines or schedule of fees) are applicable to the new regulatory function, or whether there is a need to establish additional ones. All documents used and generated out of these roadmaps should be retained in an appropriate format and medium.
2. Once the implementation roadmap has been completed, NRAs should determine and document the inputs, such as performance indicators, national legal requirements for compliance, and codes of ethics and professional conduct, as well as the potential consequences of failure, using a risk-based approach.
3. As defined in the implementation roadmaps, intermediate reviews (where practical and possible), verification steps (i.e. comparing the new application/process with a similar proven application/process) and validation exercises (i.e. testing under intended user conditions) should be conducted by NRAs, to ensure that the resulting function or product meets the requirements for the intended use.
4. The expected outputs of the design and development process will be in the form of standard operating procedures or service provision manuals that give the information necessary for all the processes required to provide intended products and services, including information to be provided by the customers.
5. Where changes are to be made in the new application or to the developed products or process(s), these changes will be identified, reviewed and controlled. A risk-based change management procedure should be documented and implemented.

5.2.8.3 Externally provided products and services

NRAs should ensure that externally provided products and services (e.g. subcontracted ICT support, purchased reference standards, or subcontracted quality control laboratory testing) required for technical and administrative functions and activities of the NRA, conform to the QMS requirements. Where national laws and regulations exist for managing the use of public NRA funds in procurement, for example, a national public procurement act, with procedures based on amount thresholds for either single sourcing or open/closed bid competitions and decision levels (i.e. director-general, council, or board level), the QMS should not duplicate any procedures that are provided for public procurements. However, the NRA should ensure that the public procurement procedure conforms to the requirements described in the subsequent paragraphs of this subsection and should close gaps, if any. The NRA should also implement these requirements when it performs direct procurement.

NRAs should ensure that competence criteria are defined, documented and implemented for the evaluation, selection, performance monitoring and re-evaluation of external providers and suppliers (e.g. NRAs having documented, well-defined and transparent criteria for the selection and performance monitoring of external non-staff experts).

When NRAs must perform in-house prequalification of providers, there should be a documented procedure and policy on the competence criteria for evaluation, selection, performance monitoring, and requalification. The prequalification and requalification should focus on the competence of the individual persons and the institution or company to provide the products and/or services that meet applicable QMS requirements.

NRAs should implement measures for ensuring that the externally provided products and services do not adversely affect the organization's image and ability to consistently deliver the products and services to the customers.

The NRA should determine which specific controls are to be implemented for an external provider, and for incoming products and services provided by them. Control activities that may be considered include inspections, certificates of analysis or testing, second party audits, evaluation of statistical data and key performance indicators.

The NRA should clearly communicate the requirements and controls to be applied to the external provider, and both parties should agree as to what is required. This understanding of requirements is usually reflected in a technical service agreement, or through a purchase order or contract. The NRA should ensure that the requirements communicated to the external providers are complete and clear and address any potential issues.

5.2.8.4 Service provision

NRAs should carry out their technical and administrative functions for processing requests for services under controlled conditions. The controlled conditions should include, as applicable, the points listed next:

- use of guidelines, policies and procedures that provide the requirements for the regulatory products and services, including those for performance of activities;
- NRAs should document and implement measures for reviewing (peer-review or quality assurance [QA] review), approving and releasing the output of intermediate processes, to ensure that there are adequate controls for those activities that are involved in providing conforming products and services. For this purpose, the following guidelines should be considered for adoption and implementation, as applicable and to the extent necessary:
 - for technical processes involving review of application documents for marketing authorization for the assurance of quality, safety and efficacy, procedures and recommendations this includes, among others: *Good review practices: guidelines for national and regional regulatory authorities* (13); *Regulation and licensing of biological products in countries with newly developing regulatory authorities* (14) and *WHO guidelines on evaluation of similar biotherapeutic products (SBPs)* (15);
 - where the NRA has a unit responsible for good practices inspections, recommendations and technical requirements: *WHO Quality management systems requirements for national inspectorates* (16);
- as required, monitoring and measuring resources and equipment should be available and in use, to ensure that the processes are effective and controlled. Where measuring equipment must be used in providing regulatory services of the NRA laboratory, technical requirements and recommendations from the following guidelines should be considered for adoption and implementation, as applicable and to the extent necessary:
 - *WHO good practices for pharmaceutical quality control laboratories* (17) for physicochemical testing and *WHO good practices for pharmaceutical microbiology laboratories* (18) for microbiological testing. These two WHO guidelines can be supported and complemented with the current ISO/IEC 17025 standard (19) and the European Directorate for the Quality of Medicines and HealthCare (EDQM) *Quality management documents* (20);
- NRAs should ensure that the provided infrastructure and working environment are suitable for the operation of both technical and administrative processes and activities and for the performance of applicable regulatory functions; and

- NRAs should ensure that the appointment of personnel is based on the required competencies and qualifications and is described and documented in respective units. This should include the implementation of control measures to avoid or reduce human errors through peer- and QA reviews.

NRAs should document and implement policies and procedures on the unique identification and traceability of released regulatory products and services. As far as practical and possible, these should also be supported by systematic measures to facilitate traceability of the products and services to the equipment, software, personnel and location used by the NRA.

5.2.8.5 Property belonging to customers or external providers

NRAs should implement measures to verify, protect and safeguard properties that belong to customers and stakeholders, including providers, and avoid their loss, damage and any effects that would make them unsuitable for use. This can include properties, for example, that may have been seized and quarantined or used as input for making regulatory decisions. Examples of property include marketing authorization product dossiers, quarantined products, samples for testing, intellectual property and personal data.

The NRAs should determine those products and services (e.g. seized drugs, drug samples collected for analysis, vaccines under release, licences, market authorizations, permits or certificates to be issued) that can deteriorate or degrade, and implement appropriate storage conditions.

5.2.8.6 Release and compliance control of products and services

NRAs should document and implement practical procedures on the release of regulatory products and services through all stages up to and including the customer. The release process includes defining the responsibilities and authorities of the involved job functions. These processes should provide an internal QA procedure to ensure that the released products and services comply with all planned requirements.

NRAs should document and implement procedures for control of nonconformances and deviations that are observed or reported. If the nonconformity is discovered after the product has been delivered to the customer, the NRA should take appropriate actions to prevent unintended use or undesired consequences, and take measures such as issuing a recall or suspension. The QMS should not duplicate any existing procedures in technical units, such as a laboratory or inspectorate.

5.2.9 Performance evaluation

5.2.9.1 Monitoring and measurement

NRAs should conduct monitoring, measurement, analysis and evaluation of all planned technical and administrative activities, to determine whether the intended

results, as defined in action plans, workplans or strategic plans, are being achieved. NRAs should define what needs to be monitored and measured (e.g. characteristics of processes, products, services and potential risks) and the methods to be used for monitoring, measurement, analysis and evaluation of the performance and effectiveness of the QMS. The monitoring, measurement, analysis and evaluation of the NRA performance should be linked to the planned key performance indicators (or simply indicators), as applicable. The establishment and implementation of the indicators should be as practical as possible, to ensure that value is added through monitoring, measurement, analysis and evaluation activities. Therefore, the indicators or key performance indicators should have clear, relevant, economic, adequate and monitorable (CREAM) attributes. NRAs should determine and document the frequency of M&E of the indicators, from the implemented action and activity plans, as well as from the performance and evaluation of the QMS. NRAs should ensure that the M&E framework is consistent across different units, levels and functions of the organization. The framework should be documented and aligned with the relevant quality objectives (strategic objectives) of the NRA.

5.2.9.2 Monitoring of customer satisfaction

The NRA should develop methods to systematically seek feedback from a selected population of customers, or from every customer at planned intervals. Means to obtain feedback is provided by social and published media such as websites and message boards, opinion surveys and compliments, suggestions or complaints. The NRAs should determine the degree of customer satisfaction after the results of feedback are analysed and evaluated and then act based on this information.

NRAs should document, implement and publish comprehensive policies and procedures on handling of complaints, in order to provide guidance to customers and stakeholders on complaint submission, investigation, resolution, appeal and communication within the national legislations. The procedures should define the roles and responsibilities of a complainant and the NRA and specify timelines to effectively manage complaints related to regulatory products and services.

5.2.9.3 Analysis and evaluation

NRAs should analyse and evaluate monitoring and measurement data and information, to determine summary performance results of the following:

- compliance of regulatory products (e.g. guidelines and software applications) to quality and validity requirements;
- compliance of regulatory services to quality and timeline commitments and requirements;
- degree of customer satisfaction;

- performance and effectiveness of the QMS for the overall NRA and/or the QMS for NRA units or functions and the need for improvements to the QMS;
- level of implementation of action or activity plans and strategic plans at the time of reporting;
- effectiveness of the actions taken to address risks and opportunities (such as strengths, weaknesses, opportunities and threats (SWOT) analysis); and
- performance of external providers (including external technical experts).

5.2.9.4 Internal audit

NRAs should plan and conduct internal audits (at least once a year), to verify compliance to the QMS requirements across the organization and to verify that the QMS is effectively implemented and maintained. An internal audit programme should have defined planning requirements, frequencies, methodologies, responsibilities, competencies and reporting. Each internal audit programme should take into consideration the importance and associated risks of the processes to be audited, the internal and external changes affecting the NRA, and the results of previous audits, in order to:

- define the audit requirements for the criteria (QMS requirements) of compliance; scope (functions and departments to be audited); and methodology (interviews, examination of records, results, and trends) for each audit. The criteria for compliance may add and implement a scale for reporting observations (critical, major and minor), which should be clearly and objectively defined within the internal audit programme;
- select appropriately trained, qualified and competent auditors who can conduct the audit objectively and impartially. The impartiality can be achieved by employing auditors that audit those processes in which they are not involved while serving in the NRA;
- ensure that the internal audit reports are submitted to top management for actions;
- take appropriate corrections and corrective actions without delay and within timelines defined by top management. Where corrective actions are delayed due to unavailability of required resources, appropriate risk management plans should be implemented and documented; and
- retain records of internal audit programmes and internal audit reports, including records of corrections and corrective actions.

Further technical guidance on managing and performing internal audits can be adopted from the current version of ISO 19011 (21).

5.2.9.5 Management review

Top management of NRAs should review the QMS at planned intervals (i.e. at least once a year), to ensure its suitability, adequacy, effectiveness and alignment with the strategic direction of the organization as per strategic plans. Ideally, top management should review the QMS alongside the review of the NRA's regulatory plans (activity, action or strategic plans). This will ensure that the QMS remains integrated into regulatory processes effectively.

QMS reviews should consider inputs as provided in Table A13.2, with the listed expectations of the outputs to be presented in the minutes of the meeting (report).

Table A13.2
Inputs and outputs for review meetings

Inputs (to be reviewed)	Outputs
Status of actions from previous reviews Changes in internal and external issues that are relevant to the QMS Information on the performance and effectiveness of the QMS, including trends in: - customer satisfaction and feedback from stakeholders; - the extent to which quality objectives have been achieved; - performance on compliance to commitments and requirements for regulatory products and services; - nonconformances and deviations, and the status of implemented corrective actions; - results of M&E of indicators/key performance indicators; - results of internal and external audits; and - performance of external providers (including external technical experts) Adequacy of resources (financial, human, equipment and infrastructure)	- Decisions and actions related to opportunities for improvements - Decisions and actions related to changes required to the QMS - Actions on additional resources needed to implement improvement initiatives and suggested changes in the QMS and in other areas where resources (including human resources) are not adequate - Actions to implement for achievement of quality objectives - Responsibilities for follow-up of actions on the decisions taken in the meeting
Effectiveness of the actions taken to address risks and opportunities (such as SWOT or similar analysis) Opportunities for improvements of the QMS	Management review meeting minutes to be retained as records or reports and communicated appropriately to internal and external customers and stakeholders as per NRA communication policy

M&E: monitoring and evaluation; NRA: national regulatory authority; QMS: quality management system; SWOT: strengths, weaknesses, opportunities and threats.

Management review agenda (inputs) and meeting minutes should be retained as records or reports and communicated appropriately to internal stakeholders as per NRA communication policy.

5.2.10 Improvement

There are different methods to conduct improvement, such as correcting existing nonconformities and deviations and taking actions to prevent recurrence, or conducting ongoing, small-step improvement activities based on opportunities identified either through risk analyses or breakthrough projects. These improvement activities can lead to innovation, revision and/or improvement of existing processes, or to the implementation of new processes.

NRAs should implement and document measures to record and react to nonconformances and deviations by taking actions to control and correct them, including with related plans for managing related activities, if any. In addition, NRAs should conduct a root cause analysis (RCA) and evaluate the need to act in order to avoid recurrence of the nonconformances and deviations in the affected area, as well as in any similar processes in the organization in which such nonconformances or deviations could occur. The steps involved in this process are:

- reviewing and analysing the nonconformance or deviation;
- determining, to the extent possible, the cause(s) of the nonconformance or deviation; and
- determining whether similar nonconformances exist or could potentially occur within the affected unit or function and/or other units of the NRA or functions that have similar processes.

After implementing the corrective action, NRAs should review and document the effectiveness of the corrective action taken through practical means, including during future internal audits that look for a recurrence of the same nonconformity. The results of the RCA and the implemented corrective actions should be used to update the risk and opportunity planning, as applicable. Where corrective actions lead to changes to the process(es), NRAs should plan for similar changes to the QMS, supported by a defined change management plan. NRAs should define the communication of reports on nonconformances and corrective actions to internal and external customers, as defined in the communication policy/procedures.

For technical and administrative processes, NRAs should ensure that the handling of nonconformances, deviations and corrective actions is consistent across the entire organization. Nonconformances and deviations that are related to professional misconduct of NRA personnel should be handled in accordance with conditions of employment and service, including related national legal provisions.

Improvement can include actions to reduce process variation; increase the consistency of process outputs, products and services; and improve process capability.

This should be done to enhance the NRA's performance and give benefits to its customers and stakeholders. The results from performance monitoring and evaluation and management reviews should be used to decide which continual improvement actions should be implemented and what resources and support should be provided for their implementation by top management.

6. Quality management system implementation methodology

6.1 Supporting factors for quality management system implementation

Full commitment of the head of the NRA and the heads of technical, support and administrative units (i.e. top management) is necessary for effective implementation and maintenance of the QMS in NRAs. This commitment should be supported by demonstrating leadership, management, commitment and customer focus through all stages of the implementation of the QMS. The QMS should be designed to be integrated in regulatory processes (i.e. not standalone); supported with adequate resources (human, financial, equipment and infrastructure); and created to be simple enough to remain manageable with the available resources, while being effective enough to support consistency, effectiveness and efficiency.

Potential mechanisms that can support QMS implementation include:

- establishing effective coordination and communication mechanisms;
- receiving high-level support from top management for QMS implementation;
- establishing high-level ownership and commitment by top management for QMS implementation and maintenance;
- including QMS implementation roadmaps in NRA strategic plans by top management when submitting to an oversight body (council, board, committee or ministry of health) for approval, as applicable;
- including QMS implementation by the NRA in the national health strategic plans;
- including responsibilities and authorities for contributing to the QMS in every staff job description and human resources performance appraisal;
- creating and implementing training plans for QMS personnel, based on NRA competence frameworks;
- engaging all customers and stakeholders for communication and awareness;

- implementing applicable ICT tools for internal and external implementation of QMS and communication of quality policy awareness;
- embedding assigned QMS personnel within regulatory processes, with the dual responsibilities of regulatory job functions and QMS responsibilities to support and maintain the QMS in the respective regulatory unit.

6.2 Situational analysis of quality management system implementation status in the national regulatory authority

Regardless of the size of NRA, the scope of regulatory functions and the NRA organizational model (i.e. discrete, decentralized or centralized), the recommendations in Table A13.3 for gap and situational analyses should be considered when implementing QMS and when planning for continuous improvement of a QMS that is already implemented. NRAs should first identify existing gaps and determine the level of implementation of the QMS, with the use of Appendix 2, Table A13.3 and self-benchmarking results. Table A13.3 categorizes the key aspects relevant to the different stages of the QMS, as listed next.

- **Non-existing QMS:** NRAs should focus on ensuring that processes and activities are performed consistently, regardless of the personnel or location of execution. This may be covered for certain areas with automated systems (such as laboratory information management systems for laboratories or e-performance appraisals for human resources). NRAs should prioritize development and implementation of procedures for areas based on the related risks with respect to the products and services; the affected quality objectives; and the availability of resources for maintenance of the procedures. This means that not every area should be prioritized at the same time for QMS development and implementation (for NRAs without an implemented QMS).
- **Existing QMS without implementation:** the focus at this stage should be on ensuring that consistent procedures are developed and implemented for the QMS to support regulatory processes effectively. Careful consideration should be given at this stage to objectively addressing the activities for gap identification and validation; these steps would also be useful for NRAs that have already developed and implemented a QMS. NRAs should ensure that the person(s) identifying the gaps have the necessary competence and that top management fully supports the process. The review should be done to cover all areas in which the QMS has been implemented, and the scope should be limited to records, reports or other means of verification that procedures have been implemented and are being used to the full extent as intended. The outcome of this

review should be a root cause analysis with proposed measures to implement; these measures should take into consideration the availability of resources and associated risks of delayed implementation.

- **Ineffective implementation of QMS:** addressing this stage is considered useful once the first two stages are addressed for the respective processes and activities. This stage focuses on the main objectives of the QMS, namely, to ensure that the NRA is being effective in supporting regulatory processes and activities; providing regulatory products and services; and achieving strategic objectives. Therefore, it is important that the QMS is uncomplicated/unsophisticated and manageable enough in its implementation and maintenance to avoid diverting NRA time and resources on the QMS instead of delivering regulatory products and services to the customers as provided by national legal mandates. Increasing the effectiveness and efficiency of the QMS may also involve the adoption and implementation of ICT to remove human errors while promoting consistency; reducing time for implementation and recording; and providing long-term cost reductions.

6.3 Gap analysis for developing a roadmap for quality management system implementation

The information in Table A13.3 can be used to identify gaps and define activities to be done for QMS implementation, based on the recommendations of this guideline. The planning, prioritization and implementation should be as practical as possible and be determined by the NRA, taking into consideration the availability of resources and priorities for the provision of regulatory products and services.

Table A13.3
Gap analysis

Guideline section	Existing system	Stage 1 (non-existing QMS)	Stage 2 (existing QMS without implementation)	Stage 3 (ineffective implementation of QMS)
		Needed documents for consistency	Implemented evidence (by records, reports)	Effectiveness and efficiency
5.2.1 Introduction	Linking and integration of overall QMS to quality systems and (automated) software for: • registration and market authorization • laboratory inspections and licensing • vigilance • market surveillance and control • clinical trials oversight • lot release • environmental (waste) management • occupational health and safety • finance and accounting • e-procurement • planning, monitoring and evaluation • human resource performance appraisal, training and staff/talent retention • others	NRAs should perform an organization-wide review for consistency of practice by different staff using the same processes and the existing system. This review can be used identify a consistency gap for QMS intervention and document development. Once the reviews are completed and gaps established, reviews should be done to determine whether the existing systems and/or software have operational interfaces between one another when they all contribute towards achieving the same objective; these reviews can help to identify operational gaps in interfaces. The QMS should be used to link the processes and activities between systems and/or software by providing documents.	Where consistency and operational interfaces have been implemented and supported under the QMS, NRAs should conduct reviews to identify gaps in the level of implementation of the QMS documents. This should be evaluated by reviewing records and reports generated from the systems and/or software, to establish consistency and operational linkages for the same objectives. Where gaps are found to exist, NRAs should perform RCA and implement changes as appropriate to stage 1 QMS interventions.	NRAs should conduct reviews to identify gaps in the effectiveness and efficiency of the QMS interventions with respect to the achievement of the intended objectives based on evidence from stage 2 outputs. When gaps have been identified, NRAs should revise the QMS implementation documents to ensure that they are effective and efficient in contributing towards the achievement of the objectives.

Table A13.3 *continued*

Guideline section	Existing system	Stage 1 (non-existing QMS)	Stage 2 (existing QMS without implementation)	Stage 3 (ineffective implementation of QMS)
		Needed documents for consistency	Implemented evidence (by records, reports)	Effectiveness and efficiency
5.2.2 Scope of the QMS	Documented statement defining the scope of the regulatory functions, physical locations, processes, regulatory products and services of the NRA	To identify gaps in the scope of the QMS, NRAs should review for the existence of consistent documented scope statements, which includes all areas, locations and processes.	NRAs should review the level of implementation of the QMS across all units (including administrative) and locations, to identify gaps in the implementation of the scope.	When identifying gaps for QMS revision, NRAs should review the effectiveness and efficiency of the scope of the QMS in facilitating the provision of required products and services.
5.2.3 Organizational context of the NRA	Adequate description and mandates of NRAs in terms of: ability to define internal and external issues and customers and stakeholders	NRAs should review and identify gaps in the consistency of how issues for planning are determined among different units of the organization. QMS documents should be developed and implemented to establish consistency.	NRAs should review the planning reports and records from different units, to identify gaps in implementation of QMS documents. Where gaps are identified, RCA should be performed to ensure that procedures are implemented.	NRAs should review the contribution of QMS documents in making the planning more effective and efficient to identify gaps. Identified gaps should be addressed by implementing changes to QMS documents.

Table A13.3 *continued*

Guideline section	Existing system	Stage 1 (non-existing QMS)	Stage 2 (existing QMS without implementation)	Stage 3 (ineffective implementation of QMS)
		Needed documents for consistency	Implemented evidence (by records, reports)	Effectiveness and efficiency
5.2.4 Leadership, management and organization	Adequate description and mandates of NRAs in terms of: • ability to develop and implement organizational structure • ability to develop and implement quality policy and customer-focused initiatives • ability to assign QMS responsibilities and authorities to personnel	NRAs should review the consistency of supervisory and reporting structures, consistency in developing and implementing quality objectives, and consistency of assigned QMS responsibilities and authorities across units and locations, to identify gaps in leadership, management or organization. QMS procedures should be implemented to ensure that leadership, management and organization processes are carried out consistently in implementation of the QMS	NRAs should review the level of implementation of existing QMS procedures, to ensure consistency in organizational structures, job titles, reporting lines, quality policies, QMS responsibilities and authorities across the units and locations, to identify gaps in implementation of procedures. RCA should be done to determine changes that would improve levels of implementation of QMS procedures.	NRAs should review the effectiveness and efficiency of the procedures in supporting leadership, management and organization processes to identify gaps in the existing QMS. Procedures should be revised to ensure that they are effective and efficient in supporting the NRA and all its units in having leadership, management and organization that is able to deliver on the regulatory products and services.

Table A13.3 *continued*

Guideline section	Existing system	Stage 1 (non-existing QMS)	Stage 2 (existing QMS without implementation)	Stage 3 (ineffective implementation of QMS)
		Needed documents for consistency	Implemented evidence (by records, reports)	Effectiveness and efficiency
5.2.5 Document and data management	Documents under the QMS that are internally generated or from external origins for: • regulations • guidelines • Policies • notes and guidance • procedures (SOPs/work instructions) • lists, registers, logbooks • databases and spreadsheets • templates, forms • application documents (dossiers, files) • financial, accounting, procurement and HR records • reports, letters, emails, permits, licences, certificates, others	NRAs should identify gaps by reviewing the consistency in the development, review, approval, version and access control, distribution, storage, retrieval and disposition of documents, as applicable across all units and locations of the organization. Where gaps exist, procedures should be implemented to ensure that documents are managed consistently across all units and locations of the NRA.	NRAs should review the records in units and locations, to identify gaps in the implementation of existing procedures for management of documents. RCA should be done to determine measures to promote implementation of existing procedures.	NRAs should review the effectiveness and efficiency of the procedures in identifying gaps in the management of documents. Procedures should be revised to ensure that they are more effective and efficient in the management of NRA documents. NRAs can consider the use of IT in the management of documents, depending on the availability of resources, size of NRA and complexity of documents to be managed.

Table A13.3 *continued*

Guideline section	Existing system	Stage 1 (non-existing QMS)	Stage 2 (existing QMS without implementation)	Stage 3 (ineffective implementation of QMS)
		Needed documents for consistency	Implemented evidence (by records, reports)	Effectiveness and efficiency
5.2.6 Planning	Linking and integration of planning in quality systems and (automated) software for objectives in: • technical activities • support and administrative activities • M&E	NRAs should review the consistency in the planning, monitoring and evaluation of technical, administrative and support activities, with associated risk and change management plans to identify gaps across all units and locations. QMS procedures should be implemented to ensure that all planning, monitoring and evaluating of technical and support activities are done consistently and with related risk and change management plans.	NRAs should review the level of implementation of procedures for consistency in planning, monitoring and evaluating of technical and support activities. To identify gaps for QMS revision, the review should evaluate the consistency in implementation of risk and change management plans, based on existing records and reports. RCA should be done to ensure that procedures are implemented.	To identify gaps with existing procedures, NRAs should review the effectiveness and efficiency of the QMS procedures in support of planning, monitoring and evaluating of activities, risks and changes. QMS procedures should be revised or replaced with automated systems, based on the complexity and size of the NRA and its planning activities.

Table A13.3 *continued*

Guideline section	Existing system	Stage 1 (non-existing QMS)	Stage 2 (existing QMS without implementation)	Stage 3 (ineffective implementation of QMS)
		Needed documents for consistency	Implemented evidence (by records, reports)	Effectiveness and efficiency
5.2.7 Support and resources	Adequate and quality resources for: • personnel and competencies • organizational knowledge management • ICT • work environment • communication and awareness	NRAs should review the consistency in the allocation of personnel, training in QMS, knowledge sharing, use of ICT and communication of QMS requirements to identify gaps for QMS implementation. Procedures should be implemented to ensure consistency across all units and locations in allocation of personnel, training of staff in QMS implementation, use of intranets and other ICT tools and communication.	NRAs should review the records to identify gaps in levels of implementation of existing procedures for QMS personnel, competencies, knowledge management, ICT, work environment and communication across all units and locations. RCA should be done to ensure procedures are implemented.	To identify gaps for QMS revisions, NRAs should review the effectiveness and efficiency of the procedures in ensuring that there are adequate and quality personnel, QMS competencies, knowledge management, ICT, workspace, communication and awareness of QMS implementation. Procedures should be revised to ensure that they are effective and increase efficiency in their implementations.

Table A13.3 *continued*

Guideline section	Existing system	Stage 1 (non-existing QMS)	Stage 2 (existing QMS without implementation)	Stage 3 (ineffective implementation of QMS)
		Needed documents for consistency	Implemented evidence (by records, reports)	Effectiveness and efficiency
5.2.8 Operation	Process approach focused on the regulatory products and services and on NRA quality objectives	To identify gaps for QMS implementation, NRAs should review the consistency in the conduct of technical and administrative activities in providing products, services and operational interfaces or linkages among processes that contribute to the same product, service or quality objective. Where gaps exist, procedures should be implemented to ensure consistency and operational linkages of processes.	NRAs should review the records from technical and administrative units and locations, to identify gaps in the implementation of existing procedures. RCA should be performed, and measures should be put in place to ensure full implementation of procedures across all affected units and locations.	NRAs should review and identify gaps in the effectiveness and efficiency of the implemented procedures and quality systems in facilitating the provision of products and services that meet requirements and support the achievement of the objectives. Procedures and systems should be revised to ensure that they are effective and increase efficiency in the processes for providing products and services, and for supporting the achievement of NRA objectives.

Table A13.3 *continued*

Guideline section	Existing system	Stage 1 (non-existing QMS)	Stage 2 (existing QMS without implementation)	Stage 3 (ineffective implementation of QMS)
		Needed documents for consistency	Implemented evidence (by records, reports)	Effectiveness and efficiency
5.2.9 Performance evaluation	M&E framework with performance indicators for: • products and services requirements • quality objectives • customer complaints • QMS • resources (human, financial, ICT, equipment and infrastructure) • risk and opportunity management	NRAs should review and determine gaps in consistency in the M&E activities across all units and locations for QMS implementation. Where gaps in consistency are identified, procedures should be implemented to ensure that all M&E of performance indicators is done consistently across different units and locations of NRAs.	NRAs should review and identify gaps in the level of implementation of existing procedures and systems of the QMS for the M&E framework. RCA should be done to inform revised measures for the implementation of procedures and systems across all affected NRA units and locations.	NRAs should review and identify gaps in the effectiveness and efficiency of the implemented QMS procedures and systems used for M&E. These procedures and systems should be evaluated to ensure that their output provides evidence that is useful for planning of continuous improvements. Where gaps exist, NRAs should revise the procedures and systems to ensure that they are more effective and efficient in supporting M&E of performance indicators across all units and locations of the organizations.

Table A13.3 *continued*

Guideline section	Existing system	Stage 1 (non-existing QMS)	Stage 2 (existing QMS without implementation)	Stage 3 (ineffective implementation of QMS)
		Needed documents for consistency	Implemented evidence (by records, reports)	Effectiveness and efficiency
5.2.10 Improvement	Evidence-based improvements	NRAs should review and identify gaps in the consistency of handling and prioritization of improvements across the entire organization. Where there are inconsistencies, procedures should be implemented to ensure that all proposals for improvements are submitted with evidence and evaluated with respect to priorities and availability of resources. Procedures for improvement should define responsibilities and authorities for handling, planning and implementation of improvements.	NRAs should review and identify gaps in levels of implementation of QMS procedures for handling and implementing improvements across all units and locations of the organization. Where gaps are identified, RCA should be done with revised measures for the implementation of the procedures.	NRAs should review and identify gaps in the effectiveness and efficiency of the procedures in facilitating timely implementation of improvements. Procedures should be revised to ensure that they are more effective and efficient in facilitating timely implementation of improvements.

HR: human resources; ICT: information and communication technology; IT: information technology; M&E: monitoring and evaluation; NRA: national regulatory authority; QMS: quality management system; RCA: root cause analysis; SOP: standard operating procedure.

6.4 Quality management system development and implementation roadmap

The QMS roadmap for NRAs will depend on the respective stages of implementation. The roadmap will be used to identify activities to be done; required resources; competencies of personnel; responsibilities and authorities; timelines (time frame); and prioritization based on the needs of the NRA with respect to the regulatory products and services as mandated by national laws and regulations. Table A13.4 summarizes the steps in the development and implementation roadmap for QMS.

Table A13.4
Development of quality management system implementation roadmap

Steps	Activity	Responsible
1	Assign resources (personnel, financial, equipment and infrastructure).	Top management
2	Use Table A13.3 and results from self-benchmarking to determine the status of the QMS and submit report to top management, noting activities and areas that require actions.	Assigned staff/consultant
3	Prioritize activities based on availability of resources (internal and external); risks of non-implementation; and regulatory products and services, as mandated by national laws and regulations.	Top management
4	Allocate responsibilities and authorities with timelines for development, review, approval, implementation, and monitoring and evaluation of prioritized QMS requirements.	Top management and assigned staff/consultant
5	Validate the prioritization of QMS requirements, timelines, responsibilities and authorities with NRA staff, through collection of input and feedback to promote ownership of QMS implementation.	Top management and assigned staff/consultant
6	Consolidate the feedback and input into an activity/action plan, as a roadmap for QMS implementation for the NRA.	Assigned staff/consultant
7	Integrate the QMS roadmap (activity/action plan) into the NRA organizational activity/action plans, the NRA strategic plans, and the ministry of health strategic plan/policy, as applicable.	Top management

NRA: national regulatory authority; QMS: quality management system.

6.5 Activity plan for quality management system implementation

Appendix 1 provides a typical action plan for the systematic development and implementation of a QMS. The plan provides a linkage between the section/subsections of this guideline and includes examples of documents and records to be established to demonstrate adequate implementation of the QMS.

References

1. Thirteenth General Programme of Work 2019–2023. Promote health, keep the world safe, serve the vulnerable. Geneva: World Health Organization; 2019 (<https://apps.who.int/iris/bitstream/handle/10665/324775/WHO-PRP-18.1-eng.pdf>, accessed 4 November 2019).
2. World Health Organization. Leadership priorities.
3. Resolution WHA67.20. Regulatory system strengthening for medical products. In: Sixty-seventh World Health Assembly, Geneva, 19–23 May 2014. Geneva: World Health Organization; 2014 (https://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R20-en.pdf, accessed 12 November 2019).
4. World Health Organization. Essential medicines and health products. WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems (<https://iris.who.int/bitstream/handle/10665/341243/9789240020245-eng.pdf?sequence=1>, accessed 15 November 2019).
5. ISO 9001:2015(en). Quality management systems – requirements (<https://www.iso.org/obp/ui/#iso:std:iso:9001:ed-5:v1:en>, accessed 5 November 2019).
6. Good regulatory practices: guidelines for national regulatory authorities for medical products. Working document QAS/16.686. Geneva: World Health Organization; 2016.
7. ISO 9000:2015(en). Quality management systems – fundamentals and vocabulary (<https://www.iso.org/obp/ui/#iso:std:iso:9000:ed-4:v1:en>, accessed 12 November 2019).
8. Compendium of quality management system (QMS) technical documents for harmonization of medicine regulation in the East African Community. Arusha: East African Community Secretariat; 2014 (EAC/TF-MED/QMS/FD/COM/N1R0).
9. WHO guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report: Annex 2. Geneva: World Health Organization; 2013 (WHO Technical Report Series, No. 981; https://iris.who.int/bitstream/handle/10665/81144/WHO_TRS_981_eng.pdf?sequence=1&isAllowed=y, accessed 12 November 2019).
10. ISO 31000:2018(en). Risk management – guidelines (<https://www.iso.org/obp/ui/#iso:std:iso:31000:ed-2:v1:en>, accessed 12 November 2019).
11. ISO 45001:2018(en) Occupational health and safety management systems – requirements with guidance for use (<https://www.iso.org/obp/ui/#iso:std:iso:45001:ed-1:v1:en>, accessed 12 November 2019).
12. ISO 14001:2015(en). Environmental management systems – requirement with guidance for use (<https://www.iso.org/obp/ui/#iso:std:iso:14001:ed-3:v1:en>, accessed 12 November 2019).

13. Good review practices: guidelines for national and regional regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report: Annex 9. Geneva: World Health Organization; 2015 (WHO Technical Report Series, No. 992; https://iris.who.int/bitstream/handle/10665/176954/9789240693968_eng.pdf?sequence=1&isAllowed=y, accessed 12 November 2019).
14. Regulation and licensing of biological products in countries with newly developing regulatory authorities. In: WHO Expert Committee on Biological Standardization: forty-fifth report: Annex 1. Geneva: World Health Organization; 1995 (WHO Technical Report Series, No. 858; https://iris.who.int/bitstream/handle/10665/36999/WHO_TRS_858.pdf?sequence=1, accessed 12 November 2019).
15. WHO guidelines on evaluation of similar biotherapeutic products (SBPs). In: WHO Expert Committee on Biological Standardization: sixtieth report: Annex 2. Geneva: World Health Organization; 2013 (WHO Technical Report Series, No. 977; https://iris.who.int/bitstream/handle/10665/89142/9789241209779_eng.pdf?sequence=1, accessed 12 November 2019).
16. Quality management systems requirements for national inspectorates. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report: Annex 5. Geneva: World Health Organization; 2020 (WHO Technical Report Series, No. 1025; <https://iris.who.int/bitstream/handle/10665/331814/9789240001824-eng.pdf?sequence=1&isAllowed=y>).
17. WHO good practices for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report: Annex 1. Geneva: World Health Organization; 2010 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y, accessed 12 November 2019).
18. WHO good practices for pharmaceutical microbiology laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report: Annex 2. Geneva: World Health Organization; 2011 (WHO Technical Report Series, No. 961; https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1, accessed 12 November 2019).
19. ISO/IEC 17025. General requirements for the competence of testing and calibration laboratories. Geneva: International Organisation for Standardisation; 2017 (<https://www.iso.org/files/live/sites/isoorg/files/store/en/PUB100424.pdf>, accessed 12 November 2019).
20. Council of Europe. European Directorate for the Quality of Medicines and HealthCare. Quality management (QM) documents.
21. ISO 19011:2018(en). Guidelines for auditing management systems (<https://www.iso.org/obp/ui/#iso:std:iso:19011:ed-3:v1:en>, accessed 13 November 2019).

Appendix 1

References to the *WHO Global Benchmarking Tool*, revision VI

The *WHO Global Benchmarking Tool* (GBT) (4) is used to assess the level of implementation of a quality management system (QMS) in a national regulatory authority (NRA). The QMS indicator, RS05, consists of 14 subindicators that are used to identify the degree of QMS implementation and the existing gaps across the NRA.

Subsection in QMS guideline	GBT VI – QMS subindicators (4)	Related GBT VI subindicators (4)
5.2.1 Introduction	RS05.06	
5.2.2 Scope of the QMS	RS05.02	RS01.01, RS01.02 VL01.01 MA01.01 MC01.01 LI01.01 RI01.01 LT01.01 CT01.01 LR01.01
5.2.3 Organizational context of the NRA	RS05.06, RS05.08	RS02.04, RS03.04, RS07.04
5.2.4 Leadership, management and organization	RS05.01, RS05.02, RS05.03, RS05.04	RS02.01, RS04.01 VL02.01, VL03.02 MA02.01, MA03.02 MC02.01, MC03.02 LI02.01, LI03.02 RI02.01, RI03.02 LT02.01, LT04.02 CT02.01, CT03.02, CT04.04 LR03.02

Table continued

Subsection in QMS guideline	GBT VI – QMS subindicators (4)	Related GBT VI subindicators (4)
5.2.5 Document and data management	RS05.07	RS01.04, RS01.05, RS01.08, RS09.06, RS09.08 VL03.04, VL04.01, VL04.02, VL04.03 MA03.04, MA04.01, MA04.02, MA04.03, MA04.10, MA05.02, MA06.01 MC03.04, MC04.01, MC04.02, MC04.03, MC04.05, MC04.07, MC04.08, MC05.01, MC05.02 LI03.04, LI04.01, LI05.01, LI06.01 RI03.04, RI04.01, RI04.02, RI04.04, RI04.05, RI04.06, RI05.01, RI05.02 LT03.02, LT03.04, LT04.04, LT06.02, LT06.03, LT08.01 CT03.04, CT04.05, CT04.06, CT04.07, CT06.01 LR01.02, LR03.04, LR04.03
5.2.6 Planning	RS05.02	RS03.03, RS04.05 VL04.04, VL04.08 MA01.12, MA04.06, MA04.07, MA06.02 MC04.04, MC05.03 LI04.03, LI05.02 RI04.03, RI05.05 LT03.01, LT08.04 CT06.02, CT06.04 LR06.04
5.2.7 Support and resources	RS05.04, RS05.14	RS02.02, RS06.01, RS06.02, RS08.01, RS08.02, RS08.03, RS09.03, RS09.07, RS09.09 VL02.02, VL03.01, VL03.02, VL03.03, VL06.01, VL06.02, VL06.03 MA02.02, MA03.01, MA03.03, MA05.01, MA05.03, MA05.04 MC02.02, MC03.01, MC03.03, MC06.01, MC06.02, MC06.03 LI02.02, LI03.01, LI03.03, LI06.02 RI02.02, RI03.01, RI03.03, RI06.01, RI06.02, RI06.03, RI06.04 LT03.03, LT04.01, LT04.03, LT05.01, LT05.02, LT06.05, LT07.01, LT09.01, LT09.02, LT09.03 CT02.02, CT03.01, CT03.03, CT05.02 LR02.02, LR03.01, LR03.03, LR05.01, LR05.02, LR06.01

Table *continued*

Subsection in QMS guideline	GBT VI – QMS subindicators (4)	Related GBT VI subindicators (4)
5.2.8 Operation	RS05.06, RS05.09	RS02.03, RS04.02, RS04.03, RS06.03, RS06.04, RS09.05, RS09.07 VL04.05, VL04.06, VL04.07 MA01.09, MA01.10, MA01.11, MA01.13, MA04.05, MA04.08, MA04.09, MA04.10 MC01.06, MC01.07 LI01.04, LI04.02, LI04.04 RI01.04, RI05.03 LT02.02, LT06.01, LT06.04, LT10.01 CT01.09, CT01.10, CT04.01, CT04.02, CT04.03, CT05.01 LR04.01, LR04.02
5.2.9 Performance evaluation	RS05.10, RS05.11, RS05.12, RS05.13	RS01.09, RS10.01, RS10.02 VL05.02 MA04.06, MA06.02 MC04.06, MC05.03 LI05.02 RI05.04, RI05.05 LT08.02, LT08.03, LT08.04 CT06.02, CT06.04 LR06.02, LR06.04
5.2.10 Improvement	RS05.05	LR06.02

GBT: *WHO Global Benchmarking Tool* (4); NRA: national regulatory authority; QMS: quality management system.

Appendix 2

Activity plan for quality management system implementation

Step	Activity	Subsection of QMS guideline	Recommendations of documents and records to be established	Responsibility within the NRA
1.	Appointment of QMS focal person(s) or lead(s)	5.2.4.3	Official letters of appointment with defined responsibilities and authorities in the QMS	Head of the NRA
2.	QMS focal person(s) understands the QMS requirements	5.2.7.2	• Competency matrix for QMS focal person(s)/lead(s) • Training plans for competency gaps in QMS implementation • Training records of QMS focal person(s)/lead(s) • Training/orientation records in development and implementation of QMS documents (quality manual, standard operating procedures and/or forms and templates)	Top management
3.	QMS focal person(s)/lead(s) conducts a gap analysis of the current system based on Tables A13.3 and A13.4 of the guideline and develops a QMS action plan (as part of the strategic plan)	6.1	• Documented gap or situation analysis report • Documented roadmap with resources, timelines and responsibilities (part of NRA strategic and action plans)	• Top management • QMS focal person(s)/lead(s)

Table continued

Step	Activity	Subsection of QMS guideline	Recommendations of documents and records to be established	Responsibility within the NRA
4.	QMS focal person(s)/lead(s) conduct(s) orientation and awareness sessions for NRA employees on QMS development and implementation (with roles and responsibilities)	5.2.7.5	Accessible and available QMS orientation and awareness sessions records and materials in appropriate format	QMS focal person(s)/lead(s)
5.	- Establishment of NRA current context (SWOT analysis), if already available - Determination of the comprehensiveness of the legal provisions (Acts and regulations) in describing interested parties relevant to the QMS - Identification of QMS processes, sequences, linkages and interdependencies - Determination of the scope of the QMS and relationships of its processes	5.2.3.1	- Documented official organizational chart covering NRA governance and top management and internal and external operational relationships - Documented description of internal and external issues, including SWOT analysis of the NRA (with defined customers and stakeholders based on legal provisions) - Documented description of internal and external customers and stakeholders, with their respective needs and expectations (if not adequately described in the national legislations) - Documented statement of scope for the QMS - Documented flowcharts, process maps and their operational linkages for all processes under the scope of the QMS, with related products and services	- Top management - QMS focal person(s)/lead(s)

Table *continued*

Step	Activity	Subsection of QMS guideline	Recommendations of documents and records to be established	Responsibility within the NRA
6.	Documentation of a quality policy within the context and strategic direction of the NRA	5.2.4.2	Documented, accessible (publicly) and available quality policy understood by NRA staff	• Top management • QMS focal person(s)/ lead(s)
7.	Use information from step 5 above, as input, to determine risks and opportunities and develop risk and opportunity management plans	5.2.6.2	• Documented and controlled registry of assessed and categorized risks and opportunities (from SWOT analysis) • Risk and opportunity responsibility matrix (based on responsible, accountable, consulted and informed [RACI] principles)	• Top management • QMS focal person(s)/ lead(s)
8.	Development and documentation of SMART quality objectives, including a plan for M&E with related required resources	5.2.4.2	Documented quality objectives (and their short- and long-term targets), resources, responsibilities (ideally in NRA's strategic plan) and M&E indicators	Top management

Table *continued*

Step	Activity	Subsection of QMS guideline	Recommendations of documents and records to be established	Responsibility within the NRA
9.	Development of new or harmonization with existing procedures for control of measuring equipment, organizational knowledge management, personnel training and communication	5.2.7.4	Documented and implemented procedures for: • staff recruitment (based on a defined competency framework for different levels and positions), training and retraining based on established gaps as per organizational competency framework • management and maintenance of measuring equipment, as applicable in making regulatory decisions (laboratory and/or inspection equipment) • management of organizational knowledge (e.g. retirements, resignations and new knowledge acquisition) • management of internal and external communication of regulatory decisions, products, services and other engagements with customers and stakeholders • use of IT in technical and administrative processes, including management of templates used in the software or equipment or in other procedures needed to manage resources as described in the guideline	• Top management • QMS focal person(s)/ lead(s)

Table *continued*

Step	Activity	Subsection of QMS guideline	Recommendations of documents and records to be established	Responsibility within the NRA
10.	Development of new or harmonization with existing procedures for all processes in technical and administrative units of the NRA	5.2.8	Documented and implemented procedures for all applicable technical and administrative processes within the NRA and that contain the appropriate level of detail based on the complexity of the processes and associated risks. The procedures should address all activities that are involved in provision of products and services as mandated by national legislations	• Top management • QMS focal person(s)/ lead(s)
11.	Development of procedures for monitoring of customer satisfaction, internal audit, management review and complaints handling, and put them into practice	5.2.9	• Documented and implemented procedures for customer complaints and satisfaction, along with publications of guidance to the public on the procedures and communication • Documented and implemented internal audit programmes • Documented and implemented regular reviews of QMS implementation and performance by top management	• Top management • QMS focal person(s)/ lead(s)
12.	Development of procedures for corrections, corrective actions and improvements, and put them into practice	5.2.10	Documented and implemented procedures for corrective actions and change management, along with a link for updating risk and opportunity management plans	• Top management • QMS focal person(s)/ lead(s)

IT: information technology; M&E: monitoring and evaluation; NRA: national regulatory authority; QMS: quality management system; SMART: specific, measurable, attainable, realistic and time-bound; SWOT: strengths, weaknesses, opportunities and threats.

4.4 Quality management system requirements for national inspectorates

Annex 5, WHO Technical Report Series, 1025, 2020 (revised)

Background

During the Joint Meeting on Regulatory Guidance for Multisource Products (Copenhagen, July 2016), several World Health Organization (WHO) guidance documents were identified for update. In October 2016, the Fiftieth WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) confirmed the need to update the selected guidelines.

Following up on the recommendation from the Fiftieth ECSPP, the WHO Secretariat conducted a detailed analysis of the cluster of guidelines proposed for revision. The outcome of this analysis was discussed during the informal consultation on Good Practices for Health Products Manufacture and Inspection (Geneva, July 2018). In particular, considering that the *WHO Quality systems requirements for national good manufacturing practice inspectorates* (1) defines the basic requirements applicable to quality systems for the operation of inspection services within national regulatory authorities (NRAs) concerned with good manufacturing practices (GMP) inspections, the WHO Secretariat proposed a strategy for revision that includes aligning the guidance with the principles of ISO 9001:2015 (2) and with relevant Pharmaceutical Inspection Convention/Co-operation Scheme (PIC/S) guidance (3), as well as broadening its scope to include all good practices (GXP)-related inspections conducted by an NRA.

The Fifty-second ECSPP endorsed the proposal for revision and recommended the WHO Secretariat to revise the *WHO Quality systems requirements for national good manufacturing practice inspectorates* (1), aligning its content to international standards and the latest quality management systems (QMS) principles, and to expanding the scope.

1. Introduction	478
2. Scope	478
3. Glossary	478
4. Quality management system	479
5. Context of the inspectorate	480
6. Management and leadership	480

7. Management system planning	481
8. Resources	482
9. Documentation	483
10. Operational planning and performance evaluation	486
11. Publications	487
References	487
Further reading	488

1. Introduction

- 1.1 This document describes the quality management system (QMS) requirements for the operation of inspection services within national regulatory authorities (NRA) or other state structures (for the purpose of this guidance, the term “NRA” will be used in the text to represent both NRAs and other state structures). It is intended that each inspection service uses these requirements as the basis for developing and implementing its own QMS. Where the inspectorate operates under the umbrella of the NRA QMS, consideration should be given to the *WHO guideline on the implementation of quality management systems for national regulatory authorities* (4).
- 1.2 The adoption of a common standard for QMS requirements is an essential element in achieving consistency in inspection practices and facilitating structured communication with other units of the NRA, as well as enabling mutual confidence and permitting recognition between pharmaceutical inspectorates.

2. Scope

- 2.1 This document outlines the QMS requirements for pharmaceutical inspectorates that are competent for the oversight of GXP operations.

3. Glossary

The definitions given below apply to the terms used in this guideline that are not defined in existing WHO terms and definitions databases. They may have different meanings in other contexts.

corrective actions. Steps taken to eliminate the cause of existing nonconformities in order to prevent recurrence. The corrective action process tries to make sure that existing nonconformities and potentially undesirable situations do not happen again.

good practices (GXP). The group of good practice guides governing the preclinical, clinical, manufacturing, testing, storage, distribution and post-market activities for regulated pharmaceuticals, biologicals and medical devices, such as good laboratory practices (GLP), good clinical practices (GCP), good manufacturing practices (GMP), good pharmacovigilance practices (GPP) and good distribution practices (GDP).

internal audit. An examination and assessment of all or part of a quality system, with the specific purpose of improving it. An internal audit should be conducted by an independent (of the function to be audited) and qualified team of experts designated by the management for this purpose.

quality indicators. Selected data intended to be monitored and used in assessing trends in performance.

quality management system. An appropriate infrastructure, encompassing the organizational structure, procedures, processes, resources and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

quality manual. A document that includes the quality policy and objectives and describes the various elements of the QMS.

quality policy. A brief statement that describes the organization's purpose, overall intentions and strategic direction; provides a framework for quality objectives; and includes a commitment to meet applicable requirements.

rapid alert. An urgent notification submitted by an NRA participating in the rapid alert system concerning measures taken against a product placed on the market that poses a risk to consumers' health and/or safety.

risk management. The systematic application of quality management policies, procedures and practices to the tasks of assessing, controlling, communicating and reviewing risk.

standard operating procedure (SOP). An authorized written procedure giving detailed instructions for performing a task or following a process in accordance with legislation, official guidance or internal standards.

4. Quality management system

- 4.1 The concept of a QMS is wide-ranging and covers all matters that are necessary to implement the inspectorate's quality policy and to meet predefined objectives.
- 4.2 The QMS should define the inspectorate's scope and context within the regulatory mandate, as well as covering all functions, processes and activities.
- 4.3 The primary aims of an inspectorate's QMS are:
 1. to ensure its ability to consistently provide services that meet the organization's objectives, legal requirements and interested parties' expectations; and
 2. to facilitate continual improvement and provide a sound basis for sustainable development to comply with statutory and regulatory requirements.

- 4.4 The QMS should at least describe and manage organizational structure, responsibilities, procedures, systems, processes and resources required, to provide value and achieve results for the inspectorate and relevant interested parties.
- 4.5 Typically, the legal basis for the establishment of the inspectorate, its mandate, the quality policy and the principles of the QMS should be documented in a quality manual or equivalent document.
- 4.6 The QMS should enable senior (“top”) management to best use available resources and systems in order to achieve the inspectorate’s targets and quality objectives. Senior management’s commitment and active participation is essential to ensure implementation of the QMS and to support staff within the inspectorate.

5. Context of the inspectorate

- 5.1 The legal basis for the establishment of the inspectorate and its mandate, as well as statutory and regulatory responsibilities and functions, should be clearly defined.
- 5.2 The inspectorate should determine its scope and strategic direction, in order to achieve the intended objectives.
- 5.3 The structure and operation of the inspectorate should be such that impartiality and independence are safeguarded. Rules for deontology, confidentiality, ethics and conflicts of interest should be clearly defined and obeyed. Where relevant, the inspectorate should implement a policy that distinguishes between the process of inspection and that of providing an advisory service. This service should be of benefit to all of industry and not solely to individual organizations.
- 5.4 The relationship of the inspectorate with other departments within the same NRA, and other agencies and organizations outside the inspectorate, as well as any other stakeholders, should be described and documented where relevant.

6. Management and leadership

- 6.1 Senior management should make a formal commitment to the implementation of a documented quality policy that is compatible with statutory requirements and relevant objectives.
- 6.2 Senior management should ensure that the inspectorate’s services and functions are aligned with regulatory requirements and the NRA’s objectives, as well as meeting interested parties’ expectations.
- 6.3 Senior management is accountable for the integration of QMS requirements into the inspectorate’s processes and functions; for communicating the importance of

QMS principles; and for the overall effectiveness of the QMS. In addition, senior management should promote the application of risk management principles and support the engagement and contribution of personnel in improving the QMS.

- 6.4 Senior management should ensure that the pharmaceutical inspectorate has sufficient and appropriate resources at all levels to enable it to meet its objectives. Responsibilities, authorities and the reporting structure for relevant roles should be clearly defined and documented in the QMS. The structure should be defined in organization charts.
- 6.5 An appropriately experienced and qualified person should be nominated as a QMS responsible person. This person should have direct access to senior management. If necessary, this task may be assigned to more than one person.
- 6.6 There shall be a system for periodic management review of the QMS effectiveness, including process improvements. Such reviews should be documented and records should be maintained for a defined period.

7. Management system planning

- 7.1 The inspectorate should establish appropriate objectives for the intended level of service and of its functions, which should be consistent with the quality policy and regulatory requirements. Principles of risk management and sustainable development should be considered for the establishment of these objectives.
- 7.2 These objectives should be communicated to personnel at all levels and be updated whenever necessary.
- 7.3 Appropriate resources should be available to meet these objectives. Roles and responsibilities should be defined and, where appropriate, timelines for completion should be established. Systems for monitoring and evaluating results should be established. All necessary information on quality objectives should be maintained.
- 7.4 A documented change management system should be established, to ensure that change requests are assessed, approved or rejected; that appropriate resources are allocated; and that roles and responsibilities are defined. Any change should be documented, communicated to the personnel and evaluated after implementation, to ensure the objectives are met. The change management system should ensure that continual improvement is undertaken in a timely and effective manner.

8. Resources

- 8.1 The inspectorate should have an organizational structure, required resources (financial, human, facilities and others) and documented procedures that enable it to meet its objectives; to perform inspection activities in accordance with official GXP guidelines and national legislation; and to carry out its functions and operations satisfactorily. Where necessary, measures and resources for the safety of personnel should be available.

Personnel

- 8.2 The inspectorate should employ the required personnel possessing the appropriate expertise to perform its functions, including inspections, and to determine whether the inspected entities comply with the principles of current GXP guidelines and with relevant legislation.
- 8.3 Personnel responsible for inspections should have appropriate qualifications, including education, training, experience and knowledge of the inspection process and subject, and should be periodically evaluated. They should have the ability to make professional judgements as to the conformity of the inspected party with the requirements of GXP and the relevant legislation, and be able to apply risk management principles in their decision-making process.
- 8.4 The inspectorate should ensure that induction and continuous training is provided to inspection personnel on administrative, regulatory and technical topics, to maintain the inspectors' competency aligned with current industry practice, technological advancements and regulatory changes. Training should be documented and its effectiveness assessed periodically.
- 8.5 The inspectorate should maintain documented and up-to-date information on the relevant qualifications, training and experience of each inspector.
- 8.6 Personnel should have clear, up-to-date and documented job descriptions specifying their duties and responsibilities.
- 8.7 When products are procured from a third party and/or services are subcontracted to an external body or expert, the inspectorate should ensure that the third party meets predefined documented criteria, qualifications and the relevant requirements of the quality management system. Senior management should ensure that these external bodies or experts are periodically evaluated. Third party responsibilities and liability should be clearly defined in the contract or agreement.
- 8.8 All personnel employed or contracted by the inspectorate should be bound by the requirements of the quality system, obey the inspectorate's code of conduct and

not be subject to any commercial, financial or other pressures that might affect their judgement and freedom to act. They should not be under the control of the pharmaceutical industry and must be assessed for potential conflict of interest. Personnel and third-party declarations of conflict of interest should be maintained, reviewed periodically and updated where necessary. It should be ensured that any decision-making process remains with the inspectorate and is not influenced by any third party.

Infrastructure

8.9 Personnel should be provided with the necessary infrastructure and appropriate work environment to enable them perform their functions and meet the quality objectives. Infrastructure includes, but is not limited to:

- buildings, workspace and associated facilities;
- qualified equipment, including hardware and software;
- transportation resources; and
- information and communication technology.

9. Documentation

General

- 9.1 The inspectorate should establish and maintain a system for the control of all documentation, including electronic files, relating to the inspectorate's QMS and activities. This should include policies, procedures, guidelines, records and any documents of external origin, such as legislation, which may directly or indirectly influence the activities of the inspectorate; or documents received from pharmaceutical companies and relevant organizations, as appropriate.
- 9.2 The inspectorate should ensure that its functions and operations are described in SOPs that clearly define the required responsibilities, processes and actions. These may include, but not be limited to, training; inspections; reporting after inspections; handling of complaints; licensing (issue, suspension, withdrawal); certification; handling of quality, safety and efficacy issues; documentation control; change and deviation management; inspection planning; risk management; and the handling of appeals.
- 9.3 The system and activities relating to advising on, issue, withdrawal or suspension of licences, registration or certifications; and the application of other regulatory sanctions on facilities, organizations, products or operations, should be detailed in procedures and be in accordance with relevant guidelines and national legislation.

- 9.4 The inspectorate should establish procedures describing communication with other NRA units and external interested parties (e.g. industry, media) considering any statutory and regulatory requirements, where appropriate. Similarly, a procedure for exchanging regulatory information with other NRAs or national quality control laboratories should be available.
- 9.5 Activities relating to the sampling and testing of pharmaceutical products and raw materials should be described in a procedure that should also include the process for handling nonconforming products (e.g. substandard or falsified medical products).
- 9.6 The inspectorate should have procedures on handling quality, safety and efficacy issues that may lead to recall or withdrawal of products from the market. Where applicable, the inspectorate should establish and maintain a system for communicating rapid alerts. Records of recalls and withdrawals should be maintained in accordance with national legislation.
- 9.7 The inspectorate should have documented procedures for dealing with complaints arising from its activities or those of its personnel and any contracted person or organization. A record should be maintained of all complaints received and the actions taken by the inspectorate. These records should be retained for a specified period of time.
- 9.8 The inspectorate should have procedures for consideration of appeals against its decisions.
- 9.9 The documentation control system should ensure that:
 - documents are identified by title, author, reviewer, approver and unique identification. They should be dated and authorized by the appropriate persons prior to issue;
 - current versions of documents are held by nominated personnel;
 - a register of all relevant documents and document holders is maintained;
 - superseded documents are withdrawn from use but are retained for defined periods of time;
 - any changes to documents are made in a controlled manner and are properly authorized. There should be a means of identifying changes in individual documents;
 - records relating to the inspectorate's activities and functions are readily available and are retained for an adequate period, in line with legal requirements or internal standards;
 - records comply with the relevant obligations under national legislation;

- records are safely stored during their retention period and held under conditions that guarantee their security and confidentiality unless otherwise required by national legislation. The destruction of records after their retention period should follow a predefined procedure; and
- electronic documentation and record management systems provide at least the same level of assurance, compliance, accuracy and security as a manual system.

Inspection process and documents

- 9.10 An inspection should be categorized in accordance with GXP guidelines (e.g. GMP, GDP, GCP) and its scope (e.g. product, process) and type (e.g. triggered, routine, follow-up) should be appropriately defined and documented.
- 9.11 The inspectorate should plan inspections in advance and elaborate a written programme as part of the inspectorate's annual workplan. Risk management principles should be considered when establishing an inspection programme and prioritizing inspections, as well as when conducting an inspection. Where repeated inspections of a company or organization have to be carried out, the frequency should be determined based on risk management principles defined in a procedure.
- 9.12 Inspection-related documents and records, as defined in relevant inspection procedures (e.g. inspection plan, aide-mémoire, checklists, worksheets and company documents and records), should be maintained for a defined period.
- 9.13 When more than one inspector is involved in an inspection, a lead inspector should be appointed to coordinate inspection activities. The inspection report should be prepared by the lead inspector, with the assistance of all participating inspectors and/or experts, and should be agreed upon by all participating inspectors and/or experts.
- 9.14 The inspection report should follow a pre-approved format. Observations and/or data obtained in the course of inspection should be recorded in a timely manner, in order to prevent loss of relevant information.
- 9.15 The inspection report should be sent to the inspected company or organization within the inspectorate's established timelines. The lead inspector and all concerned inspectors and/or experts should participate in assessing the company's response, to determine the appropriateness of corrective and preventive actions as well as the GXP compliance status of the company or organization.
- 9.16 Completed inspections should be reviewed to ensure that all reporting and regulatory requirements are met.

10. Operational planning and performance evaluation

- 10.1 An annual workplan should be developed, documented and periodically reviewed by senior management, including all the inspectorate's activities, in accordance with a written procedure. Regulatory, statutory and scientific requirements should be taken into account during the planning of operations and services. Consideration should also be given to the availability of required resources and the ability to consistently provide services that meet legislative requirements and stakeholder expectations. Risk management principles should be used during planning, to determine, monitor and manage risks and to identify opportunities for process improvements. Any changes to the workplan should follow the inspectorate's change management system.
- 10.2 Appropriate quality indicators and methods should be established, in order to monitor and periodically evaluate the inspectorate's processes and level of improvement and service (including contracted-out services) and demonstrate that they were carried out as planned and met predefined quality objectives. These quality indicators, methods, analyses and results should be documented.
- 10.3 The results of the analyses should be used to evaluate the performance and effectiveness of the QMS, the adequacy of actions taken to address risks, and the need for further improvements.

Internal audits

- 10.4 The inspectorate should implement a system of periodic and documented internal audits of its operations, to assess compliance with the requirements of the QMS. Internal audits should be conducted at least once a year.
- 10.5 Internal audit processes, criteria, scope and documents should be defined. Auditors' qualifications and selection criteria should be documented. Internal audit records, including the findings, conclusions, recommendations and follow-up actions, should be retained for a defined period.
- 10.6 Corrective actions corresponding to audit findings should be identified, documented and implemented in a timely manner. The effectiveness of these actions should be evaluated and the risk plan should be updated to take note of the root causes of the nonconformances.

Management review

- 10.7 Senior management should review the inspectorate's QMS at planned intervals, to ensure its continuing suitability, adequacy, effectiveness and alignment with

the inspectorate's strategic direction and legislative requirements. Management reviews should be conducted at least once a year.

10.8 A management review should include, but not be limited to:

- the status of the actions from previous management reviews;
- any internal or external changes affecting the QMS;
- any deviations affecting the functionality of the QMS;
- the extent to which quality objectives have been met;
- process performance analyses;
- audit results and the effectiveness of corrective actions;
- complaints and appeals;
- the adequacy of resources;
- any identified risks and mitigation measures; and
- opportunities for improvements.

11. Publications

11.1 The inspectorate should issue and maintain an up-to-date list of inspected and licensed facilities and organizations, including information on the outcome of inspections. This list may become publicly available in accordance with national legislation.

11.2 The inspectorate should ensure that other relevant publications, such as technical guides, GXP guidelines and regulatory requirements, are publicly available.

References

1. Quality systems requirements for national good manufacturing practice inspectorates. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-sixth report. Geneva: World Health Organization; 2002: Annex 8 (WHO Technical Report Series, No. 902; https://iris.who.int/bitstream/handle/10665/42424/WHO_TRS_902.pdf?sequence=1&isAllowed=y, accessed 4 November 2019).
2. ISO 9001:2015(en). Quality management systems – requirements (<https://www.iso.org/obp/ui/#iso:std:iso:9001:ed-5:v1:en>, accessed 5 November 2019).
3. Recommendation on quality system requirements for pharmaceutical inspectorates (PI 002-3). Geneva: Pharmaceutical Inspection Convention/Co-operation Scheme (PIC/S); 2007 (PI 002-3; <http://academy.gmp-compliance.org/guidemgr/files/PICS/PI%20002-3%20%20RECOMMENDATION%20ON%20QUALITY%20SYSTEM.PDF>, accessed 15 November 2019).

4. WHO guideline on the implementation of quality management systems for national regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 13 (WHO Technical Report Series, No. 1025; <https://iris.who.int/bitstream/handle/10665/331814/9789240001824-eng.pdf?sequence=1&isAllowed=y>).

Further reading

- WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986; https://iris.who.int/bitstream/handle/10665/112733/WHO_TRS_986_eng.pdf?sequence=1&isAllowed=y, accessed 15 November 2019).
- WHO good manufacturing practices for active pharmaceutical ingredients. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 2 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y, accessed 15 November 2019).
- WHO good practices for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 1 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y, accessed 15 November 2019).
- Good storage and distribution practices for medical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 7 (WHO Technical Report Series, No. 1025; <https://iris.who.int/bitstream/handle/10665/331814/9789240001824-eng.pdf?sequence=1&isAllowed=y>).
- Good trade and distribution practices for pharmaceutical starting materials. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 1 (WHO Technical Report Series, No. 996; <https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>, accessed 15 November 2019).
- Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. In: WHO Expert Committee on Biological Standardization: sixth report. Geneva: World Health Organization; 1995: Annex 3 (WHO Technical Report Series, No. 850; https://iris.who.int/bitstream/handle/10665/37340/WHO_TRS_850.pdf?sequence=1&isAllowed=y, accessed 15 November 2019).
- Compilation of community procedures on inspections and exchange of information. Amsterdam: European Medicines Agency; 2014 (EMA/572454/2014 Rev. 17).
- ISO 9000:2015(en). Quality management systems – fundamentals and vocabulary (<https://www.iso.org/obp/ui/#iso:std:iso:9000:ed-4:v1:en>, accessed 15 November 2019).
- ISO 9004:2018(en). Quality management – quality of an organization – guidance to achieve sustained success. International Standard ISO 9004. Geneva, International Organization for Standardization, 2018 (<https://www.iso.org/obp/ui/#iso:std:iso:9004:ed-4:v1:en>, accessed 15 November 2019).

- ISO 17020:2012(en). Conformity assessment -- requirements for the operation of various types of bodies performing inspection (<https://www.iso.org/obp/ui/#iso:std:iso-iec:17020:ed-2:v1:en>, accessed 15 November 2019).
- ISO 31000:2018(en). Risk management – guidelines (<https://www.iso.org/obp/ui/#iso:std:iso:31000:ed-2:v1:en>, accessed 12 November 2019).
- ISO 19011:2018(en). Guidelines for auditing management systems (<https://www.iso.org/obp/ui/#iso:std:iso:19011:ed-3:v1:en>, accessed 15 November 2019).
- ISO 13485:2016(en). Medical devices – quality management systems – requirements for regulatory purposes (<https://www.iso.org/obp/ui/#iso:std:iso:13485:ed-3:v1:en>, accessed 15 November 2019).
- ICH Q10. Pharmaceutical quality system (PQS). Amsterdam: European Medicines Agency; 2008 (EMA/CHMP/ICH/214732/2007; <https://www.ema.europa.eu/en/ich-q10-pharmaceutical-quality-system>, accessed 15 November 2019).

4.5 WHO guidelines on quality risk management

Annex 2, WHO Technical Report Series, 981, 2013

1. Introduction	491
1.1 Background and scope	491
1.2 Principles of quality risk management	493
2. Glossary	496
3. Quality risk management process	499
3.1 Initiating a QRM process	499
3.2 Personnel involved in QRM	499
3.3 Knowledge of the product and process	499
3.4 Risk assessment	500
3.5 Risk control	501
3.6 Risk review	502
3.7 Verification of QRM process and methodologies	503
3.8 Risk communication and documentation	504
4. QRM application for pharmaceuticals	504
4.1 Training and education	504
4.2 Responsibilities	505
4.3 QRM application during product development	506
4.4 QRM application during validation and qualification	506
4.5 QRM application during commercial manufacturing	507
4.5.1 QRM integration with key quality system elements	508
4.5.2 QRM application in product manufacturing operations	509
5. QRM considerations for medicines regulatory authorities	510
5.1 Introduction	510
5.2 QRM application to inspection strategy	510
5.2.1 Risk management in inspections	510
5.2.2 Inspection planning and conduct	511
5.2.3 Corrective action and preventive action review, and scheduling of routine inspections	512
5.2.4 Complaint handling and investigation	512
5.3 Inspection of QRM at a manufacturing site	512
5.4 QRM applied to dossier review (assessment)	513
6. Risk management tools	515
References	520

1. Introduction

1.1 Background and scope

In most countries compliance with good manufacturing practices (GMP) (1, 2) (including validation), medicines regulatory activities and inspections, together with supply chain controls throughout the product life-cycle, provide good assurance that risks are largely controlled. However, where control is less effective, patients may be put at risk through the production of medicines of inadequate quality. The assessment of individual risks related to specific products and starting materials and the recognition of hazards at specific stages of production or distribution should permit regulatory authorities to improve control of medicines by increasing the effectiveness of their activities within the limits of the available resources. Quality risk management (QRM) is a process that is relevant to all countries and should provide a rationale to understand risk and mitigate it through appropriate and robust controls.

The aim of these guidelines is to assist the development and implementation of effective QRM, covering activities such as research and development, sourcing of materials, manufacturing, packaging, testing, storage and distribution. In the past, hazard analysis and critical control point (HACCP) methodology, traditionally a food safety management system but subsequently applied to other industries, has been the basis of WHO risk management guidance to the pharmaceutical industry (3).

More recently international guidance has emerged (2, 4–7) that is of specific relevance to the pharmaceutical industry and which addresses the full scope of pharmaceutical industry QRM more effectively than HACCP principles, including how to structure regulatory filings using a risk-based approach. Consequently, these WHO guidelines have been developed as an update on WHO's advice to the pharmaceutical industry, taking account of this new guidance.

To protect patients in terms of quality, safety and efficacy of medicines, international medicines regulatory authorities (MRAs) are recommending pharmaceutical manufacturers to adopt a risk-based approach to the life-cycle of a pharmaceutical product. Some MRAs require the adoption of a risk-based approach for specific areas in the life-cycle of a pharmaceutical product, e.g. environmental monitoring in sterile products manufacture. The level of QRM activity and the density of associated documentation will evolve as the product progresses from early development through to routine production.

QRM is the overall and continuing process of appropriately managing risks to product quality throughout the product's life-cycle in order to optimize its benefit–risk balance. It is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

While the choice of the tools to support the QRM approach is optional and may vary, the tools chosen need to be appropriate for the intended use.

In return for using this approach, there are potential opportunities for both MRAs and pharmaceutical manufacturers (8) as summarized in the following sections.

- Quality risk management (QRM) principles can be applied to both MRAs and pharmaceutical manufacturers:
 - MRAs: systematic and structured planning of reviews and inspections that are risk-based. The submission review and inspection programmes can also operate in a coordinated and synergistic manner.
 - Manufacturers: design, development, manufacture and distribution, i.e. the life-cycle of a pharmaceutical product. QRM should be an integral element of the pharmaceutical quality system (QS).
- Science-based decision-making can be embedded into QRM processes:
 - MRAs: decisions regarding review, inspection or inspection frequency should consider product risk and GMP compliance of the manufacturer. The MRA accepts residual risks through understanding the QRM decisions involved.
 - Manufacturers: quality decisions and filing commitments can be based on a science-based understanding of the process and QRM (when using the quality by design approach, and other approaches where appropriate). Its effective application should offer manufacturers greater freedom to decide how to comply with the principles of GMP and this, therefore, should encourage innovation.

The control strategy for the process focuses on critical quality attributes and critical process parameters.

- Resources can be focused on risks to patients:
 - MRAs: QRM can be used to determine the best allocation of inspection resources, both in terms of product types and for specific areas of focus for a given inspection. This enables the most efficient and effective scrutiny of the most significant health risks. Those manufacturers with poor histories of GMP compliance can also be more closely and frequently evaluated by on-site inspection than those manufacturers with better records.
 - Manufacturers: evaluation of quality risk through science-based decisions can be linked ultimately to protection of the patient by ensuring the quality, safety and efficacy of the product. A corporate culture is supported to produce cost-effective medicines, without

compromising quality, while maintaining the focus on the patient as a primary stakeholder in all activities.

- Restrictive and unnecessary practices can be avoided:
 - MRAs: regulatory scrutiny should consider the level of risk to patients. Improvement and innovation by manufacturers should be encouraged.
 - Manufacturers: instead of having systems designed to inhibit change and minimize business risk, changes can be managed within a company's quality management system. Innovation and the adoption of the latest scientific advances in manufacturing and technology are supported. Unnecessary testing can be eliminated, for example, with real-time release testing.
- Communication and transparency are facilitated:
 - MRAs: facilitate dialogue with pharmaceutical manufacturers and communicate clearly to the industry and the public how the inspection programme may be adjusted based on the risk to patients. Information-sharing between MRAs will contribute to a better risk management approach globally.
 - Manufacturers: matrix team approach, stakeholders are kept informed through science-based decisions. This builds a culture of trust and a “one-team” mindset with a focus on the product and the patient.

These guidelines will align with the general framework described in other current international guidance on this subject.

1.2 Principles of quality risk management

It is not always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or internal procedures, e.g. standard operating procedures (SOPs)). The use of an informal risk management process (using empirical tools or internal procedures) can also be considered acceptable.

The two primary principles of QRM are that:

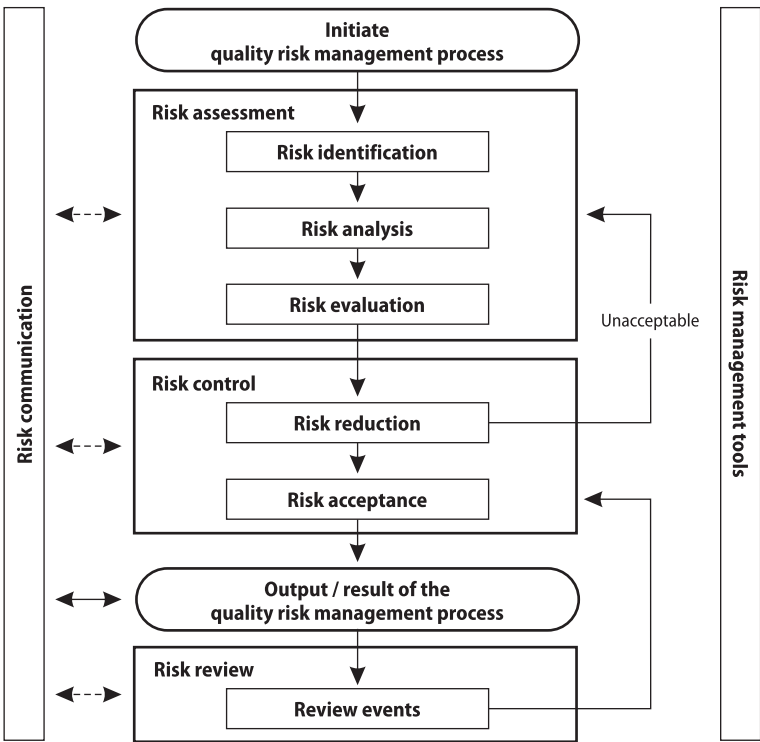
- The evaluation of the risk to quality should be based on scientific knowledge and ultimately linked to the protection of the patient.
- The level of effort, formality and documentation of the QRM process should be commensurate with the level of risk.

In addition to the two principles above, the following principles are also part of the QRM methodology:

- When applied, processes using QRM methodologies should be dynamic, iterative and responsive to change.
- The capability for continual improvement should be embedded in the QRM process.

This guidance describes the WHO approach to QRM, using the concepts described in ICH Q9 (6) and illustrated in Figure A3.1. The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.

Figure A3.1
Overview of a typical quality risk management process



Reproduced from reference 5: ICH Q9: Quality Risk Management.

Decision points are not shown in the diagram above because decisions can occur at any point in the process. The decision might be:

- to return to the previous step and seek further information;
- to adjust the risk models; or even
- to terminate the risk management process based upon information that supports such a decision.

The approach described in these guidelines may be used to:

- systematically analyse products and processes to ensure that the best scientific rationale is in place to improve the probability of success;
- identify important knowledge gaps associated with processes that need to be understood to properly identify risks;
- provide the communication process that will best interface with all relevant parties involved in the QRM activities;
- facilitate the transfer of process knowledge and product development history to ease product progression throughout its life-cycle and to supplement already available knowledge about the product;
- enable the pharmaceutical industry to adopt a risk-based approach to development as described in regulatory guidance (4–6). The QRM outputs will potentially serve as reference documents to support product development and control strategy discussions in regulatory filings.

Early in development, the purpose of the QRM process may be to acquire sufficient product and process knowledge to assess risks associated with formulation development of the finished pharmaceutical product (FPP) according to the quality target product profile (QTPP). In recognizing risks and knowledge gaps, the QRM process plays a significant role in proactively enabling the prioritization and mitigation of risks. The objective is to develop the FPP through maximizing product and process knowledge and risk mitigation.

As FPP development progresses, in addition to supporting that development, the purpose of the QRM process is to determine and manage risks to bioavailability, safety, efficacy and product quality. QRM in development should differentiate process parameters and quality attributes from critical process parameters (CPPs) and critical quality attributes (CQAs), thereby contributing to defining and refining the control strategy.

The long process of product development is inevitably complex and requires the continual exchange of data, decisions and updates both internally within companies and, where required, with external stakeholders, such as MRAs. A crucial aspect of product development and QRM is the maintenance of an effective and secure knowledge

management and documentation system. Such a system must facilitate transparent communication and the highlighting of key issues to stakeholders and must also include a well-structured archive. Clearly, the ability to organize diverse data and information effectively and then retrieve it as required for updating and further evaluation, e.g. for the purposes of process validation, would be hugely beneficial.

Finally, it should be noted that QRM activities are focused on the product/process development and product manufacturing, ultimately to ensure a robust, safe and effective FPP.

2. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

control strategy

A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active pharmaceutical ingredients (APIs) and finished pharmaceutical product (FPP) materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

critical quality attribute (CQA)

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

failure mode

Different ways that a process or subprocess can fail to provide the anticipated result.

failure mode, effects and criticality analysis (FMECA)

A systematic method of identifying and preventing product and process problems.

finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling.

formal experimental design

A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as “design of experiments”.

occurrence

Probability of negative events within a fixed time frame.

pharmaceutical product

Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

pharmaceutical product target profile (PPTP)

A definition of the target properties of the FPP, including dosage form and strength(s), route of administration and relevant drug release and pharmacokinetic requirements.

planned risk assessment

An assessment that is conducted in advance of an activity, either before any work is conducted or before further work is conducted. This enables quality to be built into activities and risk to be reduced, e.g. design of high containment facilities for manufacture of cytotoxic products.

process robustness

Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality.

qualification

The action of proving and documenting that any premises, systems and equipment are properly installed and/or work correctly and lead to the expected results. Qualification is often a part (the initial stage) of validation, but the individual qualification steps alone do not constitute process validation.

quality critical process parameter

A process parameter which could have an impact on the critical quality attribute.

quality risk management

A systematic process for the assessment, control communication, and review of risks to the quality of the pharmaceutical product across the product life-cycle.

risk

Combination of the probability of occurrence of harm and severity of the harm.

risk analysis

The estimation of the risk associated with the identified hazards.

risk assessment

A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the evaluation of risk associated with exposure to those hazards.

risk control

The sharing of information about risk and risk management between the decision-maker and other stakeholders.

risk evaluation

The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.

risk identification

The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description.

risk priority number (RPN)

A numeric assessment of risk assigned to a process, or steps in a process, as part of failure mode effects analysis (FMEA). Each failure mode gets a numeric score that quantifies likelihood of occurrence, likelihood of detection and severity of impact. The product of these three scores is the RPN for that failure mode. $RPN = \text{severity rating} \times \text{occurrence rating} \times \text{detection rating}$.

risk review

Review or monitoring of output or results of the risk management process considering (if appropriate) new knowledge and experience about the risk.

stakeholder

Any individual, group or organization that can affect, be affected by, or perceive itself to be affected by a risk. Primary stakeholders are the patient, health-care professional, MRAs and the pharmaceutical industry.

unplanned risk assessment

An assessment that is conducted to assess the impact of a situation that has already occurred, e.g. impact of a deviation from normal ways of working.

validation

The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results.

verification

The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with the quality risk management activities.

3. Quality risk management process

3.1 Initiating a QRM process

QRM activities should be performed using systematic processes designed to coordinate, facilitate and improve science-based decision-making with respect to risk. The possible steps to be taken in initiating and planning a QRM process might include the following (5):

- define the problem and/or risk question, including pertinent assumptions identifying the potential for risk;
- assemble background information and/or data on the potential hazard, harm or human health impact relevant to the risk assessment;
- identify a leader and the necessary resources;
- specify a timeline, the deliverables, and an appropriate level of decision-making for the risk management process.
- Internal SOPs should define steps, stakeholders, roles and responsibilities (governance and management responsibilities).

3.2 Personnel involved in QRM

The implementing party, i.e. the pharmaceutical manufacturer or regulatory authority, should assure that personnel with appropriate product-specific knowledge and expertise are available to ensure effective planning and completion of QRM activities. This may be best accomplished by assembling a multidisciplinary team according to the guidance provided in section 4.2.

The personnel appointed should be able to:

- conduct a risk analysis;
- identify and analyse potential risks;
- evaluate risks and determine which ones should be controlled and which ones can be accepted;
- recommend and implement adequate risk control measures;
- devise procedures for risk review, monitoring and verification;
- consider the impact of risk findings on related or similar products and/or processes.

QRM activities should be defined and documented.

3.3 Knowledge of the product and process

QRM should be based on knowledge of the product or processes concerned, according to the stage of the product life-cycle.

A flow diagram may be helpful, covering all operations and controls in the process under evaluation. When applying QRM to a given operation, the steps preceding and following that operation should also be considered. A block-type diagram may be sufficiently descriptive. Amendments to the flow diagram may be made where appropriate, and should be documented.

3.4 Risk assessment

When risk assessment is conducted, safety and efficacy need to be considered in addition to the quality concerns.

During the assessment all the risks that may reasonably be expected to occur when conducting the activity under evaluation should be listed. This is usually done when the risk assessment is made for the first time, i.e. initiated, when there is a change or a concern and may also be applied to existing processes. An analysis should be conducted to identify which risks it is essential to eliminate or to reduce to acceptable levels.

A thorough risk assessment is required to ensure effective risk control. Risk assessment should review the materials, operations, equipment, storage, distribution and intended use of the product. Typically a list of the potential risks (biological, chemical and physical) which may be introduced, increased or controlled in each area should be drawn up. In the risk assessment the following basic questions should be addressed:

- What might go wrong?
- What is the nature of possible risks?
- What is the probability of their occurrence and how easy is it to detect them?
- What are the consequences (the severity)?

It should then be decided which of the potential risks should be addressed by the QRM activities and what control measures, if any, should be taken for each risk. If a risk has been identified at a step where control is necessary for safety, and no control measure exists at that step or at any other, the product or process should be modified at that step, or at an earlier or later stage, to include such a control measure. More than one control measure may be required to control a specific risk and more than one risk may be controlled by a specified control measure.

Options for risk assessment methodologies are described in section 5.

Risk assessment can be aided by the use of a decision-tree, which facilitates a logical approach. The way that a decision-tree is used will depend on the operation concerned, e.g. production, packaging, reprocessing, storage or distribution. The best use of QRM tools is discussed further in section 5.

Normally, potential risks in relation to the following should be considered:

- materials and ingredients;
- physical characteristics and composition of the product;
- processing procedures;
- microbial limits, where applicable;
- premises;
- equipment;
- packaging;
- sanitation and hygiene;
- personnel (human error);
- utilities;
- supply chain.

The output of a risk assessment is either a quantitative estimate of risk (numeric probability) or a qualitative description of a range of risk (e.g. high/medium/low) and may be related to a risk matrix (see section 5). The scoring system and trigger points for mitigating action are subjective so the rationale for score categorization should be defined in as much detail as possible. If the score and trigger action are supported by factual evidence it should be more obvious what mitigating action is required – the mitigating action is as important as the score assigned. Professional judgement should be used in interpreting the factual evidence but must be subject to justification.

Records of risk assessments should be maintained.

The expectation of QRM is to assess risks to the product quality and to the patient and then manage these risks so that they are kept at an acceptable level. It is appropriate for companies to assess their control systems so as to implement the appropriate controls to ensure product quality and patient safety. An important principle in QRM is to design risks out of the process or eliminate such risks prospectively, whenever practical and feasible. Risk assessment and mitigation to achieve cost savings, but which could be to the detriment of the well-being of the patient, is an unacceptable practice (9).

3.5 Risk control

Risk control is a decision-making activity designed to reduce and/or accept risks. It usually occurs after risk assessment, and at a fundamental level its purpose is to reduce the risk to an acceptable level.

During risk control activities the following key questions should be asked:

- What can be done to reduce or eliminate risks?
- What is the appropriate balance between benefits, risks and resources?

- Are new risks introduced as a result of the identified risks being controlled?

Risk control can include:

- not proceeding with the risky activity;
- taking the risk;
- removing the risk source;
- changing the likelihood of the risk;
- changing the consequences of the risk;
- sharing the risk with another party (e.g. contractor);
- retaining the risk by informed decision.

Risk control activities usually involve identifying controls and measures which may reduce or control the risk associated with a failure mode or negative event. Risk control activities can serve to determine critical process parameters for certain controls, how they will be monitored, and the level of qualification and validation, if any, which may be required for such controls.

If risk assessments are conducted and risk controls are employed they should be documented. If the risk assessment is conducted for an ongoing activity it should be subject to periodic review and the frequency of review should be appropriate for the nature of the activity.

Based on the criticality or level of risk, specific corrective actions should be developed to prevent recurrence of instances where there have been deviations from established risk control measures, especially for high risks. These actions should ensure that the risk is brought under control as soon as possible in compliance with the established deviation handling procedures.

Specific corrective actions should be developed in advance for each identified risk, including what is to be done when a deviation occurs and who is responsible for implementing the corrective actions. A record should be kept and maintained of the actions taken.

3.6 Risk review

Appropriate systems should be in place to ensure that the output of the QRM process is periodically monitored and reviewed, as appropriate, to assess new information that may impact on the original QRM decision. Examples of such changes include changes to control systems, changes to equipment and processes, changes in suppliers or contractors and organizational restructuring

Monitoring is the scheduled measurement or observation of a specific risk control measure relative to its acceptance limits. Monitoring should be recorded.

All records and documents associated with risk review should be signed and dated by the person(s) carrying out the review and by a responsible official(s) of the quality unit of the company.

3.7 Verification of QRM process and methodologies

Once in production, the QRM documentation can be integrated into the quality system and used to provide input into the product process.

The established QRM process and methodologies need to be verified. Verification and auditing methods, procedures and tests, including random sampling and analysis, can be used to determine whether the QRM process is working appropriately. The frequency of verification should be sufficient to confirm the proper functioning of the QRM process.

Verification activities include:

- review of the QRM process and its records;
- review of deviations and product dispositions (management control);
- confirmation that identified risks are being kept under control.

Initial verification of the planned QRM activities is necessary to determine whether they are scientifically and technically sound, that all risks have been identified and that, if the QRM activities are properly completed, the risks will be effectively controlled.

Information reviewed to verify the QRM process should include:

- expert advice and scientific studies;
- in-plant observations, measurements and evaluations.

Subsequent verifications should be performed and documented by a QRM team or an independent expert, as needed. For example, verifications may be conducted when there is an unexplained system failure, when a significant change in product, process or packaging occurs or new risks are recognized. Where possible, verification should include actions to confirm the efficacy of all elements of the QRM activities.

In addition, a comprehensive review of the QRM process and specific instances of QRM application by an independent third party may be useful. This would include a technical evaluation of the risk analysis and each element of the QRM process and its application as well as an on-site review of all flow diagrams and appropriate records of the operation of the QRM activity. Such a comprehensive verification is independent of other verification procedures and should be performed to ensure that the QRM process is resulting in the control of the risks. If the results of the comprehensive verification identify deficiencies, the QRM process should be modified as necessary.

Individuals doing verification should have appropriate technical expertise to perform this function.

3.8 Risk communication and documentation

Communication of the QRM process should include key stakeholders. Engaging the key stakeholders in both the data collection process for the risk assessment and the decision-making for risk control will ensure their commitment and support for the QRM. The output of the QRM process and associated risk analysis justifying the approach taken should be documented and endorsed by the organization's quality unit and management. Additionally, this information should be communicated to stakeholders to keep them informed and to ensure their support.

There should be a report for every risk assessment, but the level of effort, formality and documentation necessary will be commensurate with the level of risk (2).

Regarding conclusions of a risk assessment, the mitigation controls should minimize the likelihood of risk to patient safety to an acceptable level of assurance, on the understanding that no risk whatsoever is unlikely in reality. The degree of risk tolerated very much depends on the circumstances, the proximity to the patient and other controls that might follow in response to the process being assessed before the product reaches the patient (2). It is expected that risk mitigation plans will be developed and implemented wherever any risk to patient safety is posed. Companies should take the holistic view and be mindful that critical issues often arise where multiple failures in systems occur together, so mitigation plans should be sufficiently robust to cover this scenario. Inspectors will assess whether risk assessments underrate the likelihood of occurrence and the consequences of overrating detection such that the patient risk is underestimated. The factual evidence behind statements should be robust to challenge by inspectors.

All risk assessments performed by an organization should be documented. The documentation should list and track all key risks as perceived by the organization and summarize how the risks have been mitigated. There should be a clear reference to risk assessments and a list of risk assessments conducted should be maintained. A management process should be in place to review QRM – this may be incorporated into the quality management review process.

4. QRM application for pharmaceuticals

4.1 Training and education

Training of relevant personnel in industry, MRAs and universities in QRM principles and applications is essential for its effective implementation. Industry employees should understand what QRM is, possess the skills necessary to apply it properly, and have access to appropriate resources to enable the effective practice of the QRM principles.

In developing the training programme to support QRM activities, working instructions and procedures should be drawn up which clarify the strategy and define the tasks of all personnel involved in these activities. Specific training should be provided as

required to enhance awareness. Staff with the responsibility for managing and reviewing risks should receive formal training in the relevant procedures.

Cooperation between producers, traders and responsible authorities is vital. Opportunities should be provided for the joint training of industrial staff and MRAs to encourage and maintain a continuous dialogue and create a climate of understanding in the practical application of QRM.

The success of QRM depends on the education and training of management and employees to understand the importance of QRM in producing and supplying safe pharmaceuticals.

4.2 Responsibilities

Successful application of QRM is dependent on a clear understanding of responsibilities by all personnel involved in the QRM activities. It is recommended that a cross-functional matrix of assigned responsibilities and accountabilities is drawn up and shared with all relevant personnel.

The pharmaceutical manufacturer should ensure that appropriate knowledge and expertise are available for the effective planning and completion of QRM activities. QRM activities are usually, but not always, undertaken by a matrix of interdisciplinary teams. When teams are formed they should include experts from the appropriate areas (e.g. quality unit, product development, engineering, regulatory affairs, production operations, statistics, clinical, and others, such as sales, marketing or legal, as applicable), in addition to individuals who are knowledgeable about the QRM process.

In this respect it is acceptable for external consultants to participate in the QRM matrix team where they can provide specific expertise or knowledge. Their role should be justifiable and clearly defined and the resultant accountability must be understood. A technical agreement or other equivalent document with the consultant may be appropriate where a GMP responsibility is assumed.

Similarly, contract staff may become involved in leading or participating in risk assessments, e.g. a contract authorized person. The extent of their involvement and responsibility and accountability must be documented in a technical agreement or other equivalent document between the individual concerned and the pharmaceutical company. Regarding the authorized person it is important that a company's internal procedures are clear on where the responsibility lies for final approval of risk acceptance documents.

Effective matrix team leadership is required to take responsibility for coordinating QRM across various functions and departments of the organization and to ensure that the QRM activities are adequately defined, planned, resourced, deployed and reviewed. The leader and team will need to identify critical resources required to implement the QRM activities, and also specify a timeline, deliverables and appropriate levels of decision-making for the QRM process.

4.3 QRM application during product development

The application of QRM procedures evolves through the various stages in the development of a product.

The first QRM exercise should be performed once the QTPP is defined and preformulation work on the candidate medicine is complete. At this stage of a project there may be significant gaps in knowledge. Therefore, it will be important to apply risk tools that are appropriate for such a situation. These might include:

- cause and effect diagrams (also known as Ishikawa or Fishbone diagrams);
- flowcharts (e.g. input-process-output, IPO);
- decision-trees;
- fault-tree analysis;
- relationship matrices.

As the product progresses to later stage of development, a more detailed analysis of the risks associated with both the active pharmaceutical ingredient (API) and the FPP should be considered. Risks would cover concerns associated with stability, bioavailability and patient safety including any challenges to these areas resulting from the manufacturing process (including, for example, API form conversion under certain conditions of processing).

As product knowledge advances, more detailed QRM exercises can be considered, concentrating on areas considered to present higher priority risk. As the product's critical quality attributes (CQAs) become defined, the potential risks arising from each input material (API, excipients, any device or pack components) and each secondary product unit operation can be investigated.

Eventually, for the developed FPP, the increasingly comprehensive risk assessment will support a thorough understanding of the product and will enable all key variables to be identified, understood and controlled.

4.4 QRM application during validation and qualification

In keeping with the principles of QRM, these guidelines recommend that process validation embraces the product life-cycle concept already mentioned. Accordingly, process validation activities should involve the generation and evaluation of data throughout the process, from development to full-scale production, which will provide a science-based assurance of consistent delivery of quality product in the production operation (9–10).

It is important to emphasize that the building of scientific assurance begins early in development. It is obtained through rational design of experiments and robust evaluation of data during product and process development through to the commercial production phase, by which time the API and FPP CQAs are well understood and controlled. In this scenario, validation or (perhaps more appropriately termed)

conformance batches serve to reinforce the science- or risk-based decisions that have been made as product development has advanced and should demonstrate good control of all critical sources of variability that have been identified. Any unplanned variations within a batch or between batches should be evaluated employing suitable statistical tools, e.g. trend analysis, to check on process control.

A potential advantage of this approach is that there can be flexibility in the number of validation or conformance batches required for regulatory scrutiny prior to approval. The traditional number of batches required for validation has been three but, with QRM embedded in a product's development process, the number of conformance batches needed depends on the depth of knowledge about the process. For very low-volume products, e.g. orphan drugs, this may preclude the need to manufacture multiple batches. It would be beneficial for decisions of this nature regarding conformance batches to have an effective company–MRA dialogue to agree on requirements for a regulatory submission.

When applicable, the principles of QRM should also be applied for qualification activities.

QRM principles can be used to determine the scope of qualification. They can also be used to determine the optimal schedule for maintenance, monitoring, calibration and requalification.

Manufacturers should have sufficient knowledge of the process and product to ensure that by the time the product is commercialized, processes are optimized and risks are minimized.

4.5 QRM application during commercial manufacturing

In general, implementing QRM should not obviate a manufacturer's obligation to comply with regulatory expectations (e.g. regulatory requirements, regulatory filings and inspection commitments). All QRM activities should be structured in a way that allows responsibility for risk assessment and actions at appropriate levels of the hierarchy within the organization. Special focus can be put on the risk assessment and risk control during the life-cycle of a product, and may include:

- product quality risks;
- adverse impact on patient health resulting from product quality defects;
- interruption of product supply to patients;
- GMP and regulatory compliance risks;
- multisite risks;
- multiproduct risks;
- new facility and changes to existing facility, e.g. start-ups, new commercial manufacturing processes, technology transfers and product discontinuation.

After completion of the risk assessment and risk control activities, the outcomes should be summarized and appropriately communicated. The results may be documented in a new or existing report or they may be included as part of another document approved by appropriate decision-makers (e.g. site or functional management, system owner, or quality unit). A risk review is important if new risks or changes to existing risk levels are identified as a result of planned or unplanned events such as routine operation, changes, complaints, product returns, discrepancies or deviations, data monitoring, trends, inspections or audits, or changes in regulatory environment. Risk review may also include evaluation of, for example:

- effectiveness of risk control activities and actions;
- changes in observed risk levels or existing controls.

In principal, areas of focus when implementing QRM in commercial manufacturing include a system focus, a process focus and a product focus.

4.5.1 QRM integration with key quality system elements

Effective QRM can facilitate the decision on “What to do?” and, therefore, support better and more informed decisions. QRM should be integrated into existing quality system elements and related business processes and documented appropriately.

Accordingly, the use of QRM can be beneficial across a broad spectrum of operations, e.g.:

- integrated quality management:
 - documentation
 - training and education
 - quality defects
 - auditing and inspection
 - change management and change control (includes equipment, facilities, utilities, control and IT systems)
 - continual improvement and corrective and preventive actions (CAPA);
- facilities, equipment and utilities:
 - design
 - qualification
 - maintenance and decommissioning of facility or equipment
 - hygiene aspects
 - cleaning of equipment and environmental control

- calibration and preventive maintenance
- computer systems and computer-controlled equipment;
- supplier, materials and contract service management:
 - assessment and evaluation of suppliers and contract manufacturers
 - starting material
 - use of materials
 - storage
 - logistics and distribution conditions;
- technology transfer:
 - from development to manufacturing
 - during commercial manufacturing between sites
 - from commercial manufacturing to product discontinuation.

4.5.2 QRM application in product manufacturing operations

Effective QRM can facilitate the “How to do it?” and, therefore, ensure that the products will meet acceptable standards for safety, quality, and compliance.

Among others, QRM methodology can support the following actions to assess and control quality risks:

- production:
 - manufacturing process risks
 - validation
 - in-process sampling and testing controls
 - production planning
 - deviation and investigation management
 - change management;
- laboratory control and stability studies:
 - out-of-specification results
 - retest period and expiry date
 - method transfers;
- packaging and labelling:
 - design of packages

- selection of container-closure system
- label controls;
- storage, transport and distribution:
 - e.g. cold chain.

5. QRM considerations for medicines regulatory authorities

5.1 Introduction

A key principle of these guidelines is that all MRAs, manufacturing sites in developing countries and API manufacturers should demonstrate, wherever appropriate, application of QRM throughout the product life-cycle for development and manufacturing facilities. Inspectors will review this QRM system as part of the quality systems section of the inspection (along with complaints, recalls, deviations, product quality reviews and others).

Equally, it is recommended that QRM be applied by the MRAs (for examples see (2, 8)) themselves (reviewers and inspectorates) as there are clear benefits of a QRM-based review and inspection plan. For example, inspectors can allocate time and resources commensurate with the perceived significance of risk in any given situation and can be pragmatic regarding the level of scrutiny and degree of formality required.

5.2 QRM application to inspection strategy

5.2.1 Risk management in inspections

The inspection section or unit of an MRA should operate within a written, implemented quality management system (11). SOPs should be followed for activities including (but not limited to) inspection planning, review of corrective and preventive actions after inspections and complaint handling and investigation. Where appropriate, the procedures and activities during inspection should be in line with the principles of QRM.

The unit should have a risk management plan that describes the philosophy, approach, procedures and implementation of risk management. The risk management plan should be reviewed and updated on a continuous basis, or at least annually, and should cover all types of inspections (including GMP, good clinical practices (GCP), good laboratory practices (GLP)) and other activities.

Appropriate risk assessment tools should be used in the process, and the risk assessment for a site to be inspected should be documented on a risk assessment worksheet. Records should be maintained.

A metric system should be used for risk ratings, e.g. on a scale from 1 to 3.

5.2.2 Inspection planning and conduct

The frequency and scope of inspections should be determined based on risk assessment that covers product risk and patient risk.

Risk rating should normally be done only for sites that have been previously inspected. The risk assessment worksheet should be completed after every inspection. Inspection of a site that has not been inspected previously may be waived only in cases where a recognition procedure exists between regulatory inspection units, and where, in addition, appropriate evidence of GXP compliance is available which indicates that there is no risk or an acceptably low risk to products and patients.

Various factors should be considered in the risk assessment exercise, and these factors may be different for the different types of GXP inspections. Risk factors to be considered depend on the type of inspection, and may include:

- outcome of inspection by another regulatory authority;
- outcome of the previous inspection;
- complexity of the site (e.g. buildings, utilities);
- complexity of the product (e.g. sterile, non-sterile);
- type of product (e.g. biological, low-dose);
- complaints and recalls;
- significance of changes (e.g. equipment, key personnel);
- results of product testing;
- risk to the patient;
- complex route of synthesis (API);
- polymorphism (API);
- biopharmaceutical classification of the product;
- innovative or emerging technology.

The number of inspectors and number of days required for the inspection, as well as the scope of the inspection, should be determined based on the risk rating of the site inspection.

Inspection reports should contain findings and observations. Departures from GXP should be classified where appropriate, as “critical”, “major” or “minor”.

The unit should have an SOP that describes the classification process. Classification should be based on risk assessment. The level of risk assigned should be in accordance with the nature of the observation as well as the number of occurrences.

5.2.3 Corrective action and preventive action review, and scheduling of routine inspections

CAPA should be requested from a site, following an inspection. The CAPAs should address the observations included in an inspection report. Based on the outcome of the inspection and the acceptability of the CAPA, the risk rating of the site should be reviewed and recorded.

Inspection frequency should be defined based on the risk rating. For example, the frequency can be defined as every 6, 12, 18 or 24 months. (Note: The maximum time interval should be no more than every 36 months.)

5.2.4 Complaint handling and investigation

Handling and investigation of quality complaints should be done in accordance with a written SOP. The scope and depth of the investigation (including whether a desk review or on-site inspection will be done) should be based on risk assessment.

5.3 Inspection of QRM at a manufacturing site

Note: During inspections, inspectors should assess whether a manufacturer has appropriate skills and scientific knowledge, as well as product and process knowledge, for the QRM procedure being inspected. This is also relevant where a company has made use of contracted parties.

The company's QRM procedure should be appropriately detailed and should be integrated into the company's quality management system. It should cover at least the following areas:

- It should specify the general approach to both planned and unplanned risk assessment, including scope, responsibilities, controls, approvals, management systems, applicability and exclusions.
- Personnel should have appropriate qualifications, experience and training. Their responsibilities with regard to QRM should be clearly defined.
- Senior management should be involved in the identification and implementation of QRM principles within the company.
- The risk management procedure(s) for each area of application should be clearly defined.
- Quality assurance principles should be applied to QRM-related documentation, e.g. review, approval, implementation and archiving.

QRM policies and procedures should be clear and the workflow should be systematic and conducted in a logical order.

- The procedure for risk management should be implemented.

- Manufacturers should identify significant risks and consider all the relevant data from reliable sources.
- The level of effort and resources used in risk assessment should be appropriate to the importance of the identified problem.
- Critical issues should be addressed with appropriate urgency and formality.
- There should be a logical selection of tools for risk assessment.
- Risk acceptance criteria should be appropriate.
- Risk assessments should not underrate the severity, nor overrate detection of occurrences resulting in underestimating patient risk.
- The risk acceptance criteria should be appropriate for the specific situation in question.
- Risk controls should be effective.
- The company should have a review programme to measure the effectiveness of the measures taken.
- Risk-based decision(s) should be science-based and concordant with the predefined acceptance criteria.

All documentation related to the QRM activities should be completed within a reasonable period and should be accessible. Risk assessments performed should be reviewed when appropriate, and additional controls implemented when required.

Personnel should be trained and assessed in the principles of QRM. Where appropriate, a team of members of personnel should participate in the QRM processes.

5.4 QRM applied to dossier review (assessment)

The assessment processes of national medicines regulatory authorities (NMRAs) rely on QRM principles in the management of resources (time and assessors), as well as in the management of product-related risk factors. Efficient management of resources minimizes the risk that limited resources are not used to their best effect, and ultimately ensures that important products are made available in a timely manner. Key factors to be considered include the prioritization of dossiers, the screening process, identification of the specific risk factors inherent to a given dossier or dosage form, and allocation of resources to the various sections of a dossier for a given product. In addition, product-related risk factors must be managed throughout the life-cycle of the product, for example, through effective communication between assessors and inspectors, and by establishing systems for dealing with the products after approval.

The allocation of priority to dossiers should take into account the therapeutic needs of the regional population (e.g. disease occurrence, the need for paediatric formulations, combination products, or experience with innovative or emerging

technology) and the availability of medicines on the market. Prioritization should be a dynamic process to enable it to accommodate emerging issues such as pandemics. Other considerations related to prioritization based on medical need may include fixed-dose combinations versus single-ingredient or co-packaged products, extended release products versus products administered as two or three daily doses, second-line versus first-line products, flexible dosage forms such as dispersible tablets and variable dose products such as oral liquids.

The screening process examines the completeness of a dossier. Screening ensures that only those dossiers that meet minimum standards for completeness can enter into the full assessment process. Insufficient screening processes allow lower quality dossiers to be accepted for review, thus significantly increasing assessment time.

Identification of dossier-related and product-related risk factors allows for the allocation of appropriate resources to specific dossiers. Possible risk factors include: the experience and track record of the manufacturer, narrow therapeutic range products, sterile versus non-sterile APIs and products; API-related considerations such as use of semi-synthetic and fermentation products, complex routes of synthesis, polymorphism, isomerism and potential genotoxic impurities; and product-related considerations such as the use of novel excipients, the complexity of the formulation, single-ingredient versus fixed-dose combinations, and special delivery systems (e.g. modified release, transdermal products, and inhalation products). Once risk factors have been identified, resources should be allocated to minimize risk. For example, assessors with expertise related to the product-related risk identified should be assigned to assess the dossier whenever possible. When resources allow, the assessors may be organized according to specialization, assigning assessors to various product categories (e.g. generic products, sterile products, solid oral dosage forms, or special delivery systems). This can facilitate the development of expertise in key areas and promote consistency of review, as well as ensuring that products requiring specialized knowledge are identified and assessed by those with the appropriate expertise. Where a high level of risk is identified for a dossier, the more experienced assessors need at least to be available on a consultation basis.

The risk level associated with a dossier may change during the course of assessment. For example, rejection of the bioequivalence study will result in additional time required to conduct and assess additional studies and associated additional quality information. In such a scenario the risk relates both to the use of additional resources and to an increased risk that the overall product quality may be poor.

Allocation of resources to various aspects or sections of the dossier is an important QRM consideration, in order to ensure that the resources used are commensurate with the risk level. An understanding of the relative criticality of dossier sections or aspects is necessary for efficient use of resources. All aspects of the dossier are important to achieve overall quality, safety and efficacy; however some areas are inherently more critical from a risk perspective and warrant more attention in the assessment process. Examples include the clinical reviews, bioavailability reviews, API synthesis, specifications and

stability studies, FPP manufacturing details, pharmaceutical development studies including biowaiver justification, process validation, specifications and stability studies. An example applicable to most simple solid oral products is that more time should be allocated to the review of manufacturing steps prior to packaging than to reviewing the packaging process.

During the assessment process there should be a standard procedure for communicating to the inspectors those issues identified which may require consideration during inspection. After approval of a product, QRM principles should be applied to evaluate the impact of proposed variations or changes. Clear guidelines that outline possible post-approval changes and assign an associated risk level are an effective means to achieve this.

6. Risk management tools

A variety of tools can be used for the purposes of QRM, either alone or in combination. It is important to note that no single tool or combination of tools is applicable to every situation in which a QRM procedure is used. Examples of tools are listed in regulatory guidance (6, 8); neither list is exhaustive. The important criterion for acceptability is that the tool or tools are used effectively to support the key attributes of a good risk assessment.

The Product Quality Research Institute (PQRI) Manufacturing Technology Committee (MTC) has produced a summary (9) of common risk management principles and best practices, several working tools to foster consistency in the use of ICH Q9 (5) in day-to-day risk management decision-making, and a series of examples of risk management applications currently in use by major pharmaceutical firms. They have also produced very helpful risk tool training modules for risk ranking and filtering, failure modes effects analysis (FMEA) (12–15), hazard operability analysis (HAZOP) (16) and HACCP (3).

One aspect worth highlighting is the development of a risk matrix to facilitate categorization of risks identified during the risk assessment phase. In order to prioritize a risk, it is essential to agree upon its significance. The risk associated with any situation or event can be represented as the impact of that event multiplied by the probability of its occurrence; in other words: how likely is it to happen? and how severe would it be if it did happen? Impact and probability can each be classified, e.g. into 5 levels (1–5) or with a weighting towards the higher probability and impact ratings (e.g. 1, 3, 5, 7, 10, etc.), so that a grid or matrix can be constructed (Table A3.1).

Table A3.1
An example of a probability versus impact matrix

Probability	Impact				
	Negligible	Marginal	Moderate	Critical	Catastrophic
Almost certain	5	10	15	20	25
Likely	4	8	12	16	20
Possible	3	6	9	12	15
Unlikely	2	4	6	8	10
Rare	1	2	3	4	5

The shading in the table represents an example of how the risk values (sometimes called composite risk indices or risk index values) can be assigned a high, medium or low status. The definition for each status should be predetermined in the QRM process after consideration of the specific consequences for the process undergoing risk assessment. These consequences can be split according to the probability and impact scores, as exemplified in Table A3.2.

Table A3.2
Example of a consequences table for probability and impact

Score	Probability	Example	Score	Impact	Consequence
1	Rare	• Seen every 10–30 years	1	Negligible	• No regulatory issue • No effect on and not noticeable by patient
2	Unlikely	• Seen every 5–10 years	2	Marginal	• May require MRA notification • Decision to release product not compromised
3	Possible	• Seen every 1–5 years	3	Moderate	• MRA inspection may identify a major concern but deficiency quite easily resolved • Limited product recall possible

Table A3.2 *continued*

Score	Probability	Example	Score	Impact	Consequence
4	Likely	• Seen to occur more than once a year	4	Critical	• MRA inspection may conclude serious non-compliance • Likely product recall from one or more markets
5	Almost certain	• Seen several times a year	5	Catastrophic	• Enforcement action by MRA such as consent decree, product seizure • Global product recall

MRA, Medicines regulatory authority.

Source: Based on reference 9. This table has been amended, but was originally produced within the context of the Product Quality Research Institute (PQRI), 2107 Wilson Blvd, Suite 700, Arlington, Virginia 22201-3042, USA; web site: <https://pqri.org>. PQRI has kindly agreed to the use of its material.

This table is a very basic example and would need to be customized for the specific process in question to enable a better and more practical definition of the consequence categories. It should be cautioned that the value of a risk matrix relies very heavily upon input information and should only be used by staff with a good understanding of the embedded judgements and, as such, the resolution of the low, medium or high categorization.

As a summary of the common, well-recognized QRM tool options available for the purposes of these guidelines, Table A3.3 has been based on the one from the Product Quality Research Institute Manufacturing Technology Committee (PQRI-MTC) report (9). The list is not comprehensive but it does include some of the more frequently used approaches.

Table A3.3
Examples of common risk management tools

Risk management tool	Description, attributes	Potential applications
Tools		
Diagram analysis • Flowcharts • Check sheets • Process mapping • Cause/effect diagrams	• Simple techniques that are commonly used to gather and organize data, structure risk management processes and facilitate decision-making	• Compilation of observations, trends or other empirical information to support a variety of less complex deviations, complaints, defaults or other circumstances

Table A3.3 *continued*

Risk management tool	Description, attributes	Potential applications
Tools		
Risk ranking and filtering	• Method to compare and rank risks • Typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk, and weighting factors and risk score	• Prioritizing operating areas or sites for audit or assessment • Useful for situations when the risks and underlying consequences are diverse and difficult to compare using a single tool
Fault-tree analysis	• Method used to identify all root causes of an assumed failure or problem • Used to evaluate system or subsystem failures one at a time, but can combine multiple causes of failure by identifying causal chains • Relies heavily on full process understanding to identify causal factors	• Investigate product complaints • Evaluate deviations
Hazard operability analysis (HAZOP)	• Tool assumes that risk events are caused by deviations from the design and operating intentions • Uses a systematic technique to help identify potential deviations from normal use or design intentions	• Access manufacturing processes, suppliers, facilities and equipment • Commonly used to evaluate process safety hazards
Hazard analysis and critical control point (HACCP)	• Identify and implement process controls that consistently and effectively prevent hazard conditions from occurring • Bottom-up approach that considers how to prevent hazards from occurring and/or propagating • Emphasizes strength of preventive controls rather than ability to detect	• Better for preventive applications than reactive • Valuable precursor or complement to process validation • Assessment of the efficacy of critical control points and the ability to consistently execute them for any process

Table A3.3 *continued*

Risk management tool	Description, attributes	Potential applications
Tools		
Failure modes effects analysis (FMEA)	- Assumes comprehensive understanding of the process and that CPPs have been defined prior to initiating the assessment. Tool ensures that CPPs will be met. - Assesses potential failure modes for processes, and the probable effect on outcomes and/or product performance - Once failure modes are known, risk reduction actions can be applied to eliminate, reduce or control potential failures	Evaluate equipment and facilities; analyse a manufacturing process to identify high risk steps and/or critical parameters
Failure modes effects analysis (FMEA)	- Highly dependent upon strong understanding of product, process and/or facility under evaluation - Output is a relative "risk score" for each failure mode	

Source: Based on reference 9. This table has been amended, but was originally produced within the context of the Product Quality Research Institute (PQRI), 2107 Wilson Blvd, Suite 700, Arlington, Virginia 22201-3042, USA; web site: <https://pqri.org>. PQRI has kindly agreed to the use of its material.

References

1. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2, 2nd updated ed. Good manufacturing practices and inspection.* Geneva, World Health Organization, 2007; *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials.* World Health Organization, 2011 (CD-ROM).
2. *EudraLex The rules governing medicinal products in the European Union, Vol. 4. Good manufacturing practice (GMP) guidelines* (http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm).
3. Application of hazard analysis and critical control point (HACCP) methodology to pharmaceuticals. In: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2, 2nd updated ed. Good manufacturing practices and inspection.* Geneva, World Health Organization, 2007; *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials.* World Health Organization, 2011 (CD-ROM).
4. ICH harmonised tripartite guideline. ICH Q8(R2): Pharmaceutical development. August 2008 (<http://www.ich.org>).
5. ICH harmonised tripartite guideline. ICH Q9: Quality risk management 9 November 2005 IFPMA; Quality Risk Management ICH Q9 Briefing pack, July 2006, ICH-webpage publishing; ICH harmonised Q8/9/10 Questions & Answers, November 2010; ICH harmonised Q8/9/10 Training material, November 2010, ICH-webpage publishing; ICH harmonised points to consider for ICH Q8/Q9/Q10 implementation, 6 December 2011 (FIP, AM and IFPMA) (<http://www.ich.org>).
6. *Guidance for industry: PAT – A framework for innovative pharmaceutical development, manufacturing and quality assurance.* US Food and Drug Administration, Center for Drug Evaluation and Research (FDA CDER), September 2004 (<http://www.fda.gov/Drugs/default.htm>).
7. *Pharmaceutical cGMPs for the 21st century – A risk-based approach.* US Food and Drug Administration, Center for Drug Evaluation and Research (FDA CDER), September 2004 (<http://www.fda.gov/Drugs/default.htm>).
8. Medicines and Healthcare Products Regulatory Agency. *MHRA guidance: GMP-QRM – Frequently asked questions* (<http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodManufacturingPractice/FAQ/QualityRiskManagement/index.htm>).
9. Frank T et al. *Quality risk management principles and industry case studies* (December 2008) sponsored by the Product Quality Research Institute Manufacturing Technology Committee (PQRI-MTC) (<http://www.pqri.org>).
10. Boedecker B. GMP Inspectorate of Hannover, Germany. EU GMP requirements – quality systems. Presentation Ankara, Turkey Ministry of Health, 20–21 October 2009.
11. WHO guidelines on quality system requirements for national good manufacturing practice inspectorates. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth Report.* Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 8.
12. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER)/Center for Biologics Evaluation and Research (CBER)/Center for Veterinary Medicine (CVM) *guidance for industry – process validation: general principles and practices.* Silver Spring, MD, IFPMA, 2011 (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>).
13. Stamatis DH. *failure mode and effect analysis.* FMEA from theory to execution, 2nd ed. Milwaukee, American Society for Quality, Quality Press, 2003.

14. *Guidelines for failure modes and effects analysis (FMEA) for medical devices*. Ontario, Canada, Dyadem Press, 2003.
15. McDermott R et al. *The basics of FMEA*. Portland, OR, Productivity, 1996.
16. *IEC 61882 - Hazard operability analysis (HAZOP)*. Geneva, International Electrotechnical Commission, Headquarters (IEC 61882 Ed.1, b:2001).

Further reading

- *FDA's new process validation guidance – A detailed analysis*. European Compliance Academy, November 2008 (http://www.gmp-compliance.org/eca_news_1402_5699,6013.html).
- Validation of analytical procedures used in the examination of pharmaceutical materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 823), Annex 5.

4.6 Guideline on data integrity

Annex 4, WHO Technical Report Series, 1033, 2021

This document replaces the WHO *Guidance on good data and record management practices* (Annex 5, WHO Technical Report Series, No. 996, 2016) (1).

1. Introduction and background	523
2. Scope	523
3. Glossary	524
4. Data governance	526
5. Quality risk management	529
6. Management review	530
7. Outsourcing	531
8. Training	531
9. Data, data transfer and data processing	532
10. Good documentation practices	533
11. Computerized systems	534
12. Data review and approval	537
13. Corrective and preventive actions	537
References	537
Further reading	538
Appendix 1 Examples in data integrity management	539

1. Introduction and background

- 1.1 In recent years, the number of observations made regarding the integrity of data, documentation and record management practices during inspections of good manufacturing practice (GMP) (2), good clinical practice (GCP), good laboratory practice (GLP) and Good Trade and Distribution Practices (GTDP) have been increasing. The possible causes for this may include (i) reliance on inadequate human practices; (ii) poorly defined procedures; (iii) resource constraints; (iv) the use of computerized systems that are not capable of meeting regulatory requirements or are inappropriately managed and validated (3, 4); (v) inappropriate and inadequate control of data flow; and (vi) failure to adequately review and manage original data and records.
- 1.2 Data governance and related measures should be part of a quality system, and are important to ensure the reliability of data and records in good practice (GxP) activities and regulatory submissions. The data and records should be ‘attributable, legible, contemporaneous, original’ and accurate, complete, consistent, enduring, and available; commonly referred to as “ALCOA+”.
- 1.3 This document replaces the WHO *Guidance on good data and record management practices* (Annex 5, WHO Technical Report Series, No. 996, 2016) (1).

2. Scope

- 2.1 This document provides information, guidance and recommendations to strengthen data integrity in support of product quality, safety and efficacy. The aim is to ensure compliance with regulatory requirements in, for example clinical research, production and quality control, which ultimately contributes to patient safety. It covers electronic, paper and hybrid systems.
- 2.2 The guideline covers “GxP” for medical products. The principles could also be applied to other products such as vector control products.
- 2.3 The principles of this guideline also apply to contract givers and contract acceptors. Contract givers are ultimately responsible for the integrity of data provided to them by contract acceptors. Contract givers should therefore ensure that contract acceptors have the appropriate capabilities and comply with the principles contained in this guideline and documented in quality agreements.
- 2.4 Where possible, this guideline has been harmonised with other published documents on data integrity. This guideline should also be read with other WHO good practices guidelines and publications including, but not limited to, those listed in the references section of this document.

3. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

ALCOA+. A commonly used acronym for “attributable, legible, contemporaneous, original and accurate” which puts additional emphasis on the attributes of being complete, consistent, enduring and available throughout the data life cycle for the defined retention period.

Archiving. Archiving is the process of long-term storage and protection of records from the possibility of deterioration, and being altered or deleted, throughout the required retention period. Archived records should include the complete data, for example, paper records, electronic records including associated metadata such as audit trails and electronic signatures. Within a GLP context, the archived records should be under the control of independent data management personnel throughout the required retention period.

Audit trail. The audit trail is a form of metadata containing information associated with actions that relate to the creation, modification or deletion of GxP records. An audit trail provides for a secure recording of life cycle details such as creation, additions, deletions or alterations of information in a record, either paper or electronic, without obscuring or overwriting the original record. An audit trail facilitates the reconstruction of the history of such events relating to the record regardless of its medium, including the “who, what, when and why” of the action.

Backup. The copying of live electronic data, at defined intervals, in a secure manner to ensure that the data are available for restoration.

Certified true copy or true copy. A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

Data. All original records and true copies of original records, including source data and metadata, and all subsequent transformations and reports of these data which are generated or recorded at the time of the GMP activity and which allow full and complete reconstruction and evaluation of the GMP activity. Data should be accurately recorded by permanent means at the time of the activity. Data may be contained in paper records (such as worksheets and logbooks), electronic records and audit trails, photographs, microfilm or microfiche, audio or video files or any other media whereby information related to GMP activities is recorded.

Data criticality. This is defined by the importance of the data for the quality and safety of the product and how important data are for a quality decision within production or quality control.

Data governance. The sum total of arrangements which provide assurance of data quality. These arrangements ensure that data, irrespective of the process, format or technology in which it is generated, recorded, processed, retained, retrieved and used will ensure an attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring and available record throughout the data life cycle.

Data integrity risk assessment (DIRA). The process to map out procedures, systems and other components that generate or obtain data; to identify and assess risks and implement appropriate controls to prevent or minimize lapses in the integrity of the data.

Data life cycle. All phases of the process by which data are created, recorded, processed, reviewed, analysed and reported, transferred, stored and retrieved and monitored, until retirement and disposal. There should be a planned approach to assessing, monitoring and managing the data and the risks to those data, in a manner commensurate with the potential impact on patient safety, product quality and/or the reliability of the decisions made throughout all phases of the data life cycle.

Dynamic data. Dynamic formats, such as electronic records, allow an interactive relationship between the user and the record content. For example, electronic records in database formats allow the user to track, trend and query data; chromatography records maintained as electronic records allow the user or reviewer (with appropriate access permissions) to reprocess the data and expand the baseline to view the integration more clearly.

Electronic signatures. A signature in digital form (bio-metric or non-biometric) that represents the signatory. In legal terms, it is the equivalent of the handwritten signature of the signatory.

Good practices (GxP). An acronym for the group of good practice guides governing the preclinical, clinical, manufacturing, testing, storage, distribution and post-market activities for regulated pharmaceuticals, biologicals and medical devices, such as GLP, GCP, GMP, good pharmacovigilance practices (GVP) and good distribution practices (GDP).

Hybrid system. The use of a combination of electronic systems and paper systems.

Medical product. A term that includes medicines, vaccines, diagnostics and medical devices.

Metadata. Metadata are data that provide the contextual information required to understand other data. These include structural and descriptive metadata, which describe

the structure, data elements, interrelationships and other characteristics of data. They also permit data to be attributable to an individual. Metadata that are necessary to evaluate the meaning of data should be securely linked to the data and subject to adequate review. For example, in the measurement of weight, the number 8 is meaningless without metadata, such as, the unit, milligram, gram, kilogram, and so on. Other examples of metadata include the time or date stamp of an activity, the operator identification (ID) of the person who performed an activity, the instrument ID used, processing parameters, sequence files, audit trails and other data required to understand data and reconstruct activities.

Raw data. The original record (data) which can be described as the first-capture of information, whether recorded on paper or electronically. Raw data is synonymous with source data.

Static data. A static record format, such as a paper or electronic record, that is fixed and allows little or no interaction between the user and the record content. For example, once printed or converted to static electronic format chromatography records lose the capability of being reprocessed or enabling more detailed viewing of baseline.

4. Data governance

- 4.1 There should be a written policy on data integrity.
- 4.2 Senior management should be accountable for the implementation of systems and procedures in order to minimise the potential risk to data integrity, and to identify the residual risk using risk management techniques such as the principles of the guidance on quality risk management from WHO (5) and The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (6).
- 4.3 Senior management is responsible for the establishment, implementation and control of an effective data governance system. Data governance should be embedded in the quality system. The necessary policies, procedures, training, monitoring and other systems should be implemented.
- 4.4 Data governance should ensure the application of ALCOA+ principles.
- 4.5 Senior management is responsible for providing the environment to establish, maintain and continually improve the quality culture, supporting the transparent and open reporting of deviations, errors or omissions and data integrity lapses at all levels of the organization. Appropriate, immediate action should be taken when falsification of data is identified. Significant lapses in data integrity that may impact patient safety, product quality or efficacy should be reported to the relevant medicine regulatory authorities.

- 4.6 The quality system, including documentation such as procedures and formats for recording and reviewing of data, should be appropriately designed and implemented in order to provide assurance that records and data meet the principles contained in this guideline.
- 4.7 Data governance should address the roles, responsibilities, accountability and define the segregation of duties throughout the life cycle and consider the design, operation and monitoring of processes/systems to comply with the principles of data integrity, including control over authorized and unauthorized changes to data.
- 4.8 Data governance control strategies using quality risk management (QRM) principles (5) are required to prevent or mitigate risks. The control strategy should aim to implement appropriate technical, organizational and procedural controls. Examples of controls may include, but are not limited to:
- the establishment and implementation of procedures that will facilitate compliance with data integrity requirements and expectations;
 - the adoption of a quality culture within the company that encourages personnel to be transparent about failures, which includes a reporting mechanism inclusive of investigation and follow-up processes;
 - the implementation of appropriate controls to eliminate or reduce risks to an acceptable level throughout the life cycle of the data;
 - ensuring sufficient time and resources are available to implement and complete a data integrity programme; to monitor compliance with data integrity policies, procedures and processes through e.g. audits and self-inspections; and to facilitate continuous improvement of both;
 - the assignment of qualified and trained personnel and provision of regular training for personnel in, for example, GxP, and the principles of data integrity in computerized systems and manual/paper based systems;
 - the implementation and validation of computerized systems appropriate for their intended use, including all relevant data integrity requirements in order to ensure that the computerized system has the necessary controls to protect the electronic data (3); and
 - the definition and management of the appropriate roles and responsibilities for contract givers and contract acceptors, entered into quality agreements and contracts including a focus on data integrity requirements.
- 4.9 Data governance systems should include, for example:
- the creation of an appropriate working environment;

- active support of continual improvement in particular based on collecting feedback; and
- review of results, including the reporting of errors, unauthorized changes, omissions and undesirable results.

4.10 The data governance programme should include policies and procedures addressing data management. These should at least where applicable, include:

- management oversight and commitment;
- the application of QRM;
- compliance with data protection legislation and best practices;
- qualification and validation policies and procedures;
- change, incident and deviation management;
- data classification, confidentiality and privacy;
- security, cybersecurity, access and configuration control;
- database build, data collection, data review, blinded data, randomization;
- the tracking, trending, reporting of data integrity anomalies, and lapses or failures for further action;
- the prevention of commercial, political, financial and other organizational pressures;
- adequate resources and systems;
- workload and facilities to facilitate the right environment that supports DI and effective controls;
- monitoring;
- record-keeping;
- training; and
- awareness of the importance of data integrity, product quality and patient safety.

4.11 There should be a system for the regular review of data for consistency with ALCOA+ principles. This includes paper records and electronic records in day-to-day work, system and facility audits and self-inspections.

4.12 The effort and resources applied to assure the integrity of the data should be commensurate with the risk and impact of a data integrity failure.

4.13 Where weaknesses in data integrity are identified, the appropriate corrective and preventive actions (CAPA) should be implemented across all relevant activities and systems and not in isolation.

4.14 Changing from paper-based systems to automated or computerised systems (or vice-versa) will not in itself remove the need for appropriate data integrity controls.

4.15 Records (paper and electronic) should be kept in a manner that ensures compliance with the principles of this guideline. These include but are not limited to:

- ensuring time accuracy of the system generating the record, accurately configuring and verifying time zone and time synchronisation, and restricting the ability to change dates, time zones and times for recording events;
- using controlled documents and forms for recording GxP data;
- defining access and privilege rights to GxP automated and computerized systems, ensuring segregation of duties;
- ensuring audit trail activation for all interactions and restricting the ability to enable or disable audit trails (Note: 'back-end' changes and 'hard' changes, such as hard deletes, should not be allowed). Where audit trails can be disabled then this action should also appear in the audit trail;
- having automated data capture systems and printers connected to equipment and instruments in production (such as Supervisory Control and Data Acquisition (SCADA), Human Machine Interface (HMI) and Programme Logic Control (PLCs) systems), in , quality control, and in clinical research (such as Clinical Data Management (CDM) systems), where possible;
- designing processes in a way to avoid the unnecessary transcription of data or unnecessary conversion from paper to electronic and vice versa; and
- ensuring the proximity of an official GxP time source to site of GxP activity and record creation.

4.16 Systems, procedures and methodology used to record and store data should be periodically reviewed for effectiveness. These should be updated throughout the data life cycle, as necessary, where new technology becomes available. New technology implementation must be evaluated before implementation to verify the impact on data integrity.

5. Quality risk management

Note: documentation of data flows and data process maps are recommended to facilitate the assessment, mitigation and control of data integrity risks across the actual and intended data process(es).

- 5.1 Data Integrity Risk Assessment (DIRA) should be carried out in order to identify and assess areas of risk. This should cover systems and processes that produce data or, where data are obtained and inherent risks. The DIRAs should be risk-based, cover the life cycle of data and consider data criticality. Data criticality may be determined by considering how the data is used to influence the decisions made. The DIRAs should be documented and reviewed, as required, to ensure that it remains current.
- 5.2 The risk assessments should evaluate, for example, the relevant GxP computerised systems, supporting personnel, training, quality systems and outsourced activities.
- 5.3 DI risks should be assessed and mitigated. Controls and residual risks should be communicated. Risk review should be done throughout the document and data life cycle at a frequency based on the risk level, as determined by the risk assessment process.
- 5.4 Where the risk assessment has highlighted areas for remedial action, the prioritisation of actions (including the acceptance of an appropriate level of residual risk) and the prioritisation of controls should be documented and communicated. Where long-term remedial actions are identified, risk-reducing short-term measures should be implemented in order to provide acceptable data governance in the interim.
- 5.5 Controls identified may include organizational, procedural and technical controls such as procedures, processes, equipment, instruments and other systems in order to both prevent and detect situations that may impact on data integrity. Examples include the appropriate content and design of procedures, formats for recording, access control, the use of computerized systems and other means.
- 5.6 Efficient risk-based controls should be identified and implemented to address risks impacting data integrity. Risks include, for example, the deletion of, changes to and exclusion of data or results from data sets without written justification, authorisation where appropriate, and detection. The effectiveness of the controls should be verified (see Appendix 1 for examples).

6. Management review

- 6.1 Management should ensure that systems (such as computerized systems and paper systems) are meeting regulatory requirements in order to support data integrity compliance.
- 6.2 The acquisition of non-compliant computerized systems and software should be avoided. Where existing systems do not meet current requirements, appropriate controls should be identified and implemented based on risk assessment.

6.3 The effectiveness of the controls implemented should be evaluated through, for example:

- the tracking and trending of data;
- a review of data, metadata and audit trails (e.g. in warehouse and material management, production, quality control, case report forms and data processing); and
- routine audits and/or self-inspections, including data integrity and computerized systems.

7. Outsourcing

- 7.1 The selection of a contract acceptor should be done in accordance with an authorized procedure. The outsourcing of activities, ownership of data, and responsibilities of each party (contract giver and contract acceptor) should be clearly described in written agreements. Specific attention should be given to ensuring compliance with data integrity requirements. Provisions should be made for responsibilities relating to data when an agreement expires.
- 7.2 Compliance with the principles and responsibilities should be verified during periodic site audits. This should include the review of procedures and data (including raw data and metadata, paper records, electronic data, audit trails and other related data) held by the relevant contract acceptor identified in risk assessment.
- 7.3 Where data and document retention are contracted to a third party, particular attention should be given to security, transfer, storage, access and restoration of data held under that agreement, as well as controls to ensure the integrity of data over their life cycle. This includes static data and dynamic data. Mechanisms, procedures and tools should be identified to ensure data integrity and data confidentiality, for example, version control, access control, and encryption.
- 7.4 GxP activities, including outsourcing of data management, should not be sub-contracted to a third party without the prior approval of the contract giver. This should be stated in the contractual agreements.
- 7.5 All contracted parties should be aware of the requirements relating to data governance, data integrity and data management.

8. Training

- 8.1 All personnel who interact with GxP data and who perform GxP activities should be trained in relevant data integrity principles and abide by organization policies

and procedures. This should include understanding the potential consequences in cases of non-compliance.

- 8.2 Personnel should be trained in good documentation practices and measures to prevent and detect data integrity issues.
- 8.3 Specific training should be given in cases where computerized systems are used in the generation, processing, interpretation and reporting of data and where risk assessment has shown that this is required to relevant personnel. Such training should include validation of computerized systems and for example, system security assessment, back-up, restoration, disaster recovery, change and configuration management, and reviewing of electronic data and metadata, such as audit trails and logs, for each GxP computerized systems used in the generation, processing and reporting of data.

9. Data, data transfer and data processing

- 9.1 Data may be recorded on paper or captured electronically by using equipment and instruments including those linked to computerised systems. A combination of paper and electronic formats may also be used, referred to as a “hybrid system”.
- 9.2 Data integrity consideration are also applicable to media such as photographs, videos, DVDs, imagery and thin layer chromatography plates. There should be a documented rationale for the selection of such a method.
- 9.3 Risk-reducing measures such as scribes, second person oversight, verification and checks should be implemented where there is difficulty in accurately and contemporaneously recording data related to critical process parameters or critical quality attributes.
- 9.4 Results and data sets require independent verification if deemed necessary from the DIRA or by another requirement.
- 9.5 Programmes and methods (such as processing methods in sample analysis (see also Good Chromatography Practices, TRS 1025) should ensure that data meet ALCOA+ principles. Where results or data are processed using a different method/parameters, then each version of the processing method should be recorded. Data records, content versions together with audit trails containing the required details should allow for reconstruction of all data processing in GxP computerized systems over the data life cycle.
- 9.6 Data transfer/migration procedures should include a rationale and be robustly designed and validated to ensure that data integrity is maintained during the data

life cycle. Careful consideration should be given to understanding the data format and the potential for alteration at each stage of data generation, transfer and subsequent storage. The challenges of migrating data are often underestimated, particularly regarding maintaining the full meaning of the migrated records.

Data transfer should be validated. The data should not be altered during or after it is transferred to the worksheet or other application. There should be an audit trail for this process. The appropriate quality procedures should be followed if the data transfer during the operation has not occurred correctly. Any changes in the middle layer software should be managed through the appropriate Quality Management Systems (7).

10. Good documentation practices

Note: The principles contained in this section are applicable to paper data.

- 10.1 Good documentation practices should be implemented and enforced to ensure compliance with ALCOA+ principles.
- 10.2 Data and recorded media should be durable. Ink should be indelible. Temperature-sensitive or photosensitive inks and other erasable inks should not be used. Where related risks are identified, means should be identified in order to ensure traceability of the data over their life cycle.
- 10.3 Paper should not be temperature-sensitive, photosensitive or easily oxidizable. If this is not feasible or limited, then true or certified copies should be generated.
- 10.4 Specific controls should be implemented in order to ensure the integrity of raw data and results recorded on paper records. These may include, but are not limited to:
 - control over the issuance and use of loose paper sheets at the time of recording data;
 - no use of pencil or erasers;
 - use of single-line cross-outs to record changes with the identifiable person who made the change, date and reason for the change recorded (i.e. the paper equivalent to an electronic audit trail);
 - no use of correction fluid or otherwise, obscuring the original record;
 - controlled issuance of bound, paginated notebooks;
 - controlled issuance and reconciliation of sequentially numbered copies of blank forms with authenticity controls;
 - maintaining a signature and initial record for traceability and defining the levels of signature of a record; and

- archival of records by designated personnel in secure and controlled archives.

11. Computerized systems

(Note. This section highlights some specific aspects relating to the use of computerized systems. It is not intended to repeat the information presented in the other WHO guidelines here, such as the WHO Guideline on computerized systems (3), WHO Guideline on validation (2) and WHO Guideline on good chromatography practices (7). See references.)

- 11.1 Each computerized system selected should be suitable, validated for its intended use, and maintained in a validated state.
- 11.2 Where GxP systems are used to acquire, record, transfer, store or process data, management should have appropriate knowledge of the risks that the system and users may pose to the integrity of the data.
- 11.3 Software of computerized systems, used with GxP instruments and equipment, should be appropriately configured (where required) and validated. The validation should address for example the design, implementation and maintenance of controls in order to ensure the integrity of manually and automatically acquired data; ensure that Good Documentation Practices will be implemented; and that data integrity risks will be appropriately managed throughout the data life cycle. The potential for unauthorized and adverse manipulation of data during the life cycle of the data should be mitigated and, where possible, eliminated.
- 11.4 Where electronic instruments (e.g. certain pH meters, balances and thermometers) or systems with no configurable software and no electronic data retention are used, controls should be put in place to prevent the adverse manipulation of data and to prevent repeat testing to achieve the desired result.
- 11.5 Appropriate controls for the detection of lapses in data integrity principles should be in place. Technical controls should be used whenever possible but additional procedural or administrative controls should be implemented to manage aspects of computerised system control where technical controls are missing. For example, when stand-alone computerized systems with a user-configurable output are used, Fourier-transform infrared spectroscopy (FTIR) and UV spectrophotometers have user-configurable output or reports that cannot be controlled using technical controls. Other examples of non-technical detection and prevention mechanisms may include, but are not limited to, instrument usage logbooks and electronic audit trails.

Access and privileges

- 11.6. There should be a documented system in place that defines the access and privileges of users of systems. There should be no discrepancy between paper records and electronic records where paper systems are used to request changes for the creation and inactivation of users. Inactivated users should be retained in the system. A list of active and inactivated users should be maintained throughout the system life cycle.
- 11.7. Access and privileges should be in accordance with the role and responsibility of the individual with the appropriate controls to ensure data integrity (e.g. no modification, deletion or creation of data outside the defined privilege and in accordance with the authorized procedures defining review and approval where appropriate).
- 11.8. A limited number of personnel, with no conflict of interest in data, should be appointed as system administrators. Certain privileges such as data deletion, database amendment or system configuration changes should not be assigned to administrators without justification – and such activities should only be done with documented evidence of authorization by another responsible person. Records should be maintained and audit trails should be enabled in order to track activities of system administrators. As a minimum, activity logging for such accounts and the review of logs by designated roles should be conducted in order to ensure appropriate oversight.
- 11.9. For systems generating, amending or storing GxP data, shared logins or generic user access should not be used. The computerised system design should support individual user access. Where a computerised system supports only a single user login or limited numbers of user logins and no suitable alternative computerised system is available, equivalent control should be provided by third-party software or a paper-based method that provides traceability (with version control). The suitability of alternative systems should be justified and documented (8). The use of legacy hybrid systems should be discouraged and a priority timeline for replacement should be established.

Audit trail

- 11.10 GxP systems should provide for the retention of audit trails. Audit trails should reflect, for example, users, dates, times, original data and results, changes and reasons for changes (when required to be recorded), and enabling and disabling of audit trails.
- 11.11 All GxP relevant audit trails should be enabled when software is installed and remain enabled at all times. There should be evidence of enabling the audit

trail. There should be periodic verification to ensure that the audit trail remains enabled throughout the data life cycle.

- 11.12 Where a system cannot support ALCOA+ principles by design (e.g. legacy systems with no audit trail), mitigation measures should be taken for defined temporary periods. For example, add-on software or paper-based controls may be used. The suitability of alternative systems should be justified and documented. This should be addressed within defined timelines.

Electronic signatures

- 11.13 Each electronic signature should be appropriately controlled by, for example, senior management. An electronic signature should be:
 - attributable to an individual;
 - free from alteration and manipulation
 - be permanently linked to their respective record; and
 - date- and time-stamped.
- 11.14 An inserted image of a signature or a footnote indicating that the document has been electronically signed is not adequate unless it was created as part of the validated electronic signature process. The metadata associated with the signature should be retained.

Data backup, retention and restoration

- 11.15 Data should be retained (archived) in accordance with written policies and procedures, and in such a manner that they are protected, enduring, readily retrievable and remain readable throughout the records retention period. True copies of original records may be retained in place of the original record, where justified. Electronic data should be backed up according to written procedures.
- 11.16 Data and records, including backup data, should be kept under conditions which provide appropriate protection from deterioration. Access to such storage areas should be controlled and should be accessible only by authorized personnel.
- 11.17 Data retention periods should be defined in authorized procedures.
- 11.18 The decision for and manner in which data and records are destroyed, should be described in written procedures. Records for the destruction should be maintained.
- 11.19 Backup and restoration processes should be validated. The backup should be done routinely and periodically be restored and verified for completeness and accuracy of data and metadata. Where any discrepancies are identified, they should be investigated and appropriate action taken.

12. Data review and approval

- 12.2 There should be a documented procedure for the routine and periodic review, as well as the approval of data. Personnel with appropriate knowledge and experience should be responsible for reviewing and checking data. They should have access to original electronic data and metadata.
- 12.3 The routine review of GxP data and meta data should include audit trails. Factors such as criticality of the system (high impact versus low impact) and category of audit trail information (e.g. batch specific, administrative, system activities, and so on) should be considered when determining the frequency of the audit trail review.
- 12.4 A procedure should describe the actions to be taken where errors, discrepancies or omissions are identified in order to ensure that the appropriate corrective and preventive actions are taken.
- 12.5 Evidence of the review should be maintained.
- 12.6 A conclusion, where required, following the review of original data, metadata and audit trail records should be documented, signed and dated.

13. Corrective and preventive actions

- 13.1 Where organizations use computerized systems (e.g. for GxP data acquisition, processing, interpretation, reporting) which do not meet current GxP requirements, an action plan towards upgrading such systems should be documented and implemented in order to ensure compliance with current GxP.
- 13.2 When lapses in GxP relevant data regarding data integrity are identified, a risk-based approach may be used to determine the scope of the investigation, root cause, impact and CAPA, as appropriate. Health authorities, contract givers and other relevant organizations should be notified if the investigation identifies a significant impact or risk to, for example, materials, products, patients, reported information or data in application dossiers, and clinical trials.

References

- 1. Guidelines on good manufacturing practices for pharmaceutical products: main principle. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 986; https://iris.who.int/bitstream/handle/10665/112733/WHO_TRS_986_eng.pdf?sequence=1).

2. Good manufacturing practices: guidelines on validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations; fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; <https://iris.who.int/bitstream/handle/10665/312316/9789241210287-eng.pdf?sequence=1>).
3. Good manufacturing practices: guidelines on validation. Appendix 5. Validation of computerized systems. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations; fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; <https://iris.who.int/bitstream/handle/10665/312316/9789241210287-eng.pdf?sequence=1>).
4. Guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations; forty-seventh report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 981; https://iris.who.int/bitstream/handle/10665/81144/WHO_TRS_981_eng.pdf?sequence=1).
5. ICH harmonised tripartite guideline. Quality risk management Q9. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use; 2005 (<https://database.ich.org/sites/default/files/Q9%20Guideline.pdf>, accessed 12 June 2020).
6. Good chromatography practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations; fifty-fourth report. Geneva: World Health Organization; 2020: Annex 4 (WHO Technical Report Series, No. 1025; <https://iris.who.int/bitstream/handle/10665/331814/9789240001824-eng.pdf?sequence=1>).
7. MHRA GxP data integrity guidance and definitions; Revision 1: Medicines & Healthcare Products Regulatory Agency (MHRA), London, March 2018 (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/687246/MHRA_GxP_data_integrity_guide_March_edited_Final.pdf, accessed 12 June 2020).

Further reading

- Data integrity and compliance with CGMP guidance for industry: questions and answers guidance for industry. U.S. Department of Health and Human Services, Food and Drug Administration; 2016 (<https://www.fda.gov/files/drugs/published/Data-Integrity-and-Compliance-With-Current-Good-Manufacturing-Practice-Guidance-for-Industry.pdf>, accessed 15 June 2020).
- Good Practices for data management and integrity in regulated GMP/GDP environments. Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), November 2018 (<https://picscheme.org/layout/document.php?id=1567>, accessed 15 June 2020).
- Baseline guide Vol 7: risk-based manufacture of pharma products; 2nd edition.
- ISPE Baseline® Guide, July 2017. ISPEGAMP® guide: records and data integrity; March 2017.
- Data integrity management system for pharmaceutical laboratories PDA Technical Report, No. 80; August 2018.
- ICH harmonised tripartite guideline. Pharmaceutical Quality System Q10. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use; 2008 (<https://database.ich.org/sites/default/files/Q10%20Guideline.pdf>, accessed 2 October 2020).

Appendix 1

Examples in data integrity management

This Appendix reflects on some examples in data integrity management in order to support the main text on data integrity. It should be noted that these are examples and are intended for the purpose of clarification only.

Example 1: Quality risk management and data integrity risk assessment

Risk management is an important part of good practices (GxP). Risks should be identified and assessed and controls identified and implemented in order to assist manufacturers in preventing possible DI lapses.

As an example, a Failure Mode and Effects Analysis (FMEA) model (or any other tool) can be used to identify and assess the risks relating to any system where data are, for example, acquired, processed, recorded, saved and archived. The risk assessment can be done as a prospective exercise or retrospective exercise. Corrective and preventive action (CAPA) should be identified, implemented and assessed for its effectiveness.

For example, if during the weighing of a sample, the entry of the date was not contemporaneously recorded on the worksheet but the date is available on the print-out from a weighing balance and log book for the balance for that particular activity. The fact that the date was not recorded on the worksheet may be considered a lapse in data integrity expectations. When assessing the risk relating to the lack of the date in the data, the risk may be considered different (lower) in this case as opposed to a situation when there is no other means of traceability for the activity (e.g. no print-out from the balance). When assessing the risk relating to the lapse in data integrity, the severity could be classified as “low” (the data is available on the print-out); it does not happen on a regular basis (occurrence is “low”), and it could easily be detected by the reviewer (detection is “high”) – therefore the overall risk factor may be considered low. The root cause as to why the record was not made in the analytical report at the time of weighing should still be identified and the appropriate action taken to prevent this from happening again.

Example 2: Good documentation practices in data integrity

Documentation should be managed with care. These should be appropriately designed in order to assist in eliminating erroneous entries, manipulation and human error.

Formats

Design formats to enable personnel to record or enter the correct information contemporaneously. Provision should be made for entries such as, but not limited to,

dates, times (start and finish time, where appropriate), signatures, initials, results, batch numbers and equipment identification numbers. When a computerized system is used, the system should prompt the personnel to make the entries at the appropriate step.

Blank sheets of paper

The use of blank sheets should not be encouraged. Where blank sheets are used (e.g. to supplement worksheets, laboratory notebooks and master production and control records), the appropriate controls have to be in place and may include, for example, a numbered set of blank sheets issued which are reconciled upon completion. Similarly, bound paginated notebooks, stamped or formally issued by designated personnel, allow for the detection of unofficial notebooks and any gaps in notebook pages. Authorization may include two or three signatures with dates, for example, “prepared by” or “entered by”, “reviewed by” and “approved by”.

Error in recording data

Care should be taken when entries of data and results (electronic and paper records) are made. Entries should be made in compliance with good documentation practices. Where incorrect information had been recorded, this may be corrected provided that the reason for the error is documented, the original entry remains readable and the correction is signed and dated.

Example 3: Data entry

Data entry includes for example sample receiving registration, sample analysis result recording, logbook entries, registers, batch manufacturing record entries and information in case report forms. The recording of source data on paper records should be done using indelible ink, in a way that is complete, accurate, traceable, attributable and free from errors. Direct entry into electronic records should be done by responsible and appropriately trained individuals. Entries should be traceable to an individual (in electronic records, thus having an individual user access) and traceable to the date (and time, where relevant). Where appropriate, the entry should be verified by a second person or entered through technical means such as the scanning of bar-codes, where possible, for the intended use of these data. Additional controls may include the locking of critical data entries after the data are verified and a review of audit trails for critical data to detect if they have been altered. The manual entry of data from a paper record into a computerized system should be traceable to the paper records used which are kept as original data.

Example 4: Dataset

All data should be included in the dataset unless there is a documented, justifiable, scientific explanation and procedure for the exclusion of any result or data. Whenever

out of specification or out of trend or atypical results are obtained, they should be investigated in accordance with written procedures. This includes investigating and determining CAPA for invalid runs, failures, repeats and other atypical data. The review of original electronic data should include checks of all locations where data may have been stored, including locations where voided, deleted, invalid or rejected data may have been stored. Data and metadata related to a particular test or product should be recorded together. The data should be appropriately stored in designated folders. The data should not be stored in other electronic folders or in other operating system logs. Electronic data should be archived in accordance with a standard operating procedure. It is important to ensure that associated metadata are archived with the relevant data set or securely traceable to the data set through relevant documentation. It should be possible to successfully retrieve all required data and metadata from the archives. The retrieval and verification should be done at defined intervals and in accordance with an authorized procedure.

Example 5: Legible and enduring

Data and metadata should be readable during the life cycle of the data. Electronic data are normally only legible/readable through the original software application that created it. In addition, there may be restrictions around the version of a software application that can read the data. When storing data electronically, ensure that any restrictions which may apply and the ability to read the electronic data are understood. Clarification from software vendors should be sought before performing any upgrade, or when switching to an alternative application, to ensure that data previously created will be readable.

Other risks include the fading of microfilm records, the decreasing readability of the coatings of optical media such as compact disks (CDs) and digital versatile/video disks (DVDs), and the fact that these media may become brittle.

Similarly, historical data stored on magnetic media will also become unreadable over time as a result of deterioration. Data and records should be stored in an appropriate manner, under the appropriate conditions.

Example 6: Attributable

Data should be attributable, thus being traceable to an individual and where relevant, the measurement system. In paper records, this could be done through the use of initials, full handwritten signature or a controlled personal seal. In electronic records, this could be done through the use of unique user logons that link the user to actions that create, modify or delete data; or unique electronic signatures which can be either biometric or non-biometric. An audit trail should capture user identification (ID), date and time stamps and the electronic signature should be securely and permanently linked to the signed record.

Example 7: Contemporaneous

Personnel should record data and information at the time these are generated and acquired. For example, when a sample is weighed or prepared, the weight of the sample (date, time, name of the person, balance identification number) should be recorded at that time and not before or at a later stage. In the case of electronic data, these should be automatically date- and time-stamped. In case hybrid systems are to be used, including the use for an interim period, the potential and criticality of system breaches should be covered in the assessment with documented mitigating controls in place. (The replacement of hybrid systems should be a priority with a documented CAPA plan.) The use of a scribe to record an activity on behalf of another operator should be considered only on an exceptional basis and should only take place where, for example, the act of recording places the product or activity at risk, such as, documenting line interventions by aseptic area operators. It needs to be clearly documented when a scribe has been applied.

“In these situations, the recording by the second person should be contemporaneous with the task being performed, and the records should identify both the person performing the task and the person completing the record. The person performing the task should countersign the record wherever possible, although it is accepted that this countersigning step will be retrospective. The process for supervisory (scribe) documentation completion should be described in an approved procedure that specifies the activities to which the process applies.” (Extract taken from the Medicines & Healthcare Products Regulatory Agency (MHRA) *GxP data integrity guidance and definitions* (10).)

A record of employees indicating, their name, signature, initials or other mark or seal used should be maintained to enable traceability and to uniquely identify them and the respective action.

Example 8: Changes

When changes are made to any GxP result or data, the change should be traceable to the person who made the change as well as the date, time and reason for the change. The original value should not be obscured. In electronic systems, this traceability should be documented via computer generated audit trails or in other metadata fields or system features that meet these requirements. Where an existing computerized system lacks computer-generated audit trails, personnel may use alternative means such as procedurally controlled use of log-books, change control, record version control or other combinations of paper and electronic records to meet GxP regulatory expectations for traceability to document the what, who, when and why of an action.

Example 9: Original

The first or source capture of data or information and all subsequent data required to fully reconstruct the conduct of the GxP activity should be available. In some cases, the electronic data (electronic chromatogram acquired through high-performance liquid chromatography (HPLC)) may be the first source of data and, in other cases, the recording of the temperature on a log sheet in a room – by reading the value on a data logger. This data should be reviewed according to the criticality and risk assessment.

Example 10: Controls

Based on the outcome of risk assessment which should cover all areas of data governance and data management, appropriate and effective controls should be identified and implemented in order to assure that all data, whether in paper records or electronic records, will meet GxP requirements and ALCOA+ principles. Examples of controls may include, but are not limited to:

- the qualification, calibration and maintenance of equipment, such as balances and pH meters, that generate printouts;
- the validation of computerized systems that acquire, process, generate, maintain, distribute, store or archive electronic records;
- review and auditing of activities to ensure that these comply with applicable GxP data integrity requirements;
- the validation of systems and their interfaces to ensure that the integrity of data will remain while transferring between/among computerized systems;
- evaluation to ensure that computerized systems remain in a validated state;
- the validation of analytical procedures;
- the validation of production processes;
- a review of GxP records;
- ensuring effective review and oversight of the Batch Release Systems and processes by using different oversight and review techniques to ensure that data have not changed since the original entry; and
- the investigation of deviations, out of trend and out of specifications results.

Example 11: Accuracy

Points to consider for assuring accurate GxP records:

- the entry of critical data into a computer by an authorized person (e.g. entry of a master processing formula) requires an additional check on

the accuracy of the data entered manually. This check may be done by independent verification and release for use by a second authorized person or by validated electronic means. For example, to detect and manage risks associated with critical data, procedures would require verification by a second person;

- validation and control over formulae for calculations including electronic data capture systems;
- ensuring correct entries into the laboratory information management system (LIMS) such as fields for specification ranges;
- other critical master data, as appropriate. Once verified, these critical data fields should normally be locked in order to prevent further modification and only be modified through a formal change control process;
- the process of data transfer between systems should be validated;
- the migration of data including planned testing, control and validation; and
- when the activity is time-critical, printed records should display the date and time stamp.

4.7 WHO general guidance on variations to multisource pharmaceutical products

Annex 10, WHO Technical Report Series, 996, 2016

1. Introduction	546
2. Scope	546
3. Glossary	547
4. General considerations	548
5. Reporting categories for quality changes	549
5.1 Notifications	550
5.2 Minor variations	550
5.3 Major variations	550
6. New applications	551
7. Considerations for changes in product information and labelling	552
8. Procedures	552
8.1 General	552
8.2 Presubmission meetings	553
8.3 Proposed documentation for minor variations	553
8.4 Proposed documentation for variations requiring prior approval	554
8.5 Review procedures	554
References	555

1. Introduction

A marketing authorization (MA) holder or applicant is responsible for the quality, safety and efficacy (QSE) of a finished pharmaceutical product (FPP) that is placed on the market, throughout its life cycle. After the FPP has been authorized for marketing, the manufacturer will often wish to make changes (variations) for a number of reasons, for example, to respond to technical and scientific progress, to improve the quality of the FPP, to apply updates to the retest period for the active pharmaceutical ingredient (API) or shelf life of the FPP, to meet market requirements such as for scale-up or additional manufacturing sites, or to update product information (e.g. the information on adverse reactions). Such changes, regardless of their nature, are referred to as variations and may require the approval of the national medicines regulatory authority (NMRA) prior to implementation.

NMRAs and MA holders should recognize that:

- any change to the manufacture of the API or the FPP may impact the QSE of that FPP;
- any change to the information associated with the FPP (i.e. product labelling information) may have an impact on the safe and effective use of that FPP.

This document is intended to serve as a guide for establishing national requirements for the regulation of post-approval changes. The proposed categories of changes and reporting procedures are provided in these guidelines. It is possible that modification of these principles may be justified in light of risk–benefit and legal considerations specific to each NMRA.

2. Scope

This document provides guidance for NMRAs on the regulation of variations to the original MA dossier or MA for an authorized multisource pharmaceutical product on:

- procedures and criteria for the appropriate categorization and reporting of changes; and
- how NMRAs can establish regulatory procedures for the post-approval variations to an authorized FPP.

These guidelines can be used by NMRAs with respect to changes to the quality sections of product dossiers and should be read in conjunction with the *Guidelines on submission of documentation for a multisource (generic) finished product: quality part (1)* as well as other related WHO guidelines or applicable national guidelines. These guidelines are intended to provide an overview of the principles that NMRAs should

consider when establishing pharmaceutical product variation procedures. Specific guidance on data requirements or risk categorization of a particular change cannot be provided since the approach taken by a specific NMRA is intrinsically linked to the regulatory framework and resources available to that NMRA. Nonetheless, illustrative examples of the data required to enable NMRAs to evaluate the impact of the variation on QSE are provided in detail in the *Guidelines on variations to a prequalified product* (2) or other national guidelines.

These guidelines are applicable only to APIs manufactured by chemical synthesis or semisynthetic processes and FPPs containing such APIs. APIs produced by fermentation and APIs of biological, biotechnological or herbal origin fall outside the scope of these guidelines. For vaccines, NMRAs may refer to the *WHO Guidelines for procedures and data requirements for changes to approved vaccines* (3).

3. Glossary

The definitions provided below apply to the terms used in this guidance. They may have different meanings in other contexts and documents.

active pharmaceutical ingredient. Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form, and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

active pharmaceutical ingredient starting material. A raw material, intermediate or an active pharmaceutical ingredient (API) that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement or produced in-house.

biobatch. The batch used to establish bioequivalence or similarity to the comparator product as determined in bioequivalence or biowaiver studies, respectively.

finished pharmaceutical product. A finished dosage form of a pharmaceutical product which has undergone all stages of manufacture including packaging in its final container and labelling.

in-process control. Check performed during manufacture to monitor or to adjust the process in order to ensure that the final product conforms to its specifications.

manufacturer. A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals.

marketing authorization holder. For the purposes of this document, the term marketing authorization holder refers to any person or entity that holds the legal responsibility for the product on the market by submission of the required documentation on a product that has been listed after evaluation as registered or approved.

multisource (generic) pharmaceutical product. Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

officially recognized pharmacopoeia (or compendium). Those pharmacopoeias recognized by the national regulatory agencies (e.g. national pharmacopoeia (if applicable), the *British Pharmacopoeia*, the *European Pharmacopoeia*, *The International Pharmacopoeia*, the *Japanese Pharmacopoeia* and the *United States Pharmacopoeia*).

pilot-scale batch. A batch of an active pharmaceutical ingredient or finished pharmaceutical product manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger, unless otherwise adequately justified.

production batch. A batch of an active pharmaceutical ingredient or finished pharmaceutical product manufactured at production scale by using production equipment in a production facility as specified in the application.

register. A list of all the pharmaceutical products authorized for marketing in a particular country. The medicines regulatory authority of the country in question maintains the register.

registered medicinal products. Pharmaceutical products that have a marketing authorization.

validation. The demonstration, with documentary evidence, that any procedure, process, equipment, material, activity or system leads to the expected results.

variation. A change to any aspect of a pharmaceutical product, including but not limited to, the change of use of a starting material, a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labelling and product information.

4. General considerations

For any change, the MA holder must consider the potential impact upon the QSE of the FPP. As part of this consideration the MA holder should decide if the information in the original MA needs to be supplemented and whether this requires an official submission to the responsible NMRA or a change in the application dossier, based on the recommendations in these guidelines. Prior to implementing the variation, the MA holder should assess the effects of the variation and demonstrate through appropriate studies the absence of a significant negative effect of the change on the QSE of the FPP. MA holders should be aware that some variations generate subsequent changes that might require the submission of additional consequential variations. Therefore, for any given variation, the MA holder should consider whether it is better to submit more than

one variation. In general no variation should be implemented without the approval of the NMRA unless exempted in the national guidelines.

Even well-resourced agencies find it difficult to evaluate all the pharmaceutical changes that are made to all products. This has resulted in a shift towards increased self-assessment of changes by the MA holder. Therefore it is necessary to define those changes that can be made without the NMRA's prior approval (self-assessable changes) and those that require prior approval based on an understanding of the risk and how best to manage this risk. NMRAs may also establish an intermediate category of changes that do not require prior approval but must be notified ("notifiable" changes) and may or may not be subject to assessment.

MA holders are expected to evaluate the specific change that they are planning to make in the context of their particular circumstances to determine the impact on product QSE. In an application to vary the MA, the MA holder advises the NMRA of an intended change and submits appropriate supportive data. To encourage MA holders to give prior notice regarding such changes, submissions for variations should be processed as quickly as possible. The NMRA should consider publication of the timelines for processing the variations.

Implementation of these guidelines should not affect supply of and access to medicines. Therefore NMRAs are strongly encouraged to establish requirements that are commensurate with public health priorities and their own regulatory capacity and resources. Communication of proposed procedures and requirements to the pharmaceutical industry should also be ensured so that they can adequately plan for the implementation of any new guidance.

Regional NMRA associations or networks could serve as forums for sharing information and exchanging experience on technical issues and regulatory decisions. Use of such networks would expand the capacity of individual NMRAs through work sharing and recognition of the decisions of other NMRAs in the network and convergence of regulatory requirements, thus avoiding unnecessary repetition of evaluations of the same variation by multiple NMRAs.

In these guidelines, descriptions of the reporting categories are discussed in section 5; proposed recommendations on the regulatory procedures for the reporting of changes to the NMRAs are discussed in section 8.

5. Reporting categories for quality changes

In order to enhance predictability, guidelines on the data requirements and conditions for the various categories of variations should be established and regularly updated in light of scientific and technical progress, taking into account the impact of the variation on the product QSE and how to manage this risk.

In addition to considering the impact of the change on a product's QSE, NMRAs may also modify the risk classification of a change through the introduction of prerequisites

that must be met by the MA holder. In this way a change nominally identified as high-risk may be categorized across several risk categories depending on the conditions applied. Generally speaking the greater the number and specificity of the prerequisites the greater the possibility that the change can be self-assessed by the MA holder.

An additional consideration for NMRAs when designing their variation procedure is the determination of the default risk-category of changes not described in their variation guidance. For example, if an unspecified change defaults to a major variation, then effort should be focused on describing the conditions and data requirements for circumstances where the change might be considered as a lower risk category. In contrast, if a change defaults to a minor variation, then the conditions and data requirements of major changes and low-risk changes must be clearly defined.

The definitions outlined in the following reporting categories are intended to provide examples of change classification strategies that may be adopted by NMRAs for quality-related changes. Examples of specific variations data and conditions requirements can be found in the *WHO guidelines on variations to a prequalified product* (2) or other national regulatory guidelines that NMRAs may consult or reference; attention should be given to the default risk category underpinning the specific guidance.

NMRAs should also issue statements that whenever the MA holder is unclear about the categorization of a particular variation, the respective NMRA should be contacted.

Variations may be categorized into major variation, minor variation and notification. NMRAs may decide to have fewer categories or more categories depending on their national requirements.

5.1 Notifications

Notifications can be made for changes to the product that may have no potential or a minimal potential to have a negative impact on the QSE. The MA holder may implement such variations without prior approval by the NMRA. The NMRA may require the MA holder to submit these variations as immediate notifications (i.e. within a specific time frame after implementation) or as annual notifications.

5.2 Minor variations

Minor variations are changes to the product that may have a potential to have a moderate or negative impact on the QSE. Therefore such changes must be submitted to the NMRA with all required documentation prior to implementation. The MA holder may implement the change if no objection letter has been issued within a time period specified by the NMRA.

5.3 Major variations

Major variations are changes to the product that may have a significant potential to have a negative impact on the QSE. A major variation should be reviewed and approved by the NMRA prior to implementation of the change.

Individual changes normally require the submission of separate variations, but to increase efficiency NMRA's may accept grouping of variations under specific circumstances, for example:

- when variations are consequential to each other, e.g. introduction of a new impurity specification that requires a new analytical procedure;
- when the same change affects multiple FPPs from the same MA holder, e.g. addition of a new API manufacturing site for multiple FPPs;
- when all the changes are annual notifications;
- when variations are related to a common technical topic, for example drug master file updates or changes to the analytical procedures and specifications to comply with pharmacopoeias.

MA holders and NMRA's should exercise caution whenever several changes to the same FPP are envisaged. Although each of the individual changes may be classified in a particular category, classification within a higher-risk category may be warranted as a result of the composite effect of these changes. In all such cases, it is recommended that MA holders are able to contact the NMRA prior to submission of the variation application to obtain guidance on classifying such changes.

If changes to the dossier only concern editorial changes, such changes typically need not be submitted as a separate variation but can be included as a notification together with a subsequent variation concerning that part of the dossier. In such a case a declaration should be provided indicating that the contents of the associated sections of the dossier have not been altered by the editorial changes beyond the substance of the variation submitted.

The "timeline" and "implementation of the variation" are subject to the NMRA's specific provisions and should be made publicly available.

6. New applications

Certain changes are so fundamental that they alter the terms of the accepted dossier and consequently cannot be considered as variations. In these cases submission of a new dossier should be considered, in line with applicable national requirements for applications for MA.

- Examples of such changes are:
- change of the API to a different API;
- inclusion of an additional API in a multicomponent product;
- removal of one API from a multicomponent product;
- change in the dose and/or strength of one or more APIs;

- change from an immediate-release product to an extended- or delayed-release dosage form or vice versa;
- change from a liquid to a powder for reconstitution or vice versa;
- changes in the route of administration.

7. Considerations for changes in product information and labelling

For any change to product information¹ (summary of product characteristics (SmPC), patient information leaflet (PIL) and/or labels) the NMRA should be notified and submission of the revised product information and/or labelling is expected as per country-specific requirements.

When a variation leads to a revision of the SmPC, the PIL and/or labelling, the updated information should be submitted as part of the variation. NMRAs may request the MA holder to submit a side-by-side tabular comparison of the current and proposed changes.

Note that a change in the recommendations for use for a multisource product, such as indications or patient population would result in the product no longer being interchangeable with the comparator product. Therefore the NMRAs may need to take this into consideration prior to approval of such changes.

8. Procedures

8.1 General

NMRAs should establish procedures and criteria for adequate oversight of variations to authorized products. These should include written instructions regarding the submission procedures and timelines with action dates, to be consulted by MA holders when they prepare applications for variations. Depending on the category of the variation, different timelines may be applicable.

Regulation of post-approval variations is part of the whole regulatory framework, which includes among other aspects, MA, good manufacturing practices (GMP) inspection and post-marketing surveillance. Different branches of the NMRA often perform these activities. It is essential that these different branches interact and exchange information effectively and that the roles and responsibilities of each branch are clearly defined, particularly when they operate as separate entities. When multiple branches are involved in the evaluation of a variation a formal decision-making

¹ Different regions and countries use different terminology for product information. In this document, package insert, the PIL and label are used to refer to product information.

process should be in place to discuss, for instance, whether a change may require a GMP inspection or may be reviewed during the next routine inspection. Procedures should also be established so that the outcomes of inspections are verified or taken into account prior to the approval of variations. Good coordination and communication are pivotal.

8.2 Presubmission meetings

NMRAs should establish procedures to allow MA holders the opportunity to obtain advice prior to submitting variations. MA holders should be encouraged to contact the NMRA regarding plans for future changes and proposed filing dates for changes to authorized products to aid NMRAs in the planning and allocation of review resources.

8.3 Proposed documentation for minor variations

Where applicable the following basic information may be included as part of the description of the variation in the immediate notification, or the annual notification where prior approval is not required:

- a covering letter (including a list of changes, describing each in sufficient detail to allow for a quick assessment as to whether the appropriate reporting category has been used);
- an application form;
- a list of subsections of the current dossier affected by the change(s);
- a list and description of each change, reason for change(s) and the date each change was implemented (each change should be described in sufficient detail to allow for a quick assessment as to whether the appropriate reporting category has been used);
- the relevant summary of data from studies and tests performed to assess the effects of each variation on product quality, including (where applicable) a list of cross- references to the change control and change validation protocols and standard operating procedures (SOPs) that were used to assess or demonstrate the effect of the variation;
- copies of the updated subsections of the original dossier.

The description should also include:

- the name(s) of one or more FPP(s) affected or involved in the change (e.g. different label strengths/product presentations);
- reference to any previously approved variations, if the change affected multiple products.

Executed batch records, SOPs and data from studies and tests performed to assess the effects of each change should be kept on file and made available to the NMRA upon request (e.g. during an inspection).

In the case of annual notifications, which represents the lowest risk category, it may be permissible not to request any summary data if the acceptability of the change can be determined without them.

8.4 Proposed documentation for variations requiring prior approval

Where applicable the following basic information may be included in the application for variations requiring prior approval:

- a covering letter (including a list of changes describing each in sufficient detail to allow for a quick assessment as to whether the appropriate reporting category has been used);
- an application form;
- a list of subsections of the original dossier affected by the change(s);
- a document summarizing the current and proposed condition(s) and the reason(s) for the change(s);
- where relevant, a side-by-side comparison of the currently approved and the proposed information;
- replacement of the relevant subsections of the dossier in accordance with the acceptable dossier format for the NMRAs concerned, with the proposed changes clearly annotated;
- copies of the SmPC, PIL and labels, if relevant;
- the relevant summary of data from studies and tests performed to assess the effects of each variation on product quality, including (where applicable) a list of cross-references to change control and change validation protocols and SOPs that were used to assess or demonstrate the effect of the variation;
- registration status and date of the proposed change(s) in other countries and/or agencies that have already approved the variation(s), especially the country of origin and the reference agencies.

8.5 Review procedures

Taking into account the national situation, the capacity of the NMRA and regional harmonization initiatives, the NMRA should adopt a risk-based review strategy for assessment, concentrating most effort on those changes considered to carry the greatest

risk. A key factor in reducing workload is to ensure that the variation documentation requirements permit rapid assessment of changes. Moreover, the NMRA may consider whether it will:

- rely on decisions made by other national authorities;
- rely on assessment reports prepared by other national authorities;
- prepare its own full assessment reports;
- use some combination of these approaches.

If the decision of another NMRA is adopted, it is nevertheless essential for certain minimum information to be available. Where the NMRA has granted MA based on a reference NMRA or WHO prequalification it is recommended that any post-approval variations of such products should have prior approval from the initial reference NMRA or WHO prequalification (4, 5), as appropriate.

References

1. Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 6 (WHO Technical Report Series, No. 986; https://iris.who.int/bitstream/handle/10665/112733/WHO_TRS_986_eng.pdf?sequence=1&isAllowed=y).
2. Guidelines on variations to a prequalified product. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013: Annex 3 (WHO Technical Report Series, No. 981; https://iris.who.int/bitstream/handle/10665/81144/WHO_TRS_981_eng.pdf?sequence=1&isAllowed=y).
3. Guidelines for procedures and data requirements for changes to approved vaccines. In: WHO Expert Committee on Biological Standardization: sixty-fifth report. Geneva: World Health Organization; 2015: Annex 4 (Technical Report Series, No. 993; https://iris.who.int/bitstream/handle/10665/173739/9789240694095_eng.pdf?sequence=1).
4. Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 5 (WHO Technical Report Series, No. 986; https://iris.who.int/bitstream/handle/10665/112733/WHO_TRS_986_eng.pdf?sequence=1&isAllowed=y).
5. Collaborative procedure between the World Health Organization Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 8 (WHO Technical Report Series, No. 996; <https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>).

4.8 WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation

Annex 3, WHO Technical Report Series, 917, 2003

Preamble

The quality of pharmaceuticals has been a concern of WHO since its inception. Owing to the nature of these products, this concern includes the quality of the starting materials, i.e. active pharmaceutical ingredients (APIs) and excipients, used for the production of pharmaceuticals.

This guidance text, in combination with other recommendations and guidelines issued by WHO, will be an important step towards ensuring the quality and traceability of pharmaceutical starting materials and in assigning the responsibility for specifications within the processes of manufacture, storage and distribution of pharmaceutical starting materials.

Member States are urged to establish and maintain a legal framework and regulatory approach to ensure that good practices for the trade and distribution of pharmaceutical starting materials are followed. Member States can establish appropriate regulatory control by implementing one or both of the following approaches:

- licensing of suppliers, including traders, brokers and distributors; and/or
- a registration or notification system of suppliers, including traders, brokers and distributors.

A variety of WHO guidelines ready for use and inclusion into national legislation are available. Their implementation will be crucial throughout the process towards ensuring the availability and use of quality pharmaceutical starting materials in the manufacture of medicines.

Where a licensing system already exists, inspections should be performed by persons from the competent national or regional statutory authority to assess compliance with good trade and distribution practices (GTDP). Where a notification or registration system is to be implemented, voluntary inspections may be performed before certification for compliance with GTDP.

The use of the new certification scheme is based on the existence of a quality assurance system for the production of starting materials.

All parties involved in the trade and distribution of pharmaceutical starting materials are strongly encouraged to comply with the GTDP. Manufacturers of pharmaceutical products should encourage and assist their suppliers to use good storage practice (GSP), GTDP and the relevant parts of good manufacturing practice (GMP).

Trade associations are also encouraged to incorporate these principles into their own codes of practice to be followed by their members.

Another recommendation is the development of a global database listing information on suppliers (e.g. names and addresses) to enable customers to verify supplier information. A global database could later be established to assist in the attempt to address the problem of counterfeiting of pharmaceutical materials.

Training workshops and conferences on GTDP should be planned to promote these principles.

The establishment of model certificates for GSP and GTDP should be envisaged.

National legislation should ensure that penalties can be enforced when persons or suppliers are found to be in violation of legislation.

An alert system should be established by the competent authority to prevent trade in non-conforming materials that could put patients at risk. WHO should be informed of such instances so that this information can be made available to other national or regional authorities for action as necessary.

Ultimate goal

Close collaboration of all partners throughout the distribution and trade chain should be established and maintained to protect patients' health.

Introduction

Further to the discussion during the Thirty-sixth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1999, which was triggered by the reported incidents of contamination with diethylene glycol, several activities to control and ensure safe trade of starting materials for pharmaceutical products have been identified. The Expert Committee was informed of the recommendations of a consultation on "Starting materials for pharmaceutical products: control and safe trade", held in Geneva in May 1998, as well as of the report from this consultation which is available in Arabic, Chinese, English, French, Spanish and Russian. The report is also available on the Internet at <http://www.who.int/medicines/docs/startmats.html>.

The Committee also noted that the World Health Assembly had adopted the proposed resolution on the Revised Drug Strategy (WHA52.19) in May 1999, and was informed of a press release dated 22 May 1999 regarding the above-mentioned World Health Assembly resolution. The resolution requested WHO to prepare a new scheme for the certification of starting materials moving in international commerce. It was agreed at the thirty-eighth meeting of the Expert Committee that an increased

awareness of existing guidelines should be promoted. The Committee noted that several recommendations had been made in the report of the consultation of May 1998 for action by governments, manufacturers, traders and brokers as well as by WHO. The Organization would need to collaborate with all the parties involved. It was suggested that the above-mentioned recommendations should be consolidated and priorities assigned, and the resulting document distributed widely to relevant associations and representative bodies.

On the basis of the above considerations, a new WHO Scheme for the Certification of Pharmaceutical Starting Materials Moving in International Commerce is being proposed. The document outlining the new scheme was drafted at an informal consultation before being circulated for comments and rediscussed during a consultation held in August 2001. Further rounds of consultation took place in 2002, including a meeting held in July of that year. The text was revised in accordance with the comments received.

There is currently insufficient legislative control over the manufacture and distribution of pharmaceutical starting materials in many WHO Member States. It is, however, recognized that in some Member States, efforts have been made to ensure implementation and monitoring of good manufacturing practices for starting materials. Alternative quality systems (e.g. International Standards Organization (ISO)) have been adopted by some manufacturers. These developments have formed the basis of the newly suggested certification scheme for pharmaceutical starting materials.

The proposed scheme is based on the “WHO certification scheme on the quality of pharmaceutical products moving in international commerce”. It should be noted, however, that the concept of this proposed scheme and its application differ in certain aspects from the scheme for pharmaceutical products, namely, in the provision made for alternative quality assurance systems and self-assessment by the manufacturers of pharmaceutical starting materials. The latter may also be linked to an inspection by a national authority other than the one in the country of manufacture.

It is further suggested to consider the use of the “Model certificate of analysis for active pharmaceutical ingredients, excipients and medicinal products (COA)” that would serve in the trade of starting materials and for manufacturers of pharmaceutical substances, excipients and medicinal products, as recommended by resolution WHA52.19 (Annex 2 of reference (1)) together with the “Considerations for requesting analysis of drug samples” (Annex 3 of reference (1)) to complement this scheme.

The newly proposed scheme consists of:

1. A Model Certificate for Manufacture of Pharmaceutical Starting Materials issued by the competent national authority,
or, alternatively:
2. A Model Certificate for Manufacture of Pharmaceutical Starting Materials issued by the manufacturer.

Scope

The scheme described in this document is intended for pharmaceutical starting materials, obtained through chemical synthesis. Blood and blood derivatives are beyond the scope of this scheme.

It is envisaged to evaluate this scheme describing a new global mechanism for its applicability and use after a certain length of time.

1. Provisions and objectives	560
2. Participating Member States	560
3. Requesting a certificate	562
4. Certificates issued by competent regulatory authorities	562
5. Certificates issued by manufacturers	564
6. Notifying and investigating a quality defect	566
Appendix 1 Model Certificate for Pharmaceutical Starting Materials issued by the competent national authority	569
Appendix 2 Model Certificate for Manufacture of Pharmaceutical Starting Materials issued by the manufacturer	573
Appendix 3 Glossary and key words	578

1. Provisions and objectives

- 1.1 A comprehensive system of quality assurance should normally be founded on a reliable system of licensing and analysis of starting materials, as well as upon assurance, obtained through independent inspection, that all manufacturing operations are carried out in conformity with accepted norms referred to as good manufacturing practices (GMP). Production and quality control should be independent of one another.
- 1.2 The World Health Assembly endorsed the requirements for good practices in the manufacture and quality control of drugs (2) (referred to henceforth as “GMP as recommended by WHO”). The GMP text includes good manufacturing practices for pharmaceutical starting materials (active pharmaceutical ingredients and pharmaceutical excipients).
- 1.3 The Scheme is an administrative instrument that can be used by:
 - 1.3.1 A Member State to attest that:
 - a specific starting material is used in a pharmaceutical product authorized to be placed on the market within its jurisdiction or within another national jurisdiction; and
 - the manufacturing site in which a specific starting material is produced is subject to inspections at suitable intervals to establish that the manufacturer conforms to GMP as recommended by WHO.
 - 1.3.2 The Scheme can also be used by the manufacturer to attest compliance with a quality assurance system (subject to conditions for issuing a certificate as described in section 5 below).
- 1.4 The Scheme makes provision for a statement to indicate that the manufacturing site(s) in which the pharmaceutical starting material is produced has (have) implemented a suitable quality system.

2. Participating Member States

- 2.1 Any Member State intending to participate in the Scheme may do so by notifying the Director-General of WHO in writing, of:
 - its willingness to participate in the scheme;
 - any significant reservations it intends to observe relating to this participation (i.e. whether it intends to participate actively in the Scheme or to use it as a tool); and

- the name and address of its national regulatory authority or other competent authority.

Documentation on the national system should be provided, depending on the type of participation.

- 2.2 A Member State may opt to participate solely to control the importation of pharmaceutical starting materials. This intention should be stated explicitly in its notification to the World Health Organization.
- 2.3 A Member State intending to participate in the Scheme through issuing certificates should first satisfy itself that it can meet the following criteria.
- An effective national system is in place to identify the responsible manufacturers and distributors.
 - It can perform inspections according to GMP requirements, consonant with those recommended by WHO, to which all manufacturers of pharmaceutical starting materials are required to conform.
 - It is capable of establishing effective controls to monitor the quality of pharmaceutical starting materials manufactured within its country, and has access to an independent quality control laboratory.
 - It has a national pharmaceuticals inspectorate, operating as an arm of the national drug regulatory authority, and having the technical competence, experience and resources to assess whether GMP and other controls are being effectively implemented, and has the legal power to conduct appropriate investigations to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples.
 - It has the necessary administrative capacity to issue the required certificates, to institute enquiries in case of complaint, and to notify expeditiously both WHO and the competent authority in any Member State known to have imported a specific starting material that is subsequently associated with a potentially serious quality defect or other hazard.
- 2.4 Each Member State assumes the responsibility to determine, through a process of self-evaluation, whether it satisfies these prerequisites. The Scheme contains no provision for external inspection or assessment, either of a competent national authority or of a manufacturing facility. However, should a Member State so wish, it may approach WHO, or another drug regulatory authority, to occasionally delegate consultants to act as advisers in the course of national inspections and training activities for inspectors.

3. Requesting a certificate

- 3.1 A Certificate for Pharmaceutical Starting Materials can be requested within the scope of the Scheme by the exporter, importer or the competent authority of the importing country.

4. Certificates issued by competent regulatory authorities

- 4.1 The proposed formats for these documents are provided in Appendices 1 and 2 of these guidelines. For ease of use, these documents are presented in forms suitable for generation by a computer. All participating countries are henceforth urged to adopt these formats to facilitate the interpretation of certified information. The explanatory notes that accompany the two documents referred to above are very important. Although they are not part of the document to be certified, they should always be attached to the certificate.

- 4.2 The certificate should be issued by the competent authority in the format proposed in Appendix 1.

The following information should be listed as a minimum: for details see explanatory notes (Appendix 1).

- 4.2.1 Number of certificate given by the issuing authority.
- 4.2.2 Exporting (certifying) country.
- 4.2.3 Importing (requesting) country/countries.
- 4.2.4 Name of pharmaceutical starting material (International Nonproprietary Names (INNs) should be used whenever possible; alternatively, national nonproprietary names and/or grades, trademarks and other identifiers, such as official codes, CAS numbers etc. may be used).
- 4.2.5 Complete reference to, and compliance with, pharmacopoeial monograph(s), where applicable and/or attached specifications.
- 4.2.6 Information on whether the pharmaceutical starting material subject to this certificate is used in pharmaceutical products registered for marketing in the exporting country.
- 4.2.7 Indicate category of product, if applicable.
- 4.2.8. Marketing authorization, licence, Drug Master File or other reference(s), such as a certificate of suitability of pharmacopoeial monographs with which the starting material complies, as applicable.

- 4.2.9 Name and address of applicant for certificate.
- 4.2.10 Activities of the applicant (e.g. manufacturing, repacking or relabelling) and, if the applicant is not the original manufacturer, provide the name and address of the original manufacturer.
- 4.2.11 Compliance of facilities and operations with WHO GMP, if applicable.
- 4.2.12 Date of last inspection, if applicable.
- 4.2.13 Information regarding the certifying authority.
- 4.2.14 Stamp and date.
- 4.3 The certificate is a confidential document. As such, it can be issued by the competent authority in the exporting country (“the certifying authority”) only with the permission of the applicant.
- 4.4 Once prepared, the certificate is transmitted to the requesting authority through the applicant and, when applicable, the agent in the importing country.
- 4.5 When any doubt arises about the status or validity of a certificate, the competent authority in the importing country should request a copy directly from the certifying authority, as provided for in section 4.2.13 of these guidelines.
- 4.6 In the absence of any specific agreement to the contrary, each certificate will be prepared exclusively in the working language(s) of the certifying authority. The applicant will be responsible for providing any notarized translation that may be required by the requesting authority.
- 4.7 Since the preparation of certificates imposes a significant administrative load on the certifying authorities, the service may need to be financed by charges levied upon applicants.
- 4.8 The certificate remains valid until the specified date.
- 4.9 The certificate becomes invalid if the manufacturing process certified is changed or if the manufacturer is no longer considered to be in compliance with GMP.
- 4.10 The certifying authority is responsible for assuring the authenticity of the certified data. Certificates should not bear the WHO emblem, but a statement should always be included to indicate whether or not the document has been issued in the format recommended by WHO.
- 4.11 When the applicant is the manufacturer of the pharmaceutical starting material, the certifying authority should satisfy itself, before attesting compliance with GMP, that the applicant:

- (a) applies identical GMP standards to the pharmaceutical starting materials of all batches manufactured within the facility, including those destined exclusively for export; and
 - (b) consents, in the event of identification of a quality defect consonant with the criteria set out, to relevant inspection reports being released, in confidence, to the competent authority in the country of import, should the latter so require.
- 4.12 When the applicant is not the manufacturer of the pharmaceutical starting material, the certifying authority should similarly satisfy itself in so far as it has the authority to inspect the records and relevant activities of the applicant, that it has the applicant's consent to release relevant reports on the same basis as described in section 4.11 (b) above.
- 4.13 Whenever a starting material is purchased through a broker or another intermediary, or when more than one set of premises has been used for the manufacture and packaging of a starting material, the certifying authority should consider whether it has received sufficient information to satisfy itself that those aspects of the manufacture of the starting material for which the applicant is not directly responsible have been undertaken in compliance with GMP and good trading and distribution practices (GTDP)^a as recommended by WHO.
- 4.14 Each certificate should identify the importing country and be stamped on every page with the official seal of the certifying authority to avert potential abuse of the Scheme, to frustrate attempts at falsification, to render routine authentication of certificates by an independent authority superfluous and to enable the certifying authority to maintain comprehensive records of countries to which specific starting materials have been exported. If requested, an identical copy, clearly marked as "duplicate", should be forwarded on demand by the certifying authority directly to the requesting authority in the importing country.

5. Certificates issued by manufacturers

- 5.1 A manufacturer may issue a certificate, for instance when there is no national authority in the exporting country that could issue a certificate and/or no legal framework, and provided that there is an independent certifying body or competent authority to assess the compliance with the quality assurance system.

^a WHO Good Trading and Distribution Practices (GTDP), see guidance text in WHO Technical Report No. 917, Annex 2.

- 5.2 The certificate of the manufacturer should be accompanied by a copy of the certificate or document issued by the independent certifying body or competent authority.
- 5.3 The format of the certificate should be as in Appendix 2.
The following information should be listed.
 - 5.3.1 Number of certificate given by the manufacturer.
 - 5.3.2 Exporting country.
 - 5.3.3 Importing (requesting) country/countries.
 - 5.3.4 Name of pharmaceutical starting material (use International Nonproprietary Names (INNs) whenever possible; alternatively national nonproprietary names and/or grades, trademarks and other identifiers, such as official codes, CAS numbers, etc. may be used).
 - 5.3.5 Complete reference to, and compliance with, pharmacopoeial monograph(s), where applicable and/or attached specifications.
 - 5.3.6 Whether the pharmaceutical starting material is used for pharmaceutical purposes in the exporting country.
 - 5.3.7 Whether the pharmaceutical starting material subject to this certificate is used in pharmaceutical products registered for marketing in the exporting country.
 - 5.3.8 Type of product, if applicable.
 - 5.3.9 Name and address of manufacturer (issuer of certificate), including e-mail address, telephone number and fax number.
 - 5.3.10 (a) Activities of issuer of certificate, e.g. manufacturing or repacking, etc., and, if the issuer of the certificate is not the manufacturer, provide
(b) the name and address of the original manufacturer/manufacturing site(s).
 - 5.3.11 Indication of the main categories of materials produced at the manufacturing site.
 - 5.3.12 Additional regulatory information, such as reference to licence, Drug Master File or other reference as applicable.
 - 5.3.13 The certificate is based on the information obtained from:

5.3.13.1 Inspection by competent authority:

- name of competent authority, including e-mail address, telephone number, fax number and name and function of contact person;
- date of inspection;
- quality assurance system inspected;
- standard used for inspection;
- result of inspection; and
- certificate and supplementary documents to be attached, if available.

5.3.13.2 Audit by an independent certifying body:

- name of independent certifying body, including e-mail, telephone number, fax number and name and function of contact person;
- date of audit;
- quality assurance system audited;
- standard used for audit;
- result of audit; and
- certificate and supplementary documents to be attached, if available.

5.3.14 Name and function of responsible person issuing the statement on behalf of the manufacturer.

5.3.15 Date of issue.

5.3.16 Stamp and signature.

The period of validity of the certificate is suggested to be 2 years.

6. Notifying and investigating a quality defect

- 6.1 Recognizing that the notification of a defect is an important aspect of the quality assurance of starting materials, the manufacturer should have a system in place to notify its customers and the regulatory authorities of defects that have a potential impact on the quality and safety of the starting material and to ensure that a thorough investigation is conducted. Specifically the manufacturer should notify the recipient(s) of the certificate, as well as the competent authority, of any serious quality defect related to the starting material that was exported in accordance with the provisions of the Scheme, by communicating the relevant facts, through the competent authorities in the importing countries.

- 6.2 The competent authority should follow up on the investigation undertaken by the manufacturer and take action as necessary.
- 6.3 It is the responsibility of the Member State adhering to the Scheme to ensure that provisions for carrying out the tasks described in 6.1 and 6.2 above are in place.
- 6.4 In the case of obvious doubt, a participating national authority may request WHO to assist in providing a list of quality control laboratories to carry out tests for the purposes of quality control.
- 6.5 Each certifying authority undertakes to inform WHO and, as far as possible, all competent national authorities, of any serious hazard newly associated with a starting material exported under the provisions of the Scheme, or of any criminal abuse of the Scheme, in particular, the export of falsely labelled, spurious, counterfeited or substandard pharmaceutical starting materials. On receipt of such notification, WHO will immediately inform the competent national authority in each Member State.
- 6.6 WHO stands prepared to offer advice should any difficulty arise in implementing any aspect of the Scheme or in resolving a complaint, but it cannot be a party to any resulting litigation or arbitration.

References

1. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902; https://iris.who.int/bitstream/handle/10665/42424/WHO_TRS_902.pdf?sequence=1&isAllowed=y).
2. Quality control of drugs. In: *Twenty-second World Health Assembly, Boston, Massachusetts, 8–25 July 1969. Part 1. Resolutions and decisions, annexes.* Geneva, World Health Organization, 1969 (Official Records of the World Health Organization, No. 176): 99–105.

Further reading

- Certification scheme on the quality of pharmaceutical starting materials moving in international commerce. In: *Twenty-eighth World Health Assembly, Geneva, 13–30 May 1975. Part 1. Resolutions and decisions, annexes.* Geneva, World Health Organization, 1975 (Official Records of the World Health Organization, No. 226): 94–95.
- Good manufacturing practices for pharmaceutical starting materials. In: *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Good manufacturing practices and inspection. Volume 2, Updated edition.* Geneva, World Health Organization, 2004.
- *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirtysixth report.* Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902).
- *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirtyseventh report.* Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908).

- WHO certification scheme on the quality of pharmaceutical starting materials moving in international commerce. In: *Forty-first World Health Assembly, Geneva, 2–13 May 1988. Resolutions and decisions, annexes*. Geneva, World Health Organization, 1988 (Document WHA41/1988/REC/1): 53–55.
- Revised drug strategy. In: *Fifty-second World Health Assembly, Geneva, 17–25 May 1999*. Geneva, World Health Organization, 1999 (Resolution WHA52.19).

Appendix 1

Model Certificate for Pharmaceutical Starting Materials issued by the competent national authority

(Letterhead of issuing authority)

Certificate of a Pharmaceutical Starting Material¹

This certificate conforms to the format recommended by the World Health Organization (general instructions and explanatory notes attached).

1. Certificate number:

2. Exporting (certifying) country:

3. Importing (requesting) countries:

4. Name of Pharmaceutical Starting Material:²

5. Indicate complete reference and compliance with pharmacopoeial monograph(s), where applicable and/or attached specifications:

6. Is the Pharmaceutical Starting Material subject to this certificate used in pharmaceutical products registered for marketing in the exporting country? yes / no / unknown (*key in as appropriate*)

7. If yes, which types of product?³

8. Indicate marketing authorization, licence, Drug Master File or other reference as applicable:

9. Applicant for certificate (name and address):

10. Activities and site(s):

10.1 Activities of applicant: specify whether the manufacturer responsible for placing the Pharmaceutical Starting Material on the market:

- (a) manufactures the Pharmaceutical Starting Material;
- (b) repackages and/or relabels the Pharmaceutical Starting Material manufactured by an independent company, or;
- (c) is involved in none of the above (e.g. distributes, trades);
- (d) manufactures the Pharmaceutical Starting Material and further manufacturing sites may be involved.⁴

10.2 If answers b, c or d apply, provide name and address of the manufacturing site(s):

11. Does the manufacturer comply with WHO GMP?⁵

yes / no / not applicable⁶ (for “no” and “not applicable”: *please explain and specify*):

12. Date of last inspection, if applicable: _____

I herewith confirm that the data above are valid. Any changes that could affect the validity of this certificate shall be notified by the applicant. Under normal circumstances the certificate is valid for 2 years.

13. *Information regarding the regulatory certifying authority*

Name and address of certifying competent authority:

E-mail: _____ Telephone no.: _____ Fax no.: _____

Name and function of responsible person:

Signature of responsible person:

14. Stamp and date:

Attachments:⁷

List of documents attached:

General instructions

Please refer to the guidelines for full instructions on how to complete this form and for information on the implementation of the Scheme. Only originals or certified copies will be accepted.

The forms are suitable for generation by computer. They should always be submitted as hard copy, with responses printed in type rather than handwritten.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Certifying authorities shall indicate the total number of pages included in the certificate and shall number them, e.g. page x of y, and initial every page.

Explanatory notes

- (1) This certificate, which is in the format recommended by WHO, establishes the status of the Pharmaceutical Starting Material and of the applicant for the certificate in the exporting country. It is for a single Pharmaceutical Starting Material only.
- (2) Whenever available, use International Nonproprietary Names (INNs); alternatively, national nonproprietary names and/or grades, trademarks and other identifiers, such as official codes, CAS numbers etc. may be used.
- (3) List the dosage forms and categories. Example given below.

Pharmaceutical Product(s) ^a	Category(ies)
<i>Dosage form(s):</i>	
Tablets	Cytotoxic
	Hormone
	Penicillin
Injectables	Cefalosporin

- (4) Specify whether the manufacturer responsible for placing the Pharmaceutical Starting Material on the market:
 - (a) manufactures the Pharmaceutical Starting Material;
 - (b) repackages and/or relabels the Pharmaceutical Starting Material manufactured by an independent company, or;

^a Pharmaceutical products: Any medicine intended for human use or veterinary product administered to food-producing animals, presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

- (c) is involved in none of the above (e.g. distributes, trades);
- (d) manufactures the pharmaceutical starting material and further manufacturing sites may be involved.

If the manufacturer is not the original manufacturer, the site should be given.

- (5) The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Good manufacturing practices and inspection, Volume 2, Updated edition*. Geneva, World Health Organization, 2004.
- (6) “Not applicable” means that no legal requirements may be in place or implemented for GMP inspection of the Pharmaceutical Starting Materials for which the certificate is issued.
- (7) Including specifications referred to under point 5.

Appendix 2

Model Certificate for Manufacture of Pharmaceutical Starting Materials issued by the manufacturer

(Letterhead of the manufacturer)

Certificate of a Pharmaceutical Starting Material¹

This certificate conforms to the format recommended by the World Health Organization (general instructions and explanatory notes attached).

1. Certificate number:

2. Exporting country:

3. Importing country:

4. Name of Pharmaceutical Starting Material:²

5. Indicate complete reference and compliance with pharmacopoeial monograph(s) where applicable and/or attached specifications:

6. Is this Pharmaceutical Starting Material used for pharmaceutical purposes in the exporting country? yes / no / unknown (*key in as appropriate*)

7. Is the Pharmaceutical Starting Material subject to this certificate used in pharmaceutical products registered for marketing in the exporting country? yes / no / unknown (*key in as appropriate*)

8. If yes, which types of product:³

9. Name and address of manufacturer (issuer of certificate):

E-mail: _____ Telephone no.: _____ Fax no.: _____

10. Activities and site(s):

10.1 Activities of issuer of the certificate⁴:

State whether the issuer:

- (a) manufactures the Pharmaceutical Starting Material;
- (b) repackages and/or relabels the Pharmaceutical Starting Material manufactured by an independent company, or;
- (c) is involved in none of the above (e.g. distributes, trades);
- (d) manufactures the Pharmaceutical Starting Material and further manufacturing sites may be involved.

10.2 If answers b, c or d apply, provide name and address of the manufacturing site(s):

11. Main categories of materials produced on site:⁵

- Pharmaceutical starting materials: _____
- Active pharmaceutical ingredients: _____
- Excipients: _____
- Cosmetics: _____
- Foodstuffs: _____
- Agrochemicals: _____
- Others (please specify): _____

12. Indicate additional regulatory information, such as reference to licence, Drug Master File, or other reference as applicable:

13. Information based on:

13.1 Inspection by competent authority:

Country: _____

Name of competent authority: _____

E-mail: _____ Telephone no.: _____ Fax no.: _____

Name and function of contact person: _____

- date of inspection: _____
- quality assurance system inspected: _____
- standard used for inspection:⁶ _____
- result of inspection: _____
- attach certificate or supporting document, if available.

13.2 If answers b, c or d apply, provide name and address of the manufacturing site(s):

Name of independent certifying body: _____

E-mail: _____ Telephone no.: _____ Fax no.: _____

Name and function of contact person: _____

- date of audit: _____
- quality assurance system audited: _____
- standard used for audit: _____
- result of audit: _____
- attach certificate or supporting document, if available.

14. Name and function of responsible person:

I herewith confirm that the data above are valid. Any changes that could affect the validity of this certificate shall be notified by the applicant. Under normal circumstances the certificate is valid for 2 years.

15. Date: _____

16. Stamp and signature: _____

Attachments:⁷

List of documents attached:

General instructions

Please refer to the guidelines for full instructions on how to complete this form and for information on the implementation of the Scheme.

Only originals or certified copies of this document will be accepted.

The forms are suitable for generation by computer. They should always be submitted as hard copy, with responses printed in type rather than handwritten.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Certifying authorities shall indicate the total number of pages included in the certificate and shall number them, e.g. page x of y, and initial every page.

Explanatory notes

- (1) This certificate, which is in the format recommended by WHO, establishes the status of the Pharmaceutical Starting Material and of the applicant for the certificate in the exporting country. It is for a single Pharmaceutical Starting Material only.
- (2) Whenever available, use International Nonproprietary Names (INNs); alternatively, national nonproprietary names and/or grades, trademarks and other identifiers, such as official codes, CAS numbers etc. may be used.
- (3) List the dosage forms and categories. Example given below.

Pharmaceutical Product(s) ^a	Category(ies)
<i>Dosage form(s):</i>	
Tablets	Cytotoxic
	Hormone
	Penicillin
Injectables	Cefalosporin

- (4) Specify whether the manufacturer responsible for placing the Pharmaceutical Starting Material on the market:
 - (a) manufactures the Pharmaceutical Starting Material;
 - (b) repackages and/or relabels the Pharmaceutical Starting Material manufactured by an independent company, or;
 - (c) is involved in none of the above (e.g. distributes, trades);
 - (d) manufactures the pharmaceutical starting material and further manufacturing sites may be involved.

If the manufacturer is not the original manufacturer, the site should be given.

- (5) The categories of materials produced on site will give information about the profile of the manufacturing site.

^a Pharmaceutical products: Any medicine intended for human use or veterinary product administered to food-producing animals, presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

- (6) The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Good manufacturing practices and inspection, Volume 2, Updated edition*. Geneva, World Health Organization, 2004.
- (7) Including specifications referred to under point 5.

Appendix 3

Glossary and key words

This glossary explains terms used in these Guidelines and/or refers to relevant sections. It is intended as supplementary information and not as a formal part of the Scheme. Note that the definitions given below apply to the terms as used in these Guidelines. They may have different meanings in other contexts.

Applicant

The party applying for a certificate for a pharmaceutical starting material.

Competent authority

The national regulatory authority in the Member State. The competent authority can issue or receive certificates.

Good manufacturing practices (GMP)

That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. (In: *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Good manufacturing practices and inspection. Volume 2, Updated edition.* Geneva, World Health Organization, 2004).

GTDP

Good Trade and Distribution Practices (Annex 2, WHO Technical Report Series, No. 917).

Manufacture

All operations of purchase of materials and starting materials, production, quality control, release, storage, shipment of finished starting materials, and the related controls.

Pharmaceutical starting material

Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials. This includes active pharmaceutical ingredients (APIs) and pharmaceutical excipients.

Starting material (see pharmaceutical starting material)

Certificate of a pharmaceutical starting material

A document containing the information (as set out in Appendix 1 of these Guidelines) that is validated and issued for a specific starting material by the competent authority of

the exporting country and intended for use by the competent authority in the importing country or in the absence of such an authority by, for example, the manufacturer of the finished product when exporting.

WHO responsibility (see item 6.6 of guidelines above)

4.9 Guidelines on the implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce

Annex 9, WHO Technical Report Series, 1033, 2021

1. Introduction	581
2. Background	581
3. Provisions and objectives	582
4. Membership	583
5. Requesting a certificate	585
6. Issuing a certificate	588
7. Notifying and investigating a quality defect	589
References	590
Appendix 1 Model certificate of a pharmaceutical product	592
Appendix Model batch certificate of pharmaceutical products	597
Appendix 3 Glossary	600
Appendix 4 (Draft) model notification to the Director-General of the World Health Organization	607

1. Introduction

The World Health Organization (WHO) Certification Scheme on the quality of pharmaceutical products moving in international commerce (hereinafter referred to as the “Scheme”) is an international voluntary agreement to provide assurance to countries participating in the Scheme about the quality of pharmaceutical products moving in international commerce. The primary document of the Scheme is the certificate of a pharmaceutical product (CPP).

2. Background

The Scheme has been in operation since 1969 (World Health Assembly resolution WHA 22.50) and was amended in 1975 (WHA 28.65), 1988 (WHA 41.18), 1992 (WHA 45.29) and 1997 (WHA 50.3) (1–5). In 2007, the Forty-second ECSPP discussed and identified a number of perceived problems with the operation of the Scheme (6).

In 2008, a WHO consultation was held to make recommendations for consideration during the Forty-third WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP), taking into account the WHO working document QAS/07.240 which contains key issues and possible action (7). The report of the consultation was the working document QAS/08.279 (8). In light of the changing environment, including the rapid globalization of the pharmaceutical manufacturing sector, coupled with changes in the make-up of both the regulators and the groups involved in procurement, the Forty-third ECSPP endorsed the following recommendations (9):

- “1. The *WHO Certification Scheme on the quality of Pharmaceutical products moving in international commerce* should be revised.
2. The proposal for revision of the Scheme and modification of the guidelines should be discussed by the relevant WHO Governing Bodies – the Executive Board and the World Health Assembly – and in consultation with WHO’s Legal Counsel.
3. In the interim, a question and answer (Q&A) paper should be prepared on the function of the Scheme.”

Based on the above recommendations, as an interim measure, a Q&A document on the function of the Scheme was developed in 2010 and revised in 2015 (10, 11). However, the Scheme has not been revised since 1997.

In 2017, the Fifty-second ECSPP recommended that “the WHO Secretariat should prepare a proposal for revision of the Scheme for public consultation” (12).

The draft working document, which includes the proposed revision of the Scheme, was prepared by the WHO Secretariat and it was discussed during an informal consultation that took place from 19 to 20 May 2018.

The draft working document was circulated twice to the Member States and other interested parties for public consultation to prepare a version of the working document for endorsement by the Fifty-fifth ECSPP in 2020.

During the revision process, consideration was given to including reference to the Global Benchmarking Tool (GBT) (13) and the concept of WHO Listed Authorities (14). However, it was considered that since the GBT details are still under discussion, it was too early to add it in the Scheme. Additional wording was instead added to section 4.2 indicating that a Member State or a regional authority should possess an effective marketing authorization, vigilance and market surveillance and control systems for pharmaceutical products.

3. Provisions and objectives

- 3.1 A comprehensive system of certification must be founded on a reliable system of marketing authorization and independent analysis of the pharmaceutical product, as well as upon assurance obtained through independent inspection that all manufacturing operations are carried out in conformity with accepted norms, referred to as “good manufacturing practices” (GMP), and also within relevant provisions already approved in the marketing authorization.
- 3.2 In 1969, the Twenty-second World Health Assembly, by resolution WHA22.50, endorsed requirements for *Good practices in the manufacture and quality control of drugs* (15) (referred to henceforth as “GMP as recommended by WHO”). These comprise internationally-recognized and respected standards that all Member States are urged to adopt and to apply. These requirements have since been revised several times.
- 3.3 These standards provide the basis for the Scheme recommended initially in resolution WHA22.50 (15). The Scheme is an administrative instrument that requires each participating Member State or regional authority, upon application by a commercially interested party, to attest to the competent authority of another participating Member State or regional authority that:
 - a specific product is authorized to be placed on the market within its jurisdiction or, if it is not thus authorized, the reason why that authorization has not been accorded;
 - the manufacturing site is subject to inspections at suitable intervals to establish that the manufacturer conforms to GMP (16) as recommended by the WHO in accordance with its current publication;
 - the actual status of commercialization of the certified product on the market of the certifying authority, when authorized; and

- all product information submitted, including labelling, is currently authorized by the certifying authority.

Additionally, the Scheme facilitates the exchange of information related to the investigation of serious quality defects reported in product exported in accordance with its provisions, reliance on the results of GMP inspections performed by other authorities, and also on the results of the assessment of the dossier with the requirements of the certifying authorities.

- 3.4 The Scheme, as amended in 1975 (17), 1988 (18), 1992 (19) and 1997 (20), by resolutions WHA28.65, WHA41.18, WHA45.29 and WHA50.3, is applicable to finished dosage forms of pharmaceutical products intended for administration to human beings or to food-producing animals.
- 3.5 Provisions for certification of starting materials (active pharmaceutical ingredients {APIs} and excipients) for exporting purposes are provided in separate guidelines (21).

4. Membership

- 4.1 Any Member State, as well as regional authority that has the legal right to control the regulation of pharmaceutical products, is eligible to participate on a voluntary basis in the Scheme as a requesting authority. In order to participate, a certifying authority should comply, additionally, with the requirements stipulated in section 4.2. Membership can be voluntarily withdrawn at any time by written notification to the Director-General of WHO.
- 4.2 A Member State or a regional authority intending to become a certifying member should possess:
 - an effective marketing authorization, vigilance and market surveillance and control systems for pharmaceutical products, including the responsible manufacturers and licensing of distributors;
 - GMP requirements, consistent with those recommended by WHO in accordance with its current publication, to which all manufacturers of finished pharmaceutical products (FPP) are required to conform;
 - effective controls to monitor the quality of pharmaceutical products registered or manufactured within its country or region, including access to an independent medicine testing laboratory;
 - a pharmaceuticals inspectorate, operating as an arm of the national or regional medicines regulatory authority, and having the technical competence, experience and resources to assess whether or not GMP and

other controls are being effectively implemented, and the legal power to conduct or to coordinate appropriate investigations to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples; and

- an efficient surveillance system, administrative capacity and good regulatory practices compliance to issue the required certificates efficiently, to detect and institute inquiries in the case of complaint, and to expeditiously notify WHO and, when possible, the competent authority in the Member State or region known to have imported a specific product, or publish the information on the website about the product that is associated with a potentially serious quality defect or other hazard in a timely manner.

4.3 Membership as a certifying member and/or requesting member should be declared by notifying in writing to the Director-General of the WHO of:

- its willingness to participate in the Scheme as a certifying member and/or a requesting member;
- any significant reservations it intends to observe relating to this participation;
- the commitment of implementing the WHO guideline “*WHO Certification scheme on the quality of pharmaceutical products moving in international commerce*”, the WHO Model Certificates (WHO template) and provision of the certificates when requested by a requesting member;
- the name and address (including email address, telephone and website address) of its medicines regulatory authority or other competent authority;
- the commitment to notify any change of the information submitted related to the certifying and/or requesting member details; and
- a declaration to comply with the requirements for a certifying member as stipulated in section 4.2.

4.4 A consolidated list of information on the notification submitted by Member States and regional authorities in accordance with the provision in sections 4.2 and 4.3 will be available through WHO’s official website (*see also section 3.3*).

4.5 A Member State or regional authority should inform the WHO of any change of the information notified to the Director-General of the WHO.

5. Requesting a certificate

5.1 Two documents, if available by the certifying authority, can be requested within the scope of the Scheme:

- a certificate of a pharmaceutical product (CPP) and;
- a batch certificate of a pharmaceutical product (*for more details, please see sections 5.14 and 5.15 and the Explanatory notes in Appendix 2*).

5.2 The proposed formats for these documents are provided in appendices 1 and 2 of these guidelines. All participating Member States and regional authorities are henceforth urged to adopt these formats without deletion in order to facilitate the harmonization and interpretation of certified information. A CPP with any deleted sections is no longer considered a “CPP”.

The explanatory notes attached to the two documents referred to above are very important. Whilst they are not part of the document to be certified, they should always be attached to the certificate.

5.3 A list of addresses of national and regional authorities participating in the Scheme that are responsible for the registration of pharmaceutical products for human and/or veterinary use, together with details of any reservations they have declared regarding their participation in the Scheme, will be available on the WHO official website as indicated in section 4.4.

5.4 Each authority should issue appropriate guidelines to all agents responsible for importing pharmaceutical products for human and/or veterinary use that operate under its jurisdiction, including those responsible for public sector purchases, in order to explain the contribution of certification to the medicine regulatory process and the circumstances in which each of the two types of documents will be required, the requesting information and the methodology to follow.

Certificate of a pharmaceutical product

5.5 The certificate of a pharmaceutical product (CPP) (*Appendix 1*), issued by the certifying authority, is intended for use by the requesting authority in two situations:

- when the product in question is under consideration for a marketing authorization that will authorize its importation and sale, including the GMP compliance of the manufacturer and information on the marketing status of a product in the country of the certifying authority; and
- when administrative action is required to renew, extend, modify or review such a marketing authorization.

- 5.6 The CPP is intended to facilitate the trade of pharmaceutical products. Its use should have an impact for regulatory authorities and regional bodies in terms of quality and time on the assessment of dossiers for the marketing authorization. The Scheme facilitates reliance among the participating authorities and its use will enable a timely access to medicines.
- 5.7 All requests for CPPs should be channeled through the applicant. The applicant may submit the following information for each product to the certifying authority:
- the marketing authorization number, name and dosage form of the FPP;
 - the name and amount of active ingredient(s) per unit dose (International Nonproprietary Name(s) (INN(s)) where such exist(s));
 - the name and address of the marketing authorization holder;
 - the name and address of the manufacturing site(s);
 - the unit formulation (complete quantitative composition including all excipients);
 - the product information for health professionals, the Summary of Product Characteristics (SPC), and for the public (patient information leaflets) as approved by the certifying authority; and
 - the packaging of the FPP.

The name(s) and address(es) of manufacturing site(s) that could be submitted to the certifying authority are referred to the FPP, bulk finished product, solvent and diluents, quality control of the FPP, batch release, primary and secondary packaging.

- 5.8 The certificate is a confidential document which may be issued by the certifying authority only with the permission of the applicant or of the marketing authorization holder.
- 5.9 The certificate is intended to be incorporated into a marketing authorization application to the requesting authority. Once prepared, it is transmitted to the requesting authority through the applicant and, when applicable, the agent in the importing country.
- 5.10 When any doubt arises about the status or validity of a certificate, the requesting authority should request verification of the validity of the certificate from the certifying authority, as provided for under section 6.7 of these guidelines.
- 5.11 In the absence of any specific agreement, each certificate will be prepared always in the working language(s) of the certifying authority. Certifying authorities are encouraged to issue bilingual certificates, including English as the second language, if applicable. The applicant will be responsible for providing any certified translation that may be required by the requesting authority.

- 5.12 Since the preparation of certificates imposes a significant administrative load on certifying authorities, the service may need to be financed by charges levied upon applicants.
- 5.13 Additional information is not within the scope of the Scheme. The certifying authority is under no obligation to supply additional information.

Batch certificate

- 5.14 A batch certificate of a pharmaceutical product (Appendix 2) refers to an individual batch of a pharmaceutical product and is a vital instrument in the procurement of medicines. The provision of a batch certificate is usually a mandatory element in tender and procurement documents.
- 5.15 A batch certificate is normally issued by the manufacturer and must accompany and provide an attestation concerning the quality and expiry date of a specific batch or consignment of a product that has already obtained marketing authorization in the importing country. The batch certificate shall include all the parameters (attributes), with acceptance criteria, of the release specification of the pharmaceutical product at the time of batch release and the results. In most circumstances, these certificates are issued by the manufacturer to the importing agent (i.e. the marketing authorization holder in the importing country), but they must be made available at the request of – or in the course of any inspection made on behalf of – the competent authority.

Note: the following are examples of statements and certificates issued in connection with the Scheme. These are not considered to be part of the Scheme:

- ***Statement of marketing authorization status of pharmaceutical product(s)*** – attests only that a marketing authorization has been issued for a specified product, or products, for use in the certifying country or within the jurisdiction of the certifying regional authority. It is intended for use by importing agents when considering bids made in response to an international tender, in which case it should be requested by the agent as a condition of bidding. It is intended only to facilitate the screening and preparation of information.
- ***Batch (lot) release certificate*** (22, 23) – issued by the competent authority or competent national laboratory in the certifying country or regional authority, and it refers to the results of a batch or several batches which comply with established specifications and provisions to assure the quality, safety and efficacy (QSE) of the concerned vaccines and vaccine's individual components, as well as with WHO's good manufacturing practices (GMP) for pharmaceutical products and biological products.

6. Issuing a certificate

- 6.1 The certifying authority is responsible for assuring the authenticity of the certified data. Certificates should not bear the WHO logo, but a statement should always be included to confirm that the document is issued in the format recommended by WHO.
- 6.2 When manufacture takes place in a country other than that from which the CPP is issued, an attestation relevant to compliance of the manufacture with GMP should still be provided on the basis of inspections undertaken for registration purposes by the same authority or by another authority.
- 6.3 When the applicant is the manufacturer of the finished dosage form, the certifying authority should satisfy, before attesting compliance with GMP, that the applicant:
 - (a) applies identical GMP standards to the production of all batches of pharmaceutical products manufactured within the site, including those destined exclusively for export; and
 - (b) consents, in the event of identification of a quality defect consistent with the criteria set out in section 5.1, to relevant inspection reports being released, in confidence and where possible, to the requesting authority, should the latter so require.
- 6.4 When the applicant is not the manufacturer of the finished dosage form, the certifying authority should similarly satisfy – in so far as it has the authority to inspect the records and relevant activities of the applicant – that it has the applicant's consent to release relevant reports on the same basis, as described in section 6.3 (b) above.
- 6.5 Whenever a product is purchased through an intermediary, or when more than one set of premises has been involved in the manufacture and packaging of a product, the certifying authority should consider whether or not it has received sufficient information to satisfy that those aspects of the manufacture of the product have been undertaken in compliance with GMP as recommended by WHO.
- 6.6 The certifying authority should officially stamp and date any certificates issued or certify using a secure electronic system/electronic certificate (e-certificate). Every effort should be made to ensure that certificates and all annexed documentation are consistent with the version of the marketing authorization operative on the date of issue. Nevertheless, requesting authorities are discouraged to introduce legalization procedures or any form of authentication procedures such as notarization, embassy legalization and apostillation that may cause the undue delay of certificates.

- 6.7 To avert any potential abuse of the Scheme, to frustrate attempts at falsification, to render routine authentication of certificates by an independent authority superfluous, and to enable the certifying authority to maintain comprehensive records of countries to which certificates have been issued, each certificate should identify the requesting authority and be issued in such a way that the authenticity of the certificate can be verified using appropriate tools, such as, for example, certification and validation using a secure electronic system.

If requested, an identical copy, clearly marked as a duplicate, may be forwarded by the certifying authority without any undue delay, ideally within 20 working days.

- 6.8 The certifying authority should establish a standard time frame for the issuance of certificates, ideally within 30 working days. It should endeavour to issue a certificate within this period, as soon as the applicant submits sufficient documents, as requested in section 5.7.

7. Notifying and investigating a quality defect

- 7.1 Each certifying authority undertakes to investigate any quality defect reported in a product exported in accordance with the provisions of the Scheme, on the understanding that:

- the complaint is transmitted, together with the relevant facts, through the requesting authority;
- the complaint is considered to be of a serious nature in terms of risk by the latter authority; and
- the defect, if it appeared after the delivery of the product into the importing country, is not attributable to local climatic or storage conditions.

- 7.2 In case of doubt, a participating national or regional authority may request WHO to assist in identifying an independent quality control laboratory to carry out tests for the purposes of quality control.

- 7.3 Each certifying authority undertakes to inform WHO and, when possible, all national and regional competent authorities of any serious hazard newly associated with a product exported under the provisions of the Scheme or of any criminal abuse of the Scheme, or publish the information on the website about the product. In the case of substandard or falsified pharmaceutical products, the WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products, should be used to send the notification to WHO (24). Upon receipt of such notification, WHO will inform the competent authority as appropriate and/or issue a WHO Medical Product Alert (25).

- 7.4 WHO stands prepared to offer advice should difficulty arise in implementing any aspect of the Scheme or in resolving a complaint, but it cannot be a party to any resulting litigation or arbitration.

References

1. World Health Assembly resolution WHA22.50 (1969).
2. World Health Assembly resolution WHA28.65 (1975).
3. World Health Assembly resolution WHA41.18 (1988).
4. World Health Assembly resolution WHA45.29 (1992).
5. World Health Assembly resolution WHA50.3 (1997).
6. Forty-second WHO Expert Committee on Specifications for Pharmaceutical Preparations, Geneva (WHO Technical Report Series, No. 948; 2008. https://iris.who.int/bitstream/handle/10665/43852/WHO_TRS_948_eng.pdf?sequence=1).
7. Proposal for improvement of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce (working document QAS/07.240).
8. Draft report to the Forty-third WHO Expert Committee on Specifications for Pharmaceutical Preparations. Recommendations for improvement of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce (working document QAS/08.279) (2008).
9. Forty-third WHO Expert Committee on Specifications for Pharmaceutical Preparations, Geneva (WHO Technical Report Series, No. 953; 2009. https://iris.who.int/bitstream/handle/10665/44553/WHO_TRS_953_eng.pdf?sequence=1).
10. WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce: Question and Answers (Q&A) (QAS/10.374, 2010).
11. WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce: questions and answers (Q&A) (WHO Drug Information, Vol. 30, No. 3, 2016, WHO | WHO Drug Information, accessed 2 February 2021).
12. Fifty-second WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 1010; 2018. <https://iris.who.int/bitstream/handle/10665/272452/9789241210195-eng.pdf?sequence=1>).
13. WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems. <https://iris.who.int/bitstream/handle/10665/341243/9789240020245-eng.pdf?sequence=1>.
14. Evaluating and publicly designating regulatory authorities as WHO listed authorities: policy document. Geneva: World Health Organization; 2021. (<https://iris.who.int/bitstream/handle/10665/341749/9789240023444-eng.pdf?sequence=1>)
15. Quality control of drugs. In: Twenty-second World Health Assembly, Boston, Massachusetts, 8-25 July 1969. Part 1: Resolutions and decisions, annexes. Geneva, World Health Organization; 1969:99-105 (Official Records of the World Health Organization, No. 176).
16. WHO good manufacturing practices: Health product and policy standards. Geneva: World Health Organization (<https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/gmp>, accessed 6 February, 2021).

17. WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. In: Twenty-eighth World Health Assembly, Geneva, 13-30 May 1975. Part 1: Resolutions and decisions, annexes. Geneva, World Health Organization; 1975:94-95 (Official Records of the World Health Organization, No. 226).
18. Resolution WHA41.18 WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. In: Forty-first World Health Assembly, Geneva, 2-13 May 1988. Resolutions and decisions, annexes. Geneva, World Health Organization; 1988:53-55 (WHA41/1988/REC/1).
19. Resolution WHA45.29. Proposed guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. In: Forty-fifth World Health Assembly, Geneva, 4-14 May 1992. Resolutions and decisions, annexes. Geneva, World Health Organization; 1992:155-165 (WHA41/1992/REC/1).
20. Resolution WHA50.3 Guidelines for implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. In: Fiftieth World Health Assembly, Geneva, 5-14 May 1997. Resolutions and decisions, annexes. Geneva, World Health Organization; 1997:2-3 (WHA50/1997/REC/1).
21. WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-eighth Report. Geneva: World Health Organization: 2004: Annex 3 (WHO Technical Report Series, No. 917; https://iris.who.int/bitstream/handle/10665/42851/WHO_TRS_917.pdf?sequence=1).
22. Guidelines for independent lot release of vaccines by regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 978; https://iris.who.int/bitstream/handle/10665/89148/9789241209786_eng.pdf?sequence=1).
23. Model certificate for the release of vaccines by NRAs (Appendix 2). In: Meeting Report of the Second General Meeting of WHO National Control Laboratory Network for Biologicals, 25-27 September 2018, Rome, Italy. Available from: https://cdn.who.int/media/docs/default-source/medicines/lab-networks/report_who-nnb2018.pdf?sfvrsn=ad172ebd_5&download=true.
24. WHO Global Surveillance and Monitoring System (<https://www.who.int/who-global-surveillance-and-monitoring-system>).
25. WHO Medical Product Alerts (<https://www.who.int/teams/regulation-prequalification/incidents-and-SF/medical-product-alerts-background>).

Appendix 1

Model certificate of a pharmaceutical product

Certificate of a pharmaceutical product

This certificate conforms to the format recommended by the World Health Organization (WHO). It establishes the status of the pharmaceutical product and of the applicant for the certificate by the national certifying authority in the country or within the jurisdiction of the regional certifying authority. It is for a single product only since the manufacturing arrangements and approved information for different dosage forms and different strengths can vary. (*General instructions and explanatory notes are attached.*)

No. of certificate: _____

Certifying country or regional certifying authority: _____

Requesting country(countryes) or regional authority(authorities): _____

1. Basic information

1.1 Name: (International Nonproprietary Name (INN)/generic/chemical name); brand name of the pharmaceutical product as it is declared in the marketing authorization certificate and used within the territory of the certifying authority and, if possible, the brand name for the foreign country as declared by the requester, (if different); and, the dosage form of the finished pharmaceutical product (FPP): _____

1.2 Composition: active pharmaceutical ingredient name(s) using if possible, INNs or national nonproprietary names,. Unit formulation (complete quantitative composition including all excipients);¹: _____

1.3. Is this product authorized by the certifying authority to be marketed in the certifying country or within the jurisdiction of the certifying regional authority? Yes/No (*key in as appropriate*).

- 1.3.1 Are there restrictions of the sale, distribution or administration of the product specified in the marketing authorization? Yes/No (*key in as appropriate*). See attached information if Yes.
- 1.4 Is this product actually on the market in the certifying country or within the jurisdiction of the certifying regional authority? Yes/No/Unknown (*key in as appropriate*).

Sections 2A and 2B below are mutually exclusive, therefore:

- If the answer to 1.3 above is yes, continue with section 2A and omit section 2B.
- If the answer to 1.3 above is no, omit section 2A and continue with section 2B.

2. Information on marketing authorization

- 2.A Product that is authorized for marketing by the certifying authority.
- 2.A.1 Number of marketing authorization and date of issue. (*Indicate, when applicable, if the marketing authorization is provisional and the marketing authorization pathway, e.g. abridged, etc*): _____

- 2.A.2 Marketing authorization holder (name and address): _____

- 2.A.3 Status of marketing authorization holder (*one of the options of 3.1, if manufacturer, or specify the status as importer or any other*): _____

- 2.A.4 Is a summary basis for approval appended? Yes/No (*key in as appropriate*). See attached information if answer is Yes.
- 2.A.5 Is the attached officially approved product information complete and consistent with the marketing authorization (*such as the Summary of Product Characteristics – SPC- or similar*)? Yes/No/Not provided (*key in as appropriate*). See attached information if answer is Yes.
- 2.A.6 Name and address of applicant for the certificate as provided by the marketing authorization holder, if different: _____

2.A.7 Web-link to the product marketing authorization information (if available)

2.B Product that is not authorized for marketing by the certifying authority.

2.B.1 Applicant for certificate (name and address):

2.B.2 Why is marketing authorization lacking?

Not required/Not requested/Under consideration/Refused/Withdrawal for commercial reasons/Withdrawal for sanitary reasons (*key in as appropriate*)

2.B.3 Reason provided by the applicant for not requesting registration.

- (a) The product has been developed exclusively for the treatment of conditions (e.g. tropical diseases – not endemic in the exporting country):

- (b) The product has been reformulated - please specify:

- (c) Any other reason, please specify:

3. Information on manufacturing and inspections

3.1 List of name and address of the manufacturing site(s) and activities:

- a) manufacturing of all steps of the finished pharmaceutical product (FPP);
- b) manufacturing the bulk finished product;
- c) manufacturing of solvent and diluents;
- d) quality control of the FPP;
- e) batch release of the FPP;
- f) primary packaging of the dosage form;
- g) secondary packaging of the product;
- h) other(s) (specify and list in new arrows).

Name of manufacturing site	Address	Activity

- 3.2 Does the certifying authority arrange for periodic inspection of the manufacturing site in which the of the FPP is produced? Yes/No (*key in as appropriate*). If not, proceed to question 4.
- 3.3 Periodicity of routine inspections: _____
- 3.4 Has the manufacturer of the dosage form of the FPP been inspected? Yes/No (key in as appropriate). If Yes, when feasible, insert date of inspection(s) (*dd/mm/yyyy*).
- 3.5 Do the facilities and operations of the manufacturer of the FPP conform to good manufacturing practices (GMP) as recommended by WHO?² Yes/No (*key in as appropriate*).
- 3.6 It is recommended that for products approved, but not manufactured in the country of the certifying authority, the source of information that assures the GMP compliance of the manufacturer(es) is declared.
4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product? Yes/No (*key in as appropriate*)³. If the answer is No, please explain: _____

Address of certifying authority: _____

Telephone number: _____ Website: _____

Email address: _____

Name and job title of authorized person: _____

Validity of the certificate⁴ (optional): _____

Signature: _____

Stamp and date (*electronic whenever possible*): _____

General instructions

Please refer to the guidelines for full instructions on how to complete this form and for information on the implementation of the Scheme.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

- ¹ Details of quantitative composition are preferred but their provision is subject to the agreement of the marketing authorization holder.
- ² The requirements for good practices in the manufacture and quality control of pharmaceutical products referred to in the certificate, are those included in the Thirty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series, No. 986, 2014, Annex 2 (*WHO Good manufacturing practices for pharmaceutical products: main principles*). Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (*WHO Good manufacturing Practices for biological products*, WHO Technical Report Series, No. 996, 2016, Annex 3).
- ³ It is of particular importance when contractors are involved in the manufacture of the product. The applicant should supply the certifying authority with information in order to identify the contracting parties responsible for each stage of manufacture of the finished dosage form and the extent and nature of any controls exercised over each of these parties.
- ⁴ A period of validity can be provided by the authority on the certificate.

Appendix 2

Model batch certificate of pharmaceutical products

Manufacturers/official¹ batch certificate of a pharmaceutical product

This certificate conforms to the format recommended by the World Health Organization (WHO) (*general instructions and explanatory notes are attached*).

1. No. of certificate: _____
2. Importing (requesting) authority: _____
3. Name: (International Nonproprietary Name (INN)/generic/chemical name); brand name of the pharmaceutical product as it is declared in the marketing authorization certificate and, if possible, brand name for the foreign country, if different:

- 3.1 Dosage form: _____
- 3.2 Composition: Active pharmaceutical ingredient name(s) using, if possible, International Nonproprietary Names (INNs) or national nonproprietary names. Unit formulation (complete quantitative composition including all excipients):

- 3.2.1 Is the composition of the product identical to that registered in the country of export? *Yes/No/Not applicable (key in as appropriate)*² _____
If No: please attach the formula (including excipients) of both products.
4. Marketing authorization holder³ (name and address): _____

- 4.1 Marketing authorization number³: _____
- 4.2 Date of issue³: _____
- 4.3 Marketing authorization issued by³: _____
- 4.4 Certificate of a pharmaceutical product (CPP) number^{3,4}: _____

5. Pharmaceutical product information: _____
- 5.1 Batch number: _____
- 5.2 Date of manufacture: _____
- 5.3 Shelf life (years): _____
- 5.4 Contents of container: _____
- 5.5 Nature of primary container: _____
- 5.6 Nature of secondary container/wrapping: _____
- 5.7 Specific storage conditions: _____
- 5.8 Temperature range: _____
6. Quality analysis: _____

- 6.1 What specifications apply to this dosage form? Either specify the pharmacopoeia or append company specifications.⁵ _____

- 6.1.1 In the case of a product registered by the certifying country or regional authority, have these company specifications⁵ been accepted by the competent authority? Yes/No (*key in as appropriate*) _____
- 6.2 Does the batch comply with all parts of the above specifications? Yes/No (*key in as appropriate*) _____
- 6.3 Append certificate of analysis. Identify and explain any discrepancies from specifications.

It is hereby certified that the above declarations are correct and that the results of the analyses and assays on which they are based will be provided on request to the competent authorities in both the importing and exporting countries.

Name and address of authorized person: _____

Validity of the certificate⁶: _____

Telephone number: _____ Website: _____

Email address: _____

Signature of authorized person: _____

Stamp and date (*electronic whenever possible*): _____

General instructions

Please refer to the guidelines for full instructions on how to complete this form and for information on the implementation of the Scheme.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

The certification of individual batches of a pharmaceutical product is only undertaken on an exceptional basis by the competent authority. Even then, it is rarely applied other than to biological products, such as vaccines, blood and plasma derivatives. For other products, the responsibility for any requirement to provide batch certificates rests with the marketing authorization holder in the certifying country or within the jurisdiction of the certifying regional authority. The responsibility to forward certificates to the competent authority in the importing country is most conveniently assigned to the importing agent.

Any inquiries or complaints regarding a batch certificate should always be addressed to the certifying competent authority. A copy should also be sent to the marketing authorization holder.

¹ Strike out whichever does not apply.

² “Not applicable” means that the product is not registered in the country of export.

³ All items under 4 refer to the marketing authorization or the certificate of a pharmaceutical product (CPP) issued in the certifying country or within the jurisdiction of the certifying regional authority.

⁴ This refers to the CPP as recommended by WHO.

⁵ For each of the parameters to be measured, specifications give the values that have been accepted for batch release at the time of product registration.

⁶ The validity of the certificate should not be confused with the expiry period of the batch/lot.

Appendix 3

Glossary

In order to facilitate understanding, this glossary explains terms in the guidelines and/or refers to relevant sections. It is considered as supplementary information and not as being a formal part of the World Health Organization (WHO) Certification Scheme on the quality of pharmaceutical products moving in international commerce (hereinafter referred to as the “Scheme”).

abuse of Scheme. Actions addressed to the falsification of the certificates of the Scheme, its traceability, to issue them by non-authorized authorities or individuals, and any other activity against the authenticity of the certificates.

active pharmaceutical ingredient (API). Any substance or mixture of substances intended to be used in the manufacture of a finished pharmaceutical product (FPP) and that, when used in the production of a pharmaceutical product, becomes an active ingredient of the FPP. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

applicant. The party applying for a certificate of a pharmaceutical product (CPP). This is normally the agent responsible for importing pharmaceutical products, the marketing authorization holder or other commercially-interested party. In all instances, having regard to the commercial confidentiality of certain data, the certifying authority must obtain permission to release these data from the marketing authorization holder or, in the absence of a marketing authorization holder, from the manufacturer.

batch (synonym: lot). A defined quantity of starting material, packaging material or finished pharmaceutical product (FPP) processed in a single process or a series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

batch certificate (synonym: lot certificate). A document containing information, as set out in Appendix 2 of the guidelines for use, will normally be issued for each batch by the manufacturer. Furthermore, exceptionally, a batch certificate may be validated or issued by the competent authority, particularly for vaccines, sera and other biological products.

The batch certificate travels with every major consignment as a vital instrument in the procurement of medicines. The provision of a batch certificate is usually a mandatory element in tender and procurement documents.

batch number (synonym: lot number). A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, etc.

bulk product. Any product that has completed all processing stages up to, but not including, final packaging.

certificate of a pharmaceutical product (CPP). A document containing the information as set out in Appendix 1 of the guidelines that is validated and issued for a specific product by the competent authority of the issuing country or regional authority and intended for use by the competent authority in the importing country/region or, in the absence of such an authority, by the procurement agency.

certifying authority. This is the competent authority in the Member State and regional authority that issues certificates. It shall ensure that it possesses the capacities listed in section 4.2 of the guidelines.

charges for CPPs. Charges levied upon applicants for the issue of a CPP to be paid to the certifying authority due to the significant administrative load imposed to these authorities during the service of preparation of certificates.

competent authority. This is the national or regional authority, as identified in the formal notification to the WHO Director-General, in which each Member State or regional authority informs WHO of its intention to participate in the Scheme. The competent authority can issue or receive certificates. The extent of participation should be indicated in the notification to the WHO Director-General as stipulated in section 4.3 of the guidelines. WHO makes available a continuously updated list of addresses of competent authorities and the specific conditions for participation (see section 4.4 of the guideline).

dosage form (synonym: pharmaceutical form). The form of the completed pharmaceutical product (e.g. tablet, capsule, elixir, suppository).

expiry date. The date given on the individual container (usually found on the label) of a pharmaceutical product up to and including the date on which the product is expected to remain within specifications, if stored correctly. It is established for each batch by adding the shelf life to the date of manufacture.

falsified pharmaceutical product. A pharmaceutical product that deliberately or fraudulently misrepresents their identity, composition or source. Any consideration

related to intellectual property rights does not fall within this definition. Such deliberate or fraudulent misrepresentation refers to any substitution, adulteration, reproduction of an authorized pharmaceutical product or the manufacture of a pharmaceutical product that is not an authorized product.

“Identity” shall refer to the name, labelling or packaging or to documents that support the authenticity of an authorized pharmaceutical product.

“Composition” shall refer to any ingredient or component of the pharmaceutical product in accordance with applicable specifications authorized/recognized by a national or regional regulatory authority (NRRRA).

“Source” shall refer to the identification, name and address of the marketing authorization holder, manufacturer, importer, exporter, distributor or retailer, as applicable.

A “pharmaceutical product” should not be considered as falsified solely on the grounds that they are unauthorized for marketing in any given country.

finished pharmaceutical product (FPP). A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling.

good manufacturing practices (GMP). That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

importer. An individual or company or similar legal entity importing or seeking to import a medical product. A “licensed” or “registered” importer is one who has been granted a licence for such purpose.

importing agents, guidelines for. Guidelines on import procedures for pharmaceutical products issued for certifying authorities to all agents responsible for importing pharmaceutical products for human and/or veterinary use that operate under its jurisdiction, including those responsible for public sector purchases, to explain the contribution of certification to the medicine regulatory process and the circumstances in which each of the three types of documents will be required.

intermediaries. Intermediaries in the purchasing of pharmaceutical products for human use. Within the scope of the Scheme, they are responsible for supplying sufficient information to the national or regional certifying authorities to satisfy that those aspects of the manufacture of the product, for which the applicant is not directly responsible, have been undertaken in compliance with good manufacturing practice (GMP) as recommended by WHO.

international nonproprietary name (INN). The shortened scientific name based on the active ingredient. WHO is responsible for assigning INNs to pharmaceutical substances.

manufacture. All operations of the purchase of materials and products, production, quality control, release, storage, distribution of pharmaceutical products and related controls.

manufacturer. A company that carries out operations such as the production, packaging, repackaging, labelling and relabelling of the finished pharmaceutical product and the issuing of the certification.

marketing authorization. A legal document issued by the competent medicines regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It must set out, inter alia, the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using International Nonproprietary Names (INNs) or national generic names where they exist), the shelf life and storage conditions and packaging characteristics. It specifies the information on which authorization is based (e.g. “The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence.”). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization and the period of validity of the authorization. Once a product has been given marketing authorization, it is included on a list of authorized products – the register – and is often said to be “registered” or to “have registration”. Marketing authorization may occasionally also be referred to as a “licence” or “product licence”.

marketing authorization holder. An individual or a corporate entity being in possession of a marketing authorization of a pharmaceutical product.

medicines regulatory authority. A national or regional body that administers the full spectrum of medicine regulatory activities, including at least all of the following functions in conformity with national or regional medicine legislation:

- the marketing authorization of new products and variations of existing products;
- quality control laboratory testing;
- the monitoring of adverse drug reactions;
- the provision of information on medicines and the promotion of rational use of medicines;
- good manufacturing practice (GMP) inspections and licensing of manufacturers, wholesalers and distribution channels;
- enforcement operations; and
- the monitoring of drug utilization.

notarization, embassy legalization or apostillation. Processes of authentication or legalization of certificates addressed to avert the potential abuse of the Scheme, to frustrate attempts at falsification, to render routine authentication of certificates by an independent authority superfluous, and to enable the certifying authority to maintain comprehensive records of countries to which specific products have been exported. In addition, this is also for ensuring that certificates and all annexed documentation are consistent with the version of the marketing authorization operative on the date of issue. It is considered enough for that goal that the complete identification of the requesting authority, and the official seal of the certifying authority (or to certify using a secure electronic system/electronic certificate) be stamped on each page. These traditional legal methods are highly discouraged in the context of the Scheme because they have caused undue delays and have not helped to afford the desired objectives.

pharmaceutical product. Any product intended for human use, or veterinary product intended for administration to food-producing animals, presented in its finished dosage form which is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required; products that may be sold to patients without a prescription; biologicals; and vaccines. It does not, however, include medical devices.

product information. This is the approved product information referred to in section 3.7 of the guidelines and item 2.A.4 of the product certificate. It normally consists of information for health professionals and the public (patient information leaflets) as approved by the related medicines regulatory authority and, when available, a data sheet or a summary of product characteristics approved by the medicines regulatory authority.

production. All operations involved in the preparation of a pharmaceutical product, from receipt of materials through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

registration (synonym: marketing authorization). *See marketing authorization.* As a process, it is any statutory system of approval required at national or regional level as a precondition for introducing a pharmaceutical product onto the market. The result of the process could be a certificate of registration or certificate of marketing authorization.

regional authority. A group of countries in the same geographical region to achieve an integrated marketing authorization system. A regional authority that is willing to participate in the Scheme as a certifying member needs to possess a legal authority stipulated in section 2.2 by itself or through its legal framework.

reliance. An act whereby a regulatory authority in one jurisdiction may take into account or give significant weight to work performed by another regulator, or other trusted institution, in reaching its own decision.

requesting authority. This is the competent authority in the Member State and regional authority that requests certificates.

specifications. A list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the test described. It establishes the set of criteria to which a material should conform in order to be considered acceptable for its intended use. “Conformance to specification” means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

substandard pharmaceutical product. Also called “out of specification”, these are authorized pharmaceutical products that fail to meet either their quality standards or their specifications, or both. When the authorized manufacturer deliberately fails to meet these quality standards or specifications due to the misrepresentation of identity, composition or source, then the pharmaceutical product should be considered “falsified”.

summary basis of approval. This refers to the document prepared by some medicines regulatory authorities that summarizes the technical basis on which the product has been licensed (*see section 6.5 of the guidelines and Explanatory note 3 of the product certificate contained in Appendix 1*).

summary product characteristics (SPC). Product information as approved by the medicines regulatory authority. The SPC serves as the basis for production of information for health personnel as well as for consumer information on labels and leaflets of medicinal products and for control of advertising (*see also product information*).

References for Appendix 3

1. WHO good manufacturing practices for active pharmaceutical ingredients. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva, World Health Organization; 2010: Annex 2 (WHO Technical Report Series, No. 957).
2. WHO good storage and distribution practices for medical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva, World Health Organization; 2020: Annex 7 (WHO Technical Report Series, No. 1025).
3. WHO guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva, World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 981).
4. WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva, World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986).
5. WHO model quality assurance system for procurement agencies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva, World Health Organization; 2014: Annex 3 (WHO Technical Report Series, No. 986).

6. Resolution WHA70. WHO Member States mechanism on substandard and/spurious/falsely-labelled/ falsified/counterfeit (SSFFC) medical products, working definitions. In: Seventieth World Health Assembly, Geneva, 22-31 May 2017. World Health Organization; 2017: Annex 12 (WHA70/2017/REC/1).

Appendix 4

(Draft) model notification to the Director-General of the World Health Organization

[Note This Annex 4 is not a part of the “Guidelines on the implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in International commerce”].

The Ministry of Health of the Government of _____ (*name of country*) / _____ (*name of regional authority*) would like to inform the Director-General of the World Health Organization (WHO) that _____ (*name of country or regional authority*) would like to participate/continue to participate in the *WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce* (referred to henceforth as the “Scheme”) as a:

- ☐ Certifying member
- ☐ Requesting member
- ☐ Certifying member and requesting member (*choose only one*).

The Ministry of Health of the Government of _____ (*name of country*) / _____ (*name of regional authority*) hereby confirms that the competent authority(ies) mentioned in the Attachment to this Annex 2 is(are) the legally established authority(-ies) to regulate/control pharmaceutical products.

(Only for certifying members)

In addition, we hereby declare that our certifying authority(-ies) in the Attachment possess(es):

- an effective marketing authorization system for pharmaceutical products, including the responsible manufacturers and licensing of distributors;
- Good manufacturing practices (GMP) requirements, consistent with those recommended by WHO in accordance with its current publication, to which all manufacturers of finished pharmaceutical products are required to conform;
- effective controls to monitor the quality of pharmaceutical products registered or manufactured within its country or region, including access to an independent quality control laboratory;

- a pharmaceuticals inspectorate, operating as an arm of the national or regional medicines regulatory authority, and having the technical competence, experience and resources to assess whether or not GMP and other controls are being effectively implemented, and the legal power to conduct or to coordinate the appropriate investigations in order to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples;
- an efficient surveillance system, administrative capacity and good regulatory practices compliance to effectively issue the required certificates; to detect and institute inquiries in the case of complaint and to expeditiously notify WHO and, when possible, the competent authority in the Member State or region known to have imported a specific product; or publish the information on the website about the product that is associated with a potentially serious quality defect or other hazard in a timely manner.

The Ministry of Health of the Government of _____ (*name of country*) / _____ (*name of regional authority*) would once more like to express its gratitude to the World Health Organization for this opportunity to participate/continue to participate in the Scheme.

We also confirm that any change of information in the Attachment will be promptly communicated to the WHO Secretariat.

Signature		Date	
Name and title			

[STAMP]

Attachment

Information on certifying/requesting authority(-ies)

☐ Certifying authority ☐ Requesting authority ☐ Certifying and requesting authority <i>(choose only one)</i>	
Name of the authority	
Address of the authority	
Telephone number	
Email address	
Website address	
Reservation as per section 4.3 of the Scheme for posting on the WHO website (if any)	
Other remarks (if any)	

(Add tables as necessary)

5. Contract research organizations

5.1 Guidance for organizations performing in vivo bioequivalence studies

Annex 9, WHO Technical Report Series, 996, 2016

Background

During an informal consultation held in 2014, and at the forty-ninth meeting of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations, discussion took place regarding the possible revision of the guidance for organizations performing in vivo bioequivalence studies (WHO Technical Report Series, No. 937, Annex 9, 2006). The WHO Expert Committee on Specifications for Pharmaceutical Preparations agreed that in light of the new developments a draft for revision would be prepared.

These new guidelines take into consideration the revision of the multisource guidelines, as well as the creation of new guidance on good data management. The revision will also take into account the experience accumulated in the area of assessing and inspecting bioequivalence (BE) studies since 2006. In areas where the same problems are repeatedly identified by inspectors, the new guidelines provide clarifications, and supplementary details have been added on bioanalysis. The guidelines also put increased emphasis on subject safety and data integrity.

Based on the first working document: this second version incorporates the numerous comments and the feedback received from the public consultation, the WHO Prequalification Team (PQT) and from the Consultation on data management, bioequivalence, GMP and medicines' inspection held in 2015.

WHO/PQT was set up in 2001 to assure that medicinal products supplied for procurement meet WHO norms and standards with respect to quality, safety and efficacy (<http://www.who.int/prequal/>). Specifically, there is a requirement that the submitted product dossier with all its necessary contents is assessed and found acceptable, and that the manufacturing sites for the finished pharmaceutical product (FPP), as well as the active pharmaceutical ingredient (API), are inspected and found to comply with WHO good manufacturing practices (GMP). Since products submitted to WHO/PQT are usually multisource (generic) products, therapeutic equivalence is generally demonstrated by performing a BE study, for example in a contract research organization (also known as a clinical research organization) (CRO). For prequalification of such a product it is vital that, in addition to the above-mentioned requirements, the CRO used by the sponsor

for BE studies complies with WHO good clinical practices (GCP) and considers relevant elements from WHO good laboratory practices (GLP) and good practices for quality control (QC) laboratories to ensure integrity and traceability of data. In addition, if local legal provisions exist, CROs should be licensed by the respective national medicines authority. Where required by national regulations, BE studies should be authorized by the national regulatory authority. Those involved in the conduct and analysis of BE studies on products to be submitted for prequalification therefore need to ensure that they comply with the relevant WHO norms and standards so that they can be prepared for any inspections by WHO.

Introduction	615
1. Scope	615
2. Glossary	616
A. GENERAL SECTION	620
3. Organization and management	620
4. Computer systems	621
General	622
Hardware	622
Software	622
Networks	624
Data management	624
5. Quality management	625
6. Archive facilities	626
7. Premises	627
8. Personnel	628
B. CLINICAL SECTION	629
9. Clinical phase	629
10. Clinical laboratory	631
11. Ethics	631
11.1 Independent ethics committee	631
11.2 Informed consent	632
12. Monitoring	632
13. Investigators	633
14. Receiving, storage and handling of investigational products	634
15. Case report forms	637
16. Volunteers and recruitment methods	638
17. Food and fluids	639
18. Safety, adverse events and adverse event reporting	640
C. BIOANALYTICAL SECTION	640
19. Method development	640
20. Method validation	641

21. Sample collection, storage and handling of biological material	641
22. Analysis of study samples	642
23. Data processing and documentation	643
24. Good laboratory practices	644
 D. PHARMACOKINETIC, STATISTICAL CALCULATIONS AND REPORTING SECTION	 645
25. Pharmacokinetic and statistical calculations	645
26. Study report	646
References	647
Appendix 1 Example list of standard operating procedures at a contract research organization	648

Introduction

Multisource pharmaceutical products need to conform to the same standards of quality, efficacy and safety as the originator's (comparator) product. Specifically, the multisource product should be therapeutically equivalent and interchangeable with the comparator product. Testing the BE between a product and a suitable comparator (pharmaceutically equivalent or a pharmaceutical alternative) in a pharmacokinetic study with a limited number of subjects is one way of demonstrating therapeutic equivalence without having to perform a clinical trial involving many patients. In such a pharmacokinetic study any statement about the safety and efficacy of the test product will be a prediction based on measurement of systemic concentrations, assuming that essentially similar plasma concentrations of the active pharmaceutical ingredient (API) and/or of its metabolite will result in essentially similar concentrations at the site of action and therefore an essentially similar therapeutic outcome. The BE study thus provides indirect evidence of the efficacy and safety of a multisource pharmaceutical product. Often this will be the only evidence that the product is safe and efficacious. It is therefore crucial that the BE study is performed in an appropriate manner. Several guidance documents stress the importance of on-site inspections to verify compliance with standards of GCP (1–3).

1. Scope

The objective of this document is to provide guidance to organizations that are involved in the conduct and analysis of in vivo BE studies. This guidance supersedes the version published in the WHO Technical Report Series, No. 937, 2006 (4).

BE studies should be performed in compliance with the general regulatory requirements and good practices recommendations as specified in the WHO BE guidelines (5), GCP (1) and GLP (2) guidelines. It is acknowledged that GLP formally apply only to nonclinical safety studies. However the WHO BE guidelines require that the validation of bioanalytical methods and the analysis of BE study samples be performed following the principles of GLP. This does not imply that the laboratory in charge of the bioanalytical part of the study should be monitored as part of a national GLP compliance programme.

These guidelines provide advice on the conduct of BE studies and the bioanalysis of study samples. Particular consideration is given to premises, equipment, organization and management. Recommended documents, standard operating procedures (SOPs) and records are listed in Appendix 1, but this is not to be considered an exhaustive list – other documents may be necessary depending on each individual CRO's functional and compliance needs.

These guidelines provide information on:

- organization and management;
- study protocols;

- clinical phase of a study;
- bioanalytical phase of a study;
- pharmacokinetic and statistical analysis;
- study report;
- quality management system.

This document does not replace the above-mentioned GCP or GLP guidelines. It is therefore not a stand-alone document.

2. Glossary

The definitions given below apply to the terms used in this guidance. They may have different meanings in other contexts. Unless otherwise stated, the definitions are reproduced from *Guidelines for good clinical practice for trials on pharmaceutical products* (1).

adverse event. Any untoward medical occurrence in a clinical trial subject administered a pharmaceutical product; it does not necessarily have a causal relationship with the treatment.

audit of a trial. A systematic examination, carried out independently of those directly involved in the trial, to determine whether the conduct of a trial complies with the agreed protocol and whether the data reported are consistent with the records on site, e.g. whether data reported or recorded in the case-report forms are consonant with those found in hospital files and other original records.

bioequivalence. Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities, in terms of rate ($C_{\max}$ and $t_{\max}$) and extent of absorption (area under the curve), after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.

calibration curve samples (or calibration standards). A matrix to which a known amount of analyte has been added or spiked. Calibration standards are used to construct calibration curves.

case-report form. A document that is used to record data on each trial subject during the course of the trial, as defined by the protocol. The data should be collected by procedures which guarantee preservation, retention and retrieval of information and allow easy access for verification, audit and inspection.

comparator product (or reference product). The comparator product is a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established. If the innovator product is no longer marketed in the jurisdiction, the selection principle

as described in *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products* (5) should be used to identify a suitable alternative comparator product.

contract. A document, dated and signed by the investigator, institution and sponsor, that sets out any agreements on financial matters and delegation/distribution of responsibilities. The protocol may also serve as a contract when it contains such information and is signed. Contracts can also be signed with other parties such as vendors supplying services to the contract research organization.

contract research organization (CRO). A scientific organization (commercial, academic or other) to which a sponsor may transfer some of its tasks and obligations. Any such transfer should be defined in writing.

In the context of this guidance document, bioequivalence studies are often contracted by the sponsor to a CRO, which will perform some of the tasks of the sponsor, but which will also perform the trial. The investigator (clinical part of the study) and the study director (bioanalytical part of the study) are then employees of the CRO.

To facilitate reading, the term “CRO” is used throughout this document to designate any organization performing the trial, even though it is acknowledged that part or all of the study may be performed in-house by the sponsor itself or at a hospital.

ethics committee (6). An independent body (a review board or a committee, institutional, regional or national), constituted of medical professionals and non-medical members, whose responsibility is to verify that the safety, integrity and human rights of the subjects participating in a particular trial are protected and to consider the general ethics of the trial, thereby providing public reassurance. Ethics committees should be constituted and operated so that their tasks can be executed free from bias and from any influence of those who are conducting the trial.

final report. A comprehensive description of the trial after its completion including a description of experimental methods (including statistical methods) and materials, a presentation and evaluation of the results, statistical analysis and a critical, ethical, statistical and clinical appraisal.

good clinical practice. A standard for clinical studies which encompasses the design, conduct, monitoring, termination, audit, analysis, reporting and documentation of the studies and which ensures that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented.

good laboratory practice. A quality system concerned with the organizational process and the conditions under which nonclinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

informed consent. A subject's voluntary confirmation of willingness to participate in a particular trial and the documentation thereof. This consent should be sought only after all appropriate information has been given about the trial, including an explanation of its status as research, its objectives, potential benefits, risks and

inconveniences, alternative treatment that may be available, and of the subject's rights and responsibilities in accordance with the current revision of the Declaration of Helsinki.

inspection. An officially conducted examination (i.e. review of the conduct of the trial, including quality assurance, personnel involved, any delegation of authority and audit) by relevant authorities at the site of investigation and/or at the site of the sponsor in order to verify adherence to good clinical practices and good laboratory practices as set out in this document.

internal standard. Test compound(s) (e.g. a structurally similar analogue or stable isotope-labelled compound) added to calibration standards, quality control samples and study samples at a known and constant concentration to correct for experimental variability during sample preparation and analysis.

investigational labelling. Labelling developed specifically for products involved in a clinical trial.

investigational product (or study product). Any pharmaceutical product (see definition) or placebo being tested or used as a reference in a clinical trial.

investigator. A person responsible for the trial and for the rights, health and welfare of the subjects in the trial. The investigator should have qualifications and competence in accordance with local laws and regulations as evidenced by up-to-date curriculum vitae and other credentials. Decisions relating to, and the provision of, medical or dental care must always be the responsibility of a clinically competent person legally allowed to practise medicine or dentistry.

lower limit of quantification. The lower limit of quantification of an individual analytical procedure is the lowest amount of analyte in a sample that can be quantitatively determined with predefined precision and accuracy.

metadata. Metadata are data that describe the attributes of other data, and provide context and meaning. Typically, these are data that describe the structure, data elements, interrelationships and other characteristics of data. They also permit data to be attributable to an individual. Examples of metadata are the audit trails provided by certain types of software.

monitor. A person appointed by, and responsible to, the sponsor or contract research organization for the monitoring and reporting of progress of the trial and for verification of data.

pharmaceutical product. Any substance or combination of substances which has a therapeutic, prophylactic or diagnostic use, or is intended to modify physiological functions, and is presented in a dosage form suitable for administration to humans.

principal investigator. The investigator serving as coordinator for certain kinds of clinical trials, e.g. multicentre trials.

Note: "principle investigator" also has a specific, but different meaning in good laboratory practices, which is seldom used in bioequivalence studies. To avoid any misunderstanding, the term "principal investigator" will only be used in this guidance document with its good clinical practices meaning.

protocol. A document that states the background, rationale and objectives of the trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. The protocol should be dated and signed by the investigator, the institution involved and the sponsor. It can also function as a contract.

quality assurance relating to clinical trials. Systems and quality control procedures that are established to ensure that the trial is performed and the data are generated in compliance with good clinical practices and good laboratory practices. These include procedures to be followed which apply to ethical and professional conduct, standard operating procedures, reporting, and professional qualifications or skills of personnel.

quality control samples. A spiked sample used to monitor the performance of a bioanalytical method and to assess the integrity and validity of the results of the unknown samples analysed in an individual batch.

raw data. All records or certified copies of original observations, clinical findings or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Such material includes laboratory notes, memoranda, calculations and documents, as well as all records of data from automated instruments or exact, verified copies, e.g. in the form of photocopies or microfiches. Raw data can also include photographic negatives, microfilm, magnetic media (e.g. computer diskettes) and optical media (CD-ROMs).

serious adverse event. An event that is associated with death, admission to hospital, prolongation of a hospital stay, persistent or significant disability or incapacity, or is otherwise life-threatening in connection with a clinical trial.

sponsor. An individual, a company, an institution or an organization that takes responsibility for the initiation, management and/or financing of a clinical trial. When an investigator initiates and takes full responsibility for a trial, the investigator then also assumes the role of the sponsor.

standard operating procedures. Standard, detailed, written instructions for the management of clinical trials. They provide a general framework enabling the efficient implementation and performance of all the functions and activities for a particular trial as described in this document.

study director. According to the Organisation for Economic Co-operation and Development principles of good laboratory practice: the individual responsible for the overall conduct of the nonclinical health and environmental safety study. In a bioequivalence study the individual responsible for the conduct of the bioanalytical part of the study.

study product. *see investigational product.*

test product. Any pharmaceutical product (see definition) or placebo being tested against the reference in a clinical trial. In a bioequivalence study, this is the multisource product being tested against the comparator product.

trial subject. An individual who participates in a clinical trial, either as a recipient of the pharmaceutical product under investigation or as a control. The individual may be:

- a healthy person who volunteers to participate in a trial;
- a person with a condition unrelated to the use of the investigational product;
- a person (usually a patient) whose condition is relevant to the use of the investigational product.

upper limit of quantification. The upper limit of quantification of an individual analytical procedure is the highest amount of analyte in a sample which can be quantitatively determined with predefined precision and accuracy.

validation. Action of proving and documenting, in accordance with the principles of good clinical practices and good laboratory practices, that any procedure, process, equipment (including the software or hardware used), material, activity or system actually and consistently leads to the expected results.

verification of data. The procedures carried out to ensure that the data contained in the final report match original observations. These procedures may apply to raw data, data in case-report forms (in hard copy or electronic form), computer printouts and statistical analysis and tables.

A. GENERAL SECTION

3. Organization and management

Note: the acronym “CRO” is used throughout this document to refer not only to a contract research organization, but also to any organization involved in the conduct of in vivo BE studies or in the analysis of samples or of data from such in vivo BE studies

- 3.1 Where national requirements exist as to the legal status of a CRO these have to be complied with. This also applies to the research unit which is a subsidiary of the manufacturer.
- 3.2 The CRO should have an organization chart depicting key positions and the names of responsible persons. The organization chart should be dated, authorized and kept up to date.
- 3.3 There should be job descriptions for all personnel, including a description of their responsibilities. Every job description should be signed and dated by the staff member to whom it applies.

- 3.4 There should be a list of signatures of the authorized personnel performing tasks during each study.
- 3.5 For the bioanalytical part of the trial, the principles of GLP clearly establish the responsibilities of the test facility management. For the clinical part of the trial, the CRO management should be aware that as the investigator is an employee of the CRO, some of the responsibilities usually assigned to the investigator would in a similar way reside with the CRO management. At a minimum, the CRO management should:
- ensure that the principles of GCP and GLP, as appropriate, are complied with in the CRO;
 - ensure that a sufficient number of qualified personnel, appropriate facilities, equipment and materials are available for the timely and proper conduct of the study;
 - ensure the maintenance of a record of the qualifications, training, experience and job description for each professional and technical individual;
 - ensure that personnel clearly understand the functions they are to perform and, where necessary, provide training for these functions;
 - ensure that appropriate and technically valid SOPs are established and followed, and approve all original and revised SOPs and ensure the maintenance of a historical file of all SOPs;
 - ensure that there is a quality assurance (QA) programme with designated personnel and assure that the QA responsibility is being performed in accordance with the principles of GLP and GCP, as appropriate;
 - ensure that an individual is identified as responsible for the management of the archive(s), and ensure that the documents transferred to the archives are kept under adequate conditions for the appropriate duration;
 - ensure that supplies meet requirements appropriate to their use in a study;
 - establish procedures to ensure that computerized systems are suitable for their intended purpose, and are validated, operated and maintained in accordance with the principles of GCP and GLP, as appropriate.

4. Computer systems

Note: this section highlights only some of the requirements for computer systems that are specific to BE studies. Organizations involved in BE studies should ensure that the relevant principles of the following guidelines are appropriately followed:

- GAMP 5: A risk-based approach to compliant GxP computerized systems (7);
- *Good practices for computerised systems in regulated “GXP” environments, PIC/S guidance* (8);
- US Food and Drug Administration (FDA) *Guidance for industry: part 11* (9);
- *EU guidelines for good manufacturing practice and medicinal products for human and veterinary use Annex 11, Computerised systems* (10);
- *WHO Guidance on good data and record management practices* (11).

General

- 4.1 Computer systems should be qualified and validated (hardware, software, networks, data storage systems and interfaces (7–10). Qualification is the planning, carrying out and recording of tests on equipment and systems which form part of the validated process, to demonstrate that the equipment or system will perform as intended.

Hardware

- 4.2 There should be a sufficient number of computers to enable personnel to perform data entry and data handling, required calculations and compilation of reports.
- 4.3 Computers should have sufficient capacity and memory for the intended use.

Software

- 4.4 There should be access control to the trial-related information entered and stored in computers. The method of access control should be specified (e.g. password protection) and a list of people who have access to the database should be maintained. Secure and unique, individual-specific identifiers and passwords should be used.
- 4.5 The software programs used to perform key steps detailed in these guidelines should be suitable and validated for the intended use. Whether standard, off-the-shelf software is purchased or bespoke software is developed, developer, vendor and/or service provider qualification and/or validation certificates may be provided but it is the user’s responsibility to ensure that the software is validated for its intended use and that it was developed in a controlled manner in accordance with a QA system.
- 4.6 Formal qualification and validation should generally be carried out by the developer. Performance qualification should take account of the specific user’s requirements, of regulatory/guideline requirements for BE studies, of the operating environment in which it will be used, and of how it will be used by

an organization's staff in the context of a study. Quality risk management should be applied when deciding which components need to be validated. All phases of their life cycle should be considered. For example, when a CRO decommissions the software in use for high-performance liquid chromatography (HPLC) and mass spectrometric (MS) analysis (e.g. HPLC-MS/MS), it should ensure that the data collected by the system using this software remain fully readable. This could be done, for instance, by having the old software installed on a workstation for inspection and/or verification purposes only.

- 4.7 There should be SOPs in place for usage of each software program that is used to perform activities of a BE study.
- 4.8 There should be a system in place for the implementation of regular updates to key software programs (e.g. those used for control and data processing of chromatographic and MS systems) whenever required, following an appropriate risk assessment on the potential impact that it could have on current data and on qualification or validation status.
- 4.9 Software programs used, frequency of virus testing, storage of data and the procedure for backups and long-term archiving of all relevant electronic data should be specified in writing. The frequency of backups and archiving should be specified. If back-up data are periodically rewritten as part of the back-up procedure, the data from the backups should be archived regularly, preferably before rewriting is done.
- 4.10 The programs used should be able to provide the required quality and management information, reliably and accurately. Programs necessary for data management include word processing, data entry, databases, graphics, pharmacokinetics and statistical programs. Self-designed software programs must be suitable and validated for their intended use.
- 4.11 Since data for BE studies are often transferred electronically between organizations involved in the studies, verification that the software used by each organization is compatible with the others and that there is no impact on the data so-transferred, should be conducted prior to commencing key study-related tasks.
- 4.12 These requirements apply to all systems used in clinical BE studies, e.g. subject database, electronic case report forms, electrocardiogram (ECG) recording software, HPLC-MS/MS software, software used for pharmacokinetic analysis, for statistical analysis and any other relevant system.

Networks

- 4.13 Networks, including the full client/server architecture and interfaces such as laboratory information management systems, when used, should be appropriately designed, qualified, managed and controlled.
- 4.14 Access to each component of the system by the different users at any given organization involved in the studies, should be appropriately defined, controlled and documented.
- 4.15 There should be a documented inventory of all computerized systems on the network, with a clear identification of those which are GXP regulated. Any changes to the network, including the temporary addition or removal of systems from the network, should be documented.

Data management

- 4.16 Data entry includes transfer of the data from case report forms (CRFs), analytical data and any other data relevant to the reliability and integrity of a study, to the computerized system.
- 4.17 Data entry procedures should be designed to prevent errors. The data entry process should be specified in the SOP.
- 4.18 Data validation methodology (proofreading, double data entry, electronic logical control) should be specified in writing and performed.
- 4.19 Changes to data entered in the database should be made by authorized persons only. Changes should be specified and documented.
- 4.20 Electronic data should be backed up at regular intervals. The reliability and completeness of these backups should be verified – data should not be selected, rather all data should be comprehensively backed up.
- 4.21 All of the raw electronic data must be kept. This includes:
 - all metadata associated with a computerized system and the equipment associated with it (which includes the audit trails for integration, for results, projects and for the entire instrument);
 - validation data and metadata in the form of their source electronic files.

PDF copies are not sufficient on their own, unless it can be demonstrated that these are the raw data and that no alteration was possible after they were generated.

- 4.22 All electronic records obtained from HPLC and MS analysis (e.g. HPLC-MS/MS) are required to be retained, maintained and backed up. It should be ensured that

backup data are exact and complete and that they are secure against alteration, inadvertent erasures or loss. The printed paper copy of the chromatogram would not be considered a “true, exact and complete copy” of all the electronic raw data used to create that chromatogram. Printed chromatograms do not generally include, for example, the sample sequence, instrument method, processing method, integration settings or the full audit trail, all of which were used to create the chromatogram or are associated with its validity. Therefore there should be a greater emphasis on conservation of electronic data than paper data, as paper data are usually not considered the true source data, except, for instance, in the case of paper logbooks where the original record was handwritten.

- 4.23 If data are transformed during processing steps (such as in the example of re-integration of chromatographic data), it should always be possible to compare the original data with the processed data.

5. Quality management

- 5.1 The CRO should have appropriate QA and QC systems with written SOPs to ensure that trials are conducted and data are generated, documented and reported in compliance with the protocol, GCP, GLP, GMP and the applicable regulatory requirements.
- 5.2 QA personnel should be independent of the work they are quality assuring, including:
- conducting or monitoring of the trial;
 - conducting bioanalysis;
 - performing reporting and pharmacokinetic and statistical analyses.

As a consequence, QA personnel should not be directly involved in trial-related activities, and an in-process audit by QA personnel does not replace oversight by another person when required.

- 5.3 The QA unit should be responsible for:
- verifying all activities undertaken during the study;
 - ensuring that the quality management systems, are followed, reviewed and updated;
 - determining that the protocol and SOPs are made available to study personnel and are being followed;
 - checking all the study data for reliability and traceability;

- planning and performing self-inspections (internal audits) at regular and defined intervals in accordance with an SOP, and following up on any corrective action as required, to determine if all studies are conducted in accordance with GCP and GLP;
- ensuring that contract facilities adhere to GCP and, if applicable, to GLP: this would include auditing of such facilities, and following up on any corrective action required;
- verifying that the trial report accurately and completely reflects the data from the study and the methods and procedures followed;
- promptly reporting audit findings in writing to management, to the investigator and to the study director, as applicable.

- 5.4 The CRO should allow the sponsor to monitor the studies and to perform audits of the clinical and analytical study and sites and should provide suitable office space for these activities.
- 5.5 Both in-process and retrospective QA verifications (e.g. in bioanalysis, as the samples and standards are being prepared and tested) should be performed.
- 5.6 The quality management system should include root cause analysis, tracking for trends, ensuring all aspects of data integrity and the implementation of appropriate corrective and preventive action (CAPA).

6. Archive facilities

- 6.1 The CRO should have sufficient and appropriately secure storage space, which should be fireproof, relative humidity-controlled and pest-controlled, for archiving of the trial-related documentation. Archives should also be protected from flooding.
- 6.2 An SOP should be in place for archiving.
- 6.3 Access to archive storage areas should be controlled and restricted to authorized personnel.
- 6.4 Records of document access and return should be maintained.
- 6.5 The length of time for which study documentation, including raw data, is kept in the archive should be defined in the SOP and may vary depending on country requirements. This period should be specified in the contract between the sponsor and the CRO, which should include provisions for financing of the archiving.
- 6.6 All data, including both paper and electronic versions, should be easy to retrieve and traceable.

7. Premises

- 7.1 The facilities should be kept clean and should have adequate lighting, ventilation and, if required, environmental control. Floors, walls and working bench surfaces should be easy to clean and to decontaminate.
- 7.2 Clinical trials must be carried out under conditions that ensure adequate safety for the subjects. The site selected should be appropriate to the potential risk involved.
- 7.3 The CRO should have sufficient space to accommodate the personnel and activities required to perform the studies. The trial site must have adequate facilities, including laboratories, and equipment. The facilities used for the clinical phase of the study, including areas listed in paragraph 9.6, should be well organized in order to carry out the activities in a logical order.
- 7.4 Entry to the facility should be restricted and controlled. There should be alarm systems to detect the exit of subjects from clinical facilities, or the doors should be locked (but only if emergency evacuation can still be ensured). Any entry to and exit from the facility should be recorded.
- 7.5 Sites where clinical activities take place should include a pharmacy where investigational products should be stored under appropriate conditions with entry and exit restricted by access control. Appropriate entry/exit records of each visit to the pharmacy should be maintained.
- 7.6 Utilities such as water, air, gas and electricity should be adequate, stable and uninterrupted.
- 7.7 Access to telephone, email and facsimile facilities should be available to ensure proper communication. The CRO should have the necessary office equipment (printer, copy machine) to perform the required activities.
- 7.8 Laboratory premises should be designed to suit the operations to be carried out in them. Sufficient space should be provided to avoid mix-ups, contamination and cross-contamination. Adequate storage space suitable for samples, standards, solvents, reagents and records should be available.
- 7.9 Laboratory premises should be designed to provide adequate protection to all employees and authorized external personnel, including inspectors or auditors, by ensuring their safety while handling or working in the presence of chemicals and biological samples. Inappropriate working conditions can have a negative impact on the quality of the work performed and of the data generated.

The general rules for safe working in accordance with national regulations and SOPs normally include the following requirements.

- Safety data sheets should be available to staff before testing is carried out. Staff working in the laboratory should be familiar with and knowledgeable about the material safety data sheets for the chemicals and solvents that they are handling.
- Smoking, eating and drinking in the laboratory should be prohibited.
- Staff should know how to use the firefighting equipment, including fire extinguishers, fire blankets and gas masks.
- Staff should wear laboratory coats or other protective clothing, including eye protection.
- Appropriate care should be taken when handling, for example, highly potent, infectious or volatile substances.
- Highly toxic and/or genotoxic samples should be handled in a specially designed facility to avoid the risk of contamination.
- All containers of chemicals should be fully labelled and include prominent warnings (e.g. “poison”, “flammable” or “radioactive”) whenever appropriate.
- Adequate insulation and spark-proofing should be provided for electrical wiring and equipment, including refrigerators.
- Rules on safe handling of cylinders of compressed gases should be observed and staff should be familiar with the relevant colour identification codes.
- Staff should be aware of the need to avoid working alone in the laboratory.
- First-aid materials should be provided and staff instructed in first-aid techniques, emergency care and the use of antidotes.
- Containers containing volatile organic solvents, such as mobile phases or liquid/liquid extraction solvents should be closed with an appropriate seal.
- Volatile organic chemicals should be handled under certified fume-hoods or air extractors and safety and eye showers should be available in the laboratory.

7.10 Premises should have suitable systems in place to dispose of waste, to treat fumes and to protect the environment in conformance with local or national regulations.

8. Personnel

8.1 There should be a sufficient number of medical, paramedical, technical and clerical staff with the appropriate qualifications, training and experience to support the trial and to be able to respond effectively to all reasonably foreseeable emergencies. The number of members of staff required depends on the number

and complexity of the trials performed by the CRO. At all stages of the trial, including at night, there should be a sufficient number of appropriately qualified and trained personnel to ensure that the rights, safety and well-being of the subjects are safeguarded, and to care for the subjects in emergency situations.

- 8.2 The delegation of significant trial-related duties should be documented in writing.
- 8.3 Contract workers may be employed to perform certain activities. All contract workers who have access to the clinical or bioanalytical areas or who are performing trial-related activities should be provided with adequate information, training and job descriptions. Their contracts should be signed before beginning their work.
- 8.4 Current curricula vitae and training records should be kept for full-time and contract workers.
- 8.5 The personnel responsible for the planning and conduct of the study should have appropriate qualifications and sufficient knowledge and experience in the relevant field. They should receive the study-specific information and training required for the performance of their work.
- 8.6 Records of training and assessment of knowledge of GCP, GLP and any other relevant area or technique should be maintained.
- 8.7 There should be adequate measures in place to protect personnel from accidental infection (e.g. from accidental needle pricks) while obtaining blood samples from subjects or while handling samples that are derived from blood products (e.g. plasma and its extracts) or while handling or disposing of infectious waste.

B. CLINICAL SECTION

9. Clinical phase

Note: As in vivo BE trials are considered as clinical trials, specifically as a Phase I study, the general requirements and recommendations of GCP apply to all BE trials. Clinical trials must be carried out under conditions that ensure adequate safety of the subjects. The clinical phase of the study can be performed on the premises of a CRO or by contracting suitable premises in a hospital.

- 9.1 A CRO should have rooms meeting the requirements listed in the sections below.
- 9.2 There should be sufficient space to accommodate the study subjects.

- 9.3 Where appropriate, beds should be available for the subjects. The necessity for beds and for overnight stays depends on the type of trial and investigational product and should be specified in the trial protocol. Overnight stays are usually required for the night prior to dosing to ensure adequately controlled conditions and that there is no intake of food or medication within the number of hours that is specified in the trial protocol.
- 9.4 Systems should be in place in the accommodation facilities so that subjects can alert CRO staff in case of need.
- 9.5 Facilities for changing and storing clothes and for washing and toilet purposes should be clean, well ordered, easily accessible and appropriate for the number of users. Lockable toilets should be alarmed and doors should be designed to ensure that they can be opened from the outside should there be a medical emergency.
- 9.6 The study site should have rooms or areas, as appropriate, for the following:
 - subjects' registration and screening;
 - obtaining informed consent of individual subjects without compromising privacy;
 - subjects' housing;
 - subjects' recreation;
 - pharmaceutical operations (restricted access room, e.g. for storage, repacking, dispensing, documentation) (see also section 14);
 - administration of the investigational products and sample collection;
 - sample processing (e.g. plasma separation) and storage (freezer);
 - controlled access storage of study materials, medication and documentation including CRFs;
 - preparation of standardized meals and a dining hall;
 - proper care of subjects who require emergency or other medical care, with emergency or first-aid equipment and appropriate medication for use in emergencies;
 - archiving.
- 9.7 Provisions should be made for the urgent transportation of subjects to a hospital or clinic equipped for their emergency care, if required.
- 9.8 Access to key documents, such as the randomization list, should be restricted to specific personnel, such as the pharmacist in charge of the study. Such documents should be password-secured (if electronic) or kept under lock and key (if in the form of a hard copy) and their distribution should be documented.

- 9.9 Equipment used should be appropriately calibrated at predefined intervals.
- 9.10 The adequate function and performance of emergency-use equipment (e.g. defibrillators) should be verified at appropriate intervals.

10. Clinical laboratory

- 10.1 A suitable clinical laboratory should be used for analysing samples. Whenever possible this should be an accredited laboratory.
- 10.2 Haematological tests, urine analysis and other tests should be performed during the clinical trial as specified in the study protocol.
- 10.3 Sample labelling, receipt, storage and chain of custody should ensure full traceability and sample integrity (9).
- 10.4 The CRO should receive information about the analytical methods used in the laboratory, a dated list of laboratory normal ranges and, if available, the accreditation certificate of the laboratory. These should be available for inspection by regulatory authorities upon request.
- 10.5 The laboratory should provide the CRO with current and signed curricula vitae of the responsible individuals.
- 10.6 Individual reports should be created by the laboratory for each subject and should be included in the CRFs. Source or raw data for all tests performed should be archived by the laboratory in electronic or paper formats, depending on their source and the laboratory's storage capacity. Electronic formats are preferred.
- 10.7 Data integrity requirements apply to all tests related to the study (11). For instance, raw data should be adequately protected from modification or deletion.

11. Ethics

11.1 Independent ethics committee

Trials must be approved by an independent ethics committee (IEC) (or equivalent) before any study is conducted, according to *WHO operational guidelines for ethics committees that review biomedical research* (6), and to the legislation in force. This Committee must be independent from the sponsor, the investigator and the CRO. Detailed minutes should be kept of the discussions, recommendations and decisions of the IEC meetings. The IEC should be given sufficient time for reviewing protocols, informed consent forms (ICFs) and related documentation.

11.2 Informed consent

The following points should be borne in mind in relation to informed consent.

- Information for study participants should be given to them in a language and at a level of complexity appropriate to their understanding, both orally and in writing.
- Informed consent must always be given by the subject and documented in writing before the start of any trial-related activities, in accordance with GCP. If informed consent is also recorded by video, this recording should be retained in accordance with local legal requirements.
- The information must make clear that participation is voluntary and that the subject has the right to withdraw from the study on his or her own initiative at any time, without having to give a reason (compensation should be paid pro rata temporis). If subjects who withdraw from the study offer their reasons for doing so, those reasons should be included in the study records.
- The subject must have access to information about insurance and other procedures for compensation or treatment should he or she be injured or disabled by participating in the trial or during screening.
- The volunteers or subjects should be given the opportunity to discuss with a physician their concerns regarding potential side effects or reactions from the use of the investigational products before participating in the trial. They should also be given the opportunity and sufficient time to discuss their concerns about participating in the trial with individuals outside the CRO, such as friends and family members, if they wish.
- If the ICF is available in several languages (e.g. in English and in the local language, or in several vernacular languages) care should be taken to ensure that all versions of the form contain the same information.

12. Monitoring

Note: monitoring is an essential activity to ensure the quality of the clinical trial.

- 12.1 The monitor should be appropriately qualified (see section 8: Personnel). The main responsibility of the monitor for a BE study is to ensure that the study is conducted in accordance with the protocol, GCP, GLP and applicable ethical and regulatory requirements. This includes verification of the use of correct procedures for completion of CRFs and verification of the accuracy of data obtained.
- 12.2 The sponsor can delegate the monitoring function to the CRO. In such cases the CRO should be able to arrange for the monitoring of the trial according

to regulatory requirements. In this situation, attention should be paid to the independence of the monitoring function to avoid conflicts of interest and pressure on the monitors. The monitoring reports should always be provided to the sponsor.

- 12.3 A risk-based approach to monitoring can be considered. However, a pre- and post-study visit, as well as a monitoring visit during the conduct of the trial, are usually performed. The monitor should prepare a written report after each site visit and communicate any issues to the CRO and to the sponsor as quickly as possible, even while the study is being conducted, if possible, to enable prompt corrective action. Such communications and corrective actions should be documented.
- 12.4 When the monitoring is delegated to the CRO, SOPs should be available to describe:
 - the designation of monitors, who should be independent from the personnel performing the trial;
 - procedures for the monitoring visit;
 - the extent of source data verification, including with regard to accountability of the investigational products and adherence to the protocol.

The extent of the monitoring, including the number of visits to be performed, should be agreed with the sponsor.

- 12.5 Separate SOPs (with checklists for the monitor) for the initiation visit, routine monitoring visits and a closing visit are recommended.
- 12.6 Appropriate entry/exit records of each monitoring visit should be maintained.

13. Investigators

- 13.1 The principal investigator (PI) should have the overall responsibility for the clinical conduct of the study, including clinical aspects of study design, administration of the products under investigation, contacts with local authorities and the ethics committee and for signing the protocol and the final study report.
- 13.2 The investigator(s) should have appropriate qualifications, be suitably trained and have experience in the conduct of BE studies (the legal status of persons authorized to act as investigators differs between countries) and at least one investigator must be legally allowed to practise medicine.

- 13.3 The medically-qualified investigator should be responsible for the integrity, health and welfare of the subjects during the trial and for the accurate documentation of all trial-related clinical data.
- 13.4 The CRO is responsible for selecting investigator(s). If the investigators are not permanent employees of the CRO, external investigators should be contracted and adequately trained.

14. Receiving, storage and handling of investigational products

- 14.1 CROs should record all the information concerning the receipt, storage, handling and accountability of investigational products at every stage of the trial. CROs must keep records of information about the shipment, delivery, receipt, description, storage (including storage conditions), dispensing, administration, reconciliation, return and/or destruction of any remaining pharmaceutical products. Details of the pharmaceutical product used should include dosage form and strength, lot number, expiry date and any other coding that identifies the specific characteristics of the product tested.
- 14.2 A suitably qualified person within the CRO or a local pharmacy or hospital pharmacy should assume responsibility for storage, delivery, return and keeping records of the investigational products.
- 14.3 Pharmaceutical products should be stored under appropriate conditions as specified in the official product information provided by the sponsor.
- 14.4 All study medication should be kept in a securely locked area accessible only to authorized personnel.
- 14.5 Randomization should be performed in accordance with an SOP and records should be maintained, including the randomization list and seed, if applicable. The randomization list should normally be accessible only to the person who generates it, a dispensing pharmacist and the statistician, and should not be circulated or made available to other staff members via any medium. A system should be in place to allow the PI or delegated staff to access the randomization list in case of emergency.
- 14.6 Labelling should be performed in accordance with the following requirements.
 - The printing step should be done in a manner that reduces potential risks of mislabelling and in accordance with an SOP.
 - Each label should include the following information:

- name of the sponsor,
 - a statement reading “for clinical trial use only”,
 - trial reference number or study number,
 - batch number,
 - subject identification number (to whom the product is destined to be given),
 - study period,
 - active ingredient and dosage,
 - the storage conditions,
 - expiry date (month/year) or retest date,
 - identification of the product (i.e. test or reference).
- Compliance of all labels with the randomization list should be verified once they have been printed and prior to labelling of the containers.
 - Labels should be pasted onto the container, not on the lid, to ensure that the information is not lost once the lid is removed.
 - The system used for labelling and documenting the administration of the product should make it possible to verify that each subject did receive the product dispensed for him or her, for instance, by using labels with a tear-off portion. In this case, labels should be designed in such a way that two identical labels are pasted onto the container and the second label can be easily cut or detached and pasted onto the CRF at the time of dosing (e.g. two labels printed side by side, with only one that is actually pasted onto the container and another that remains attached but unpasted. Using two independent labels – one stuck on the container, one kept loose – should be avoided owing to the risk of mix-ups).
 - The empty containers should be labelled separately for the test and the reference investigational products and should remain adequately segregated in a secure area under lock and key to avoid the risk of any potential mix-ups, until the dispensing stage.
 - Label reconciliation should be performed.
 - Appropriate, detailed records should be maintained for each of the above steps.

14.7 Dispensing and packaging should be performed in accordance with the following requirements.

- The surface on which the product will be handled should be thoroughly cleaned before bringing bottles of the product into the area. Any product

containers (full or empty), lone dosage formulations, labelling materials, contaminants, dirt and debris should be removed from the area.

- A second person should verify that the surface area (otherwise referred to as the “line”) is indeed clear and clean before bringing in and opening containers of the product.
- Test and reference products should be handled using an appropriate instrument, such as a spatula or spoon, as opposed to gloved hands.
- Tablets should be distributed into each container in accordance with the randomization list for the comparator or for the test product as appropriate. The two products should never be handled at the same time. This also applies to the labelled containers.
- Records should be made of this step in a manner similar to that used for manufacturing batch records, as described in WHO GMP guidelines, i.e. each and every step should be recorded sequentially in detail.
- The surface upon which the product is handled and its surroundings should be cleared and cleaned immediately before and after initiating the dispensing of the next product. It is important to note that this also applies to different products used in the same study.
- Investigational product accountability and dispensing records should be maintained at all times. Each activity should be documented at the time it is performed. This includes:
 - records of doses dispensed and returned or destroyed,
 - records of cleaning and clearance of the area before dispensing,
 - record of verification of adequate cleaning and clearance of the area,
 - record of verification by a second person of each step.

Any factors that could affect the integrity of the data relating to investigational medicinal products and comparators should be recorded, monitored and controlled.

For further guidance on labelling and dispensing, please refer to the *WHO good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans* (12).

14.8 Dosing should meet the following requirements.

- Dosing should be performed in accordance with an SOP.
- Dosing should be performed under the supervision of the investigator or of a qualified staff member to whom this task has been explicitly delegated in writing.

- Whenever possible, just prior to dosing, a check should be performed to ensure that vial contents match the information on the label.
 - The exact time of dosing should be documented.
 - To ensure that the subject has swallowed the product, a mouth check should be performed by looking under the tongue, under the lips, in the corners of the mouth and between gums and cheeks, using a tongue depressor or a spatula and a penlight, in the case of solid oral dosage forms. For other dosage forms, verification of adequate administration should be performed by other suitable means. This should be documented.
 - If more than one dosage unit is administered, this should be clearly documented.
 - Dosing can be documented directly in the CRFs. If re-transcribed in the case of report forms from other documents, the original documents should be retained.
 - Investigational product reconciliation after dosing should be verified by a second responsible person.
- 14.9 The investigator should follow the protocol requirements, the randomization scheme and, where required, blinding. The investigator should ensure that the use of the investigational product is documented in such a way as to ensure appropriate dosage.
- 14.10 Samples of the product in the original container should be retained for possible confirmatory testing in the future for a period of at least one year after the expiry date of the newest product (test or reference) or in compliance with the applicable national requirements or international recommendations, as appropriate. Sample retention should be defined and described in an SOP and be specified in the contract between the sponsor and the CRO. Dispensed products that were not administered should also be retained.

15. Case report forms

- 15.1 CRFs should be used to record data on each subject during the course of the trial.
- 15.2 The CRO should have a procedure for designing CRFs if the sponsor requests the CRO to do so. The use of a standardized format or template is recommended. This should be adapted for each study protocol in accordance with the requirements for that particular study. The CRF should be reviewed against other trial documentation, such as the protocol and trial database, to ensure that appropriate information and data are captured and that the CRF is consistent with other trial documentation.

- 15.3 The data to be collected on each volunteer should be specified in the trial protocol. Any data to be recorded directly on the CRF (i.e. no prior written or electronic record of data), and to be considered to be source data, should be identified in the protocol.
- 15.4 CRFs should reflect the actual results obtained during the study and allow easy access for verification, audit and inspection of the data.
- 15.5 Appropriate procedures should be established and followed to document the investigator's certification of the accuracy of CRFs. Any errors or omissions should be clarified with the investigator, corrected, dated and signed and explained on the CRF.
- 15.6 Copies of the clinical laboratory reports and all ECGs should be included with the CRFs for each subject and should be submitted together with the dossier, if applicable, in accordance with the requirements of the regulatory authority to which the dossier is submitted.

16. Volunteers and recruitment methods

Note: The selection of subjects should be performed sufficiently far in advance to ensure that a sufficient number of subjects will be available for the study. The last-minute selection of additional subjects may result in noncompliance with the inclusion and exclusion criteria, possibly compromising the safety of the subjects and the integrity of the trial data. The use of a generic screening process to select a pool of subjects that can be enrolled in any BE study conducted at the CRO (unless the protocol foresees specific inclusion or exclusion criteria) can help to achieve this goal.

- 16.1 Procedures for the recruitment of volunteers should be available and should include a description of the potential methods that can be used by the CRO for this purpose. A database should be maintained on volunteers, to avoid cross-participation and to specify a minimum time that should elapse between a volunteer's participation in one study and the next. Access to the database should be password controlled in order to secure confidential information on volunteers or subjects.
- 16.2 Identification of volunteers and subjects should be ensured by reliable means. If a biometric system is used, this system should be periodically validated, as well as after any change made to the validated system that could affect its function.
- 16.3 The informed consent of potential subjects should be obtained for any screening procedures required to determine eligibility for the study in addition to informed consent for participation in the research portion of the study.

- 16.4 Criteria for subject selection (inclusion and exclusion criteria) and screening procedures should be described in the clinical trial protocol.
- 16.5 The results of subject screening and of trial participation should be recorded in a validated database maintained by the CRO. If a regional or national volunteer database exists, then this should be checked to find out whether any of the subjects have participated in a previous trial and participation data should be uploaded to this central repository to prevent over-volunteering. Access to the database should be password controlled in order to secure confidential subject information.
- 16.6 Ideally the CRO's database should record and allow the users to query:
- contact details;
 - sex;
 - status: e.g. eligible, disqualified, not eligible, quarantined, and the reason for this status if applicable;
 - date and place of last study participation, if applicable/if known;
 - date of last screening;
 - a unique code assigned to the subject which will never change;
 - outcome of last trial: e.g. completed, randomized but not dosed, withdrawn for personal reasons, withdrawn for medical reasons.

These data should be backed up daily and be available for review at any time.

- 16.7 Medical records should be generated for each subject and should include information obtained during each screening visit and from each study in which the subject has participated, which could be relevant for the inclusion and follow-up of the subject in subsequent trials. Access to previous medical records for individual subjects should be available and a consistency check conducted where trial-specific medical records are generated. This is important to ensure that safety issues can be assessed before a subject's enrolment in a study.

17. Food and fluids

- 17.1 As meals can significantly affect absorption of active pharmaceutical ingredients, fasting and meals should be standardized and adequately controlled and scheduled during the study days. The CRO should be able to arrange for standardized meals, snacks and drinks for the study subjects as described in the clinical trial protocol.
- 17.2 Records should be maintained of the timing, duration and amount of food and fluids consumed. Prior to samples being obtained from ambulatory subjects,

they should be asked about their food and drink consumption, if the protocol contains specific requirements.

- 17.3 Standardized meals should be designed by a dietitian with appropriate qualifications, training and experience. If such services are contracted out, a formal contract with terms of reference should be available.

18. Safety, adverse events and adverse event reporting

- 18.1 Appropriate study planning includes adequate evaluation of risk to the subjects. The study should be planned, organized, performed and monitored so that the safety profile will be acceptable, including to the volunteers.
- 18.2 First-aid equipment and appropriate rescue medication should be available and ready for emergency use at the study site where there should be adequate facilities for the proper care of subjects who require emergency or other medical treatment. Any treatment given to a subject should be documented and included in the CRF and in the supporting documentation, as necessary.
- 18.3 A medical doctor should be responsible for medical decisions in the case of adverse events and for notifying the relevant health authorities, the sponsor and, when applicable, the ethics committee, without delay in the case of serious adverse events. Appropriate timelines should be respected in accordance with national regulations.
- 18.4 The CRO should have appropriate adverse event registration and reporting forms, which should be provided to the investigator; these forms can be part of the CRF. If required the sponsor's forms may be used.

C. BIOANALYTICAL SECTION

Note: The measurement of analyte concentrations (API or metabolites) may be performed by the same CRO as conducted the clinical study, or this work may be contracted to another laboratory or CRO.

19. Method development

- 19.1 The bioanalytical laboratory should provide a detailed description of how a bioanalytical method was developed. The laboratory should keep a copy of any publications used in developing the bioanalytical method. The modifications and adaptations to the published method made by the laboratory should be documented.

- 19.2 Selection of the internal standard should be justifiable by sound scientific principles. In general, the chemical and physical properties of the internal standard should be as close to those of the analyte as possible. Both stable isotope-labelled and non-isotope-labelled internal standards are acceptable, although the use of a stable isotope-labelled internal standard is recommended when MS methods are used. The selection of a stable isotope-labelled internal standard should take into consideration factors such as the isotope labelling positions in order to limit the risk of exchange reactions.
- 19.3 The procedure for method development should ensure that methods are created in a manner that will minimize any potential human error.

20. Method validation

The most up-to-date guidelines available from stringent regulatory authorities (SRAs) on the topic of bioanalytical method validation should be followed.

- 20.1 Validation requirements for the analytical method should be described in the protocol. There should be separate SOPs for analytical method validation.
- 20.2 Data to support the stability of the samples under the stated conditions and period of storage should be available, preferably before the start of the study.
- 20.3 Method validation should be performed with at least one run that is comparable in length to those that are expected to be used for analysis of samples.

21. Sample collection, storage and handling of biological material

- 21.1 The specification of the samples (serum, plasma or urine), sampling method, volume and number of samples should be stated in the clinical trial protocol and in the information provided to the volunteers.
- 21.2 There should be documented procedures for the collection, preparation, transport or shipping and storage of samples.
- 21.3 Any specific lighting conditions foreseen by the protocol or other documents should be complied with. This should be documented.
- 21.4 Actual sampling times and deviations from the prespecified sampling times should be recorded. Deviations should be noted in the study report and should be taken into consideration when calculating the pharmacokinetic parameters.

- 21.5 Labelling of collected samples should be clear to ensure correct identification and traceability of each sample.
- 21.6 The conditions for the storage of samples depend on the analyte. However, all storage conditions (e.g. freezer temperature) should be specified in the study protocol, controlled, monitored and recorded throughout the storage period and during transportation. Procedures should be in place to ensure maintenance of sample integrity in case of system failures.
- 21.7 Records of the storage and retrieval of samples should be maintained.
- 21.8 It is recommended to keep duplicate or back-up samples, and to store and ship them separately.
- 21.9 The duration of storage of bioanalytical samples should be specified in the contract between the sponsor and the CRO.
- 21.10 Local requirements for the handling and destruction of any remaining biological materials should be complied with.

22. Analysis of study samples

The most up-to-date guidelines from SRAs on the topic of bioanalytical method validation should be followed. Additionally:

- 22.1 The results of the method validation should be available before the initiation of study sample analysis, with the possible exception of the evaluation of the long-term stability of the analyte in matrix. However, these results should be available before the study report is issued and should be submitted with the validation report in the application.
- 22.2 Each analytical run should include calibration curve (CC) standards, QC samples and subject samples processed simultaneously. The exact sequence of processing should be documented. All samples collected from a given subject during all trial periods should be analysed in the same run unless scientifically justified (e.g. where the limited stability of samples necessitates the analysis of period one samples before period two is conducted).
- 22.3 Equipment with an adequate capacity should be used to enable all samples in a run to be processed simultaneously, rather than splitting the samples into several extraction batches. However, if using several extraction batches within a single analytical run cannot be avoided, each batch should include QC samples. The acceptance criteria for the analytical run should be defined in an SOP first for the full run, then if the run is acceptable, for each individual extraction batch.

- 22.4 Every effort should be made during method development to avoid carry-over effects. If carry-over cannot be avoided, procedures should be implemented to limit its influence, for instance, by inserting wash samples into runs after samples with a high concentration.
- 22.5 With regard to the use of blank plasma in the preparation of CCs and QCs:
- the number of freeze–thaw cycles and the duration of storage that a given blank plasma sample can be submitted to should be limited as much as possible to ensure that there is no degradation and/or any change of its properties. Freezing blank plasma in small volumes should be considered to help limit the number of freeze–thaw cycles for any given blank plasma sample;
 - the anticoagulant that was used for the blank plasma should be documented. It should match the anticoagulant that was used in study samples, in nature and in proportion.
- 22.6 With regard to incurred sample reanalysis:
- incurred sample reanalysis should be performed in line with the European Medicines Agency (EMA) *Guidelines on bioanalytical method validation* (13);
 - large differences between results may indicate analytical issues and should be investigated.

23. Data processing and documentation

- 23.1 Integration settings should be science-based and fully justifiable. Smoothing should be kept low enough not to mask possible interferences and changes in peak geometry.
- 23.2 The different iterations used to obtain a CC should be saved – if a given CC fails, it is not acceptable to exclude CCs which meet acceptance criteria or, similarly, to include CC standards that do not meet criteria, just to make the calibration or the QC standards pass. The source data should contain the original, first evaluation of runs (containing all calibration samples). If several calibration samples are excluded sequentially, the CC obtained at each step should be retained to document that the criteria for excluding the next sample were met. If electronic raw data are used it is acceptable to save only the final calibration if it is possible to revert to the initial calibration during an inspection. The process and criteria for acceptance and exclusion of CC standards should be described in an SOP.
- 23.3 If the first or last calibration sample is rejected, the calibration range should be truncated, i.e. the second calibration sample becomes the lower limit of

quantification (LLOQ) in that run (or the penultimate calibration sample becomes the upper limit of quantification (ULOQ). Samples with a concentration below the revised LLOQ (or above the revised ULOQ) should be reanalysed. Alternatively, the whole run may be repeated, but this is not the preferred option.

- 23.4 Internal standard variation should be trended and used as part of the verifications of result validity. Significant changes in internal standard response could signal an analytical problem that requires an investigation and/or sample reanalysis. Significant differences between the internal standard results of CC standards or QC standards versus samples could also signal problems affecting the reliability of the results.
- 23.5 Full audit trails should be activated at all times and on all analytical instruments in a given facility, before, during and after the method validation and the study of interest.
- 23.6 All original analytical raw data (e.g. calculations, chromatograms and their associated audit trails) should be documented in a manner that will ensure traceability with respect to the sample number, equipment used, date and time of analysis and the name(s) of the technician(s). If several audit trail files are generated, all should be retained (e.g. results table audit trail, project audit trail and instrument audit trail).
- 23.7 Each data point should be traceable to a specific sample, including sample number, time of collection of the sample, time of centrifugation, if applicable, time when the sample was placed in the freezer and time of sample analysis, to be able to determine whether any aberrant results might have been caused by sample mishandling.

24. Good laboratory practices

- 24.1 Although most GLP guidelines (2) apply formally only to nonclinical safety studies, general principles of GLP should also be followed during the bioanalytical part of BE studies.
- 24.2 Analysis should be performed in a laboratory with established QA systems (14).
- 24.3 Key sample storage systems or other areas requiring environmental controls should be adequately qualified, calibrated and maintained. There should be an alarm system or an adequate monitoring system to control the temperature of the critical stage areas and key sample storage systems, such as freezers. If there is an automatic alarm system it has to be tested regularly to check its functionality. The daily monitoring and all the alarm checks should be documented. There should be a system in place to ensure that timely and appropriate action is taken following an alarm.

- 24.4 For the purposes of qualification and requalification, the temperature-mapping of the freezers and refrigerators should be run for between 24 and 72 hours, or more if justified. Remapping should be done after any significant modifications to the storage units.
- 24.5 Appropriate repairs and/or transfer of samples to other equivalent storage units should be considered whenever an analysis of temperature monitoring records shows unexplained variability outside normal operating limits.
- 24.6 Balances, other measuring devices and equipment and instruments used during the conduct of a trial should be periodically calibrated and verified before use. They should be fit for their intended purpose.
- 24.7 There should be SOPs for the operation, use, calibration, checks and preventive maintenance of equipment. Records should be maintained. Items of equipment used during the course of the trial should be identified to enable verification that they have been appropriately qualified and calibrated.
- 24.8 Chemicals, reference substances, reagents, solvents and solutions should be labelled to indicate identity, purity, concentration (if appropriate), expiry date and specific storage instructions. Information concerning source, preparation date and stability should be available.

D. PHARMACOKINETIC, STATISTICAL CALCULATIONS AND REPORTING SECTION

25. Pharmacokinetic and statistical calculations

- 25.1 The statistical model underlying any primary BE analysis should be stated in the protocol and/or a statistical analysis plan. It should be made clear which factors are fixed and which are random and whether the model is a mixed effects model, a normal linear model, or another type. If the methods of statistical analysis are amended following approval of the protocol then this should be documented in a protocol amendment and should also be reported in the clinical study report together with the reason for change.
- 25.2 Calculations should be made by suitably qualified personnel (see section 8: Personnel).
- 25.3 The means of performing pharmacokinetic and statistical calculations (both software and scripts) should be specified in the study protocol and/or a pharmacokinetic analysis plan and a statistical analysis plan. Data analysis should conform to these requirements. This should include the manner in which

area under the curve from time zero to infinity (AUC_{inf}) is derived (i.e. how the points used for extrapolation are selected).

- 25.4 Calculations should be made using validated software and scripts. Software and scripts should be validated or qualified using an SOP, ideally with datasets of varying complexity and with the alpha level(s) actually in use. Self-designed software should be demonstrated as suitable for intended use. For guidance on the use of computerized systems (see section 4: Computer systems) (8).
- 25.5 Data values input should be double-checked by a second qualified person in accordance with an SOP.
- 25.6 A database of trial records should be maintained and should ideally be locked as soon as possible after completion of the study. Once it is locked the study can be unblinded and statistical analysis performed. The dates of locking and statistical analysis should be documented and mentioned in the study report, and the process should be defined in a suitable procedure.

26. Study report

- 26.1 The clinical study report should accurately reflect all the study procedures and results.
- 26.2 The clinical study report should be well written and presented. All deviations from the protocol in the performance of the study should be reported.
- 26.3 There should be no discrepancies between the results stated in the report and the actual original (raw) data.
- 26.4 The report should comply with regulatory requirements as applicable and be presented in a standard format.
- 26.5 The study report should include a report on the bioanalytical part of the trial, including a description of the bioanalytical method used and the report of the validation of this method.
- 26.6 The clinical study report should be approved by the investigator and sponsor. The bioanalytical report should be approved by the study director.
- 26.7 The report should be approved (signed and dated) by the responsible personnel.
- 26.8 All monitoring and audit reports should be available before release of the final study report.

References

1. Guidelines for good clinical practice for trials on pharmaceutical products. In: WHO Expert Committee on Selection and Use of Essential Medicines: sixth report. Geneva: World Health Organization; 1995: Annex 3 (WHO Technical Report Series, No. 850; https://iris.who.int/bitstream/handle/10665/37340/WHO_TRS_850.pdf?sequence=1&isAllowed=y), pp. 97–137.
2. WHO handbook on good laboratory practice: Quality practices for regulated non-clinical research and development. Geneva: World Health Organization; 2009.
3. OECD series on principles of good laboratory practice and compliance monitoring, number 1: OECD principles on good laboratory practice (as revised in 1997). Paris: Organisation for Economic Co-operation and Development; 1998 (ENV/MC/CHEM(98)17. 26).
4. Additional guidance for organizations performing in vivo bioequivalence studies. In: WHO Expert Committee on Selection and Use of Essential Medicines: fortieth report. Geneva: World Health Organization; 2006: Annex 9 (WHO Technical Report Series, No. 937; https://apps.who.int/iris/bitstream/handle/10665/43443/WHO_TRS_937_eng.pdf?sequence=1).
5. Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2015: Annex 8 (WHO Technical Report Series, No. 992; https://iris.who.int/bitstream/handle/10665/176954/9789240693968_eng.pdf?sequence=1&isAllowed=y).
6. WHO Operational guidelines for ethics committees that review biomedical research. Geneva: World Health Organization; 2000 (WHO, TDR/PRD/ETHICS/2000.1).
7. The good automated manufacturing practice (GAMP) guide – A risk-based approach to compliant GxP computerized systems (GAMP5). Tampa (FL): International Society for Pharmaceutical Engineering (ISPE); 2009.
8. Good practices for computerised systems in regulated “GXP” environments, PIC/S Guidance. Geneva: Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-operation Scheme; 2007 (PI 011–3, 25).
9. Guidance for industry: part 11, electronic records; electronic signatures – scope and application. US Food and Drug Administration; 2003 (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm125125.pdf>, accessed 27 February 2016).
10. EU guidelines for good manufacturing practice and medicinal products for human and veterinary use. Annex 11, Computerised systems. Brussels: European Commission (SANCO/C8/AM/sl/ares(2010)1064599).
11. Guidance on good data and record management practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 5 (WHO Technical Report Series, No. 996; <https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>).
12. WHO good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-fourth report. Geneva: World Health Organization; 1996: Annex 7 (WHO Technical Report Series, No. 863; https://iris.who.int/bitstream/handle/10665/41849/WHO_TRS_863_%28p1-p98%29.pdf?sequence=1&isAllowed=y).
13. Guidelines on bioanalytical method validation. London: Committee for Medicinal Products for Human Use (CHMP); 2012 (EMA/CHMP/EWP/192217/2009 Rev.1 Corr.*).
14. Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples. London: European Medicines Agency; 2012 (EMA/INS/GCP/532137/2010).

Appendix 1

Example list of standard operating procedures at a contract research organization

The following is an example list of the standard operating procedures (SOPs) that should be used at contract research organizations (CROs). This list is not exhaustive as additional procedures may be necessary depending on the functional and compliance requirements at the facility concerned.

All of the documents at the CRO related to a bioequivalence (BE) clinical trial should be controlled (e.g. version date, date approved, etc.) documents. This control is easier if the documents are in the SOP format or are appended to SOPs.

SOPs should be in place at least for all the critical and major operations in the BE/clinical trial.

Number and name of SOP

1. Conduct of BE study
2. Archiving and retrieval of documents related to a BE study
3. Quality assurance of a BE study; audits of clinical and bioanalytical part of the study and the study report
4. Study files
5. Preparation and review of the protocol for the study
6. Amendment to the protocol for the study
7. Protocol deviations/violation recording and reporting
8. Sponsor/CRO quality assurance agreement on conducting the BE study
9. Process for approval of study by ethical committee
10. Bioavailability (BA)/BE report
11. Study report
12. Written informed consent
13. Obtaining written informed consent for screening from study volunteers
14. Allocation of identification numbers to volunteers at various stages in BE study
15. Investigator's brochure
16. Case report form (CRF)
17. Preparation of CRF, review and completion
18. Data collection and CRF completion
19. Adverse/serious adverse event monitoring, recording and reporting

20. Organizational chart for the study
21. Training of personnel
22. Responsibilities of the members of the research team
23. Monitoring of the study by the sponsor
24. Conduct of pre-study meeting.
25. Study start-up
26. Subject management
27. SOP on mobilization of individuals for registration in volunteer bank
28. Eligibility criteria for registration and registration of individuals in volunteer bank
29. Handling of subject withdrawal
30. Allocation of identification numbers to volunteers at various stages in the biostudy
31. Screening of volunteers enrolled for the study
32. Collection of urine samples from subjects for detection of drugs of abuse and transportation of samples to pathology laboratory
33. Custodian duties
34. Payments to research subjects for BE studies
35. Procedures for entry into and exit from clinical unit
36. Handling of subject check-in and check-out
37. Housekeeping at clinical unit
38. Planning, preparation, evaluation and service of standardized meals for bio-studies
39. Distribution of meals to study subjects
40. Operation and maintenance of nurse call system
41. Administration of oral solid dosage form of the investigational product to human subjects during BE study
42. Cannulation of study subjects
43. Collection of blood samples from study subjects
44. Identification of biological samples
45. Recording of vital signs of subjects
46. Operation and verification of fire alarm system
47. Administration of oxygen to subject from medical oxygen cylinder
48. Emergency care of subjects during BA/BE study
49. Availability of ambulance during BA/BE study
50. Centrifugation and separation of blood samples

51. Storage of plasma and serum samples
52. Segregation of bio-samples
53. Transfer of plasma and serum samples to bioanalytical laboratory
54. Procedures for washing glassware
55. Recording temperature and relative humidity of rooms
56. Instructions on operation and maintenance procedures for all the equipment in the clinical unit
57. Numbering the equipment and logbooks for use in the clinical unit
58. Control of access to pharmacy
59. Pharmacy area requirements
60. Authorization related to investigational product storage, dispensing and retrieval from storage for BE study
61. Investigational product receipt, return and accountability documentation
62. Investigational product receipt and return procedures
63. Storage of investigational products in the pharmacy
64. Line clearance before and after dispensing
65. Documentation of line clearance and dispensing; packaging records and release of dispensed products
66. Retention of samples of investigational products
67. Disposal of archived investigational products
68. Disposal of biological materials
69. Procedures for bioanalytical laboratory (SOPs for the different items of equipment, analytical methods, reagent preparation)
70. Out-of-specification in the laboratory
71. Acceptance criteria for analytical runs: acceptance of calibration curves, acceptance of the runs based on quality control samples results
72. Chromatographic acceptance criteria and chromatogram integration
73. Sample re-assay
74. Pharmacokinetic data from bioanalytical data
75. Procedure for statistical analysis in a BE study

5.2 Guidelines for the preparation of a contract research organization master file

Annex 7, WHO Technical Report Series, 957,
2010

Background	652
1. General information	652
2. Quality management system of the contract research organization	653
3. Personnel	653
4. Ethics committee	654
5. Computer systems	654
6. Equipment and instruments	654
7. Documentation	654
8. Safety monitoring	655
9. Investigational medicinal products and comparator products	655
10. Pathology	655
11. Bioanalytical laboratory	655
12. Biostatistics	656
13. Study volunteers	656
14. Other information	656

Background

A contract research organization master file (CROMF) is a document prepared by the contract research organization (CRO) containing specific and factual information about the CRO and the conduct of clinical studies as well as the analyses of samples and related operations (including clinical trials, clinical data management, pharmacokinetics and statistical analysis and regulatory affairs) carried out at the named site. If only some of the operations referred to below are carried out at the site, the master file (MF) needs to be presented only for those operations.

In a case where a CRO is responsible for activities pertaining only to bioanalytical procedures, then only sections in the CROMF relating to these should be described. Other sections may be marked as “not applicable”.

Where a CRO performs various activities, separate sections could be prepared for the different units, e.g. clinical pharmacology unit (CPU) and bioanalytical laboratory (BAL).

A CROMF provides information on the policies, approach and general activities of a CRO. It is not trial-specific as trial-specific data are submitted in a product dossier. It serves as general information to regulators and can be used during preparation for inspections by regulatory inspectors in addition to the trial-specific data and information submitted for assessment. It also provides an overview of the organization's approach to good clinical practices (GCP), good laboratory practices (GLP) and other guidelines pertaining to its activities.

A CROMF should be submitted to the national medicines regulatory authority (NMRA) where such a document is requested. It should be succinct and as far as possible not exceed 25 A4 pages (where appropriate, supportive documentation may be appended).

An updated CROMF should be submitted when requested by the NMRA, or if significant changes have been implemented by the CRO.

1. General information

- 1.1 Name and exact address of the CRO, including telephone, fax, 24-hour telephone numbers and e-mail address
- 1.2 Short description of the CRO (including size, location, number of beds, layout and plan, areas for handling samples and waste)
- 1.3 Activities as licensed/authorized by the national authority
- 1.4 Inspections and approvals
 - 1.4.1 Inspections/approvals/accreditations by any regulatory agency
 - 1.4.2 Audits of subcontractors

- 1.5 Type of studies (and indications, where appropriate) performed on site (a list of projects conducted at this site may be provided)
- 1.6 Provisions for insurance
 - 1.6.1 Number of employees engaged in studies, quality, storage and distribution
- 1.7 Contract services employed
 - 1.7.1 Use of outside scientific, analytical or other technical assistance in relation to studies and analysis (e.g. clinical laboratory, bioanalytical laboratory, X-ray facilities and caterers)
 - 1.7.2 Services outsourced, e.g. contracts with tertiary care hospital for handling of medical emergencies, ambulance facility, nutrition, biomedical waste, chemical waste, caterers, pest control and pathology laboratory

2. Quality management system of the contract research organization

(Short description including, e.g. responsibilities of the quality assurance unit. A list of quality system documents can be included)

- 2.1 Organization chart including the arrangements for quality assurance
- 2.2 Internal audits and self inspection
- 2.3 Corrective and preventive action plans (CAPA)

3. Personnel

(A brief description can be presented in tabular format)

- 3.1 Qualifications, experience and responsibilities of key personnel as applicable
 - 3.1.1 project manager
 - 3.1.2 principal investigator
 - 3.1.3 analytical investigator
 - 3.1.4 biostatistician
 - 3.1.5 clinical research associates
 - 3.1.6 data manager
 - 3.1.7 monitor
 - 3.1.8 the study director(s)
 - 3.1.9 person responsible for quality assurance

3.2 Training of personnel:

3.2.1 training policy and procedure (brief description)

3.2.2 training records

4. Ethics committee

4.1 Constitution and relation to CRO

4.2 Procedures including review and approval of protocols

5. Computer systems

(Short description)

5.1 Hardware

5.2 Software (and version number) used (e.g. in the bioanalytical laboratory, in pharmacokinetic and statistical analysis) and change control procedure

5.3 Data management systems (include a procedural flow chart and a brief description of query generation and resolution)

5.4. Security procedures

5.5 Electronic exchange of confidential information

5.6 Brief description of validation programme

5.7 Back-up and storage of electronic data

6. Equipment and instruments

6.1 Brief description of major equipment and instruments (a list of equipment is not required)

6.2 Qualification, maintenance and calibration programme, including the temperature recording systems

7. Documentation

7.1 Briefly describe document management systems

7.2 Project work flow including quality assurance and control process

7.3 Preparation of protocols

7.4 Preparation of informed consent forms and subject information forms

7.5 Preparation of report forms

7.6 Preparation of final report

8. Safety monitoring

(Brief description)

Adverse drug reaction reporting procedure

Provisions made for emergencies, including protocols and equipment available

9. Investigational medicinal products and comparator products

(Brief description)

9.1 Acquisition, storage, handling, sampling and disposal

9.2 Pharmacy and dispensing

10. Pathology

10.1 Biological sample collection and storage

10.2 Handling and analysis of biological samples

11. Bioanalytical laboratory

(Brief description)

11.1 Method development and validation

11.2 Reference standard materials used for preparation of calibration standards and quality control samples

11.3 Biological matrix storage, and handling of matrix samples

11.4 Analysis of unknown samples

11.5 Preparation and labelling of reagents

11.6 Storage of samples

11.7 Stability procedures

11.8 Waste management

12. Biostatistics

12.1 Data processing and analysis

12.2 Data management

13. Study volunteers

13.1 Procedure for recruitment

13.2 Collecting information on volunteers (e.g. databank), while confidentiality is maintained

13.3 Procedure for obtaining informed consent

14. Other information

14.1 Power supply system — uninterrupted power supply and generator availability and capacity

14.2 Brief description of any other activities performed on site by the CRO

14.3 Any other information which the CRO may feel it appropriate to add

5.3 Guidelines for good clinical practice for trials on pharmaceutical products¹

Annex 3, WHO Technical Report Series, 850, 1995

Introduction	660
Glossary	661
1. Provisions and prerequisites for a clinical trial	667
1.1 Justification for the trial	667
1.2 Ethical principles	667
1.3 Supporting data for the investigational product	667
1.4 Investigator and site(s) of investigation	667
1.5 Regulatory requirements	668
2. The protocol	668
3. Protection of trial subjects	668
3.1 Declaration of Helsinki	669
3.2 Ethics committee	669
3.3 Informed consent	670
3.4 Confidentiality	672
4. Responsibilities of the investigator	673
4.1 Medical care of trial subjects	673
4.2 Qualifications	673
4.3 Selection of trial subjects	673

¹ This text was developed in consultation with national drug regulatory authorities within WHO's Member States. It was also discussed during two informal consultations convened by the Division of Drug Management and Policies, WHO, Geneva, from 26 to 27 June 1991 and 29 June to 3 July 1992. The participants were as follows: Ms M. Cone, International Federation of Pharmaceutical Manufacturers Associations (IFPMA), Geneva, Switzerland; Professor P. Dayer, International Union of Pharmacology (IUPHAR), Brussels, Belgium; Professor I. Darmansjah, University of Jakarta, Jakarta, Indonesia; Dr J.F. Dunne, Director, Division of Drug Management and Policies, WHO, Geneva, Switzerland (*Joint Secretary*); Dr Y. Hirayama, New Drugs Division, Ministry of Health and Welfare, Tokyo, Japan; Professor E. Hyldberg, University Hospital, Copenhagen, Denmark (*Chairman*); Dr J. Idänpään-Heikkilä, Associate Director, Division of Drug Management and Policies, WHO, Geneva, Switzerland (*Joint Secretary*); Mr R. Laderman, Center for Drug Evaluation and Research, Food and Drug Administration, Bethesda, MD, USA; Professor V.H. Lepakhin, Russian State Center for Drug Expertise, Moscow, Russian Federation; Dr P. Maurice, Ciba-Geigy, Basel, Switzerland; Professor J.O.M. Pabee, School of Medicine, Lusaka, Zambia; Mr M. Tsukano, New Drugs Division, Ministry of Health and Welfare, Tokyo, Japan; Dr S. Westman-Naeser, Medical Products Agency, Uppsala, Sweden; Professor A. Zanini, Institute of Biomedical Science, São Paulo, Brazil; Professor Zhu Jun-Ren, Shanghai Medical University, Shanghai, China.

4.4	Compliance with the protocol	674
4.5	Information for subjects and informed consent	674
4.6	The investigational product	674
4.7	The trial site	675
4.8	Notification of the trial or submission to the drug regulatory authority	675
4.9	Review by an ethics committee	675
4.10	Serious adverse events or reactions	675
4.11	Financing	676
4.12	Monitoring, auditing and inspection	676
4.13	Record-keeping and handling of data	676
4.14	Handling of and accountability for pharmaceutical products for trial	676
4.15	Termination of the trial	676
4.16	Final report	676
4.17	Trials in which the investigator is the sponsor	676
5.	Responsibilities of the sponsor	676
5.1	Selection of the investigator(s)	677
5.2	Delegation of responsibilities	677
5.3	Compliance with the protocol and procedures	677
5.4	Product information	678
5.5	Safety information	678
5.6	Investigational product	678
5.7	Trial management and handling of data	679
5.8	Standard operating procedures	679
5.9	Compensation for subjects and investigators	679
5.10	Monitoring	679
5.11	Quality assurance	679
5.12	Study reports	679
5.13	Handling of adverse events	680
5.14	Termination of the trial	680
6.	Responsibilities of the monitor	680
6.1	Qualifications	680
6.2	Assessment of the trial site	680
6.3	Staff education and compliance	681
6.4	Data management	681
6.5	Case report forms	681
6.6	Investigational product	681
6.7	Communication	681
6.8	Notification of the trial or submission to the drug regulatory authority	681
6.9	Reports	682
7.	Monitoring of safety	682
7.1	Handling of and recording adverse events	682
7.2	Reporting adverse events	682
8.	Record-keeping and handling of data	683
8.1	Responsibilities of the investigator	684
8.2	Responsibilities of the sponsor and the monitor	685
8.3	Archiving of data	685

9. Statistics and calculations	686
9.1 Experimental design	686
9.2 Randomization and blinding	686
9.3 Statistical analysis	687
10. Handling of and accountability for pharmaceutical products	687
10.1 Supply and storage	688
10.2 Investigational labelling and packaging	688
10.3 Responsibilities of the investigator	688
10.4 Responsibilities of the sponsor and the monitor	689
11. Role of the drug regulatory authority	689
11.1 General responsibilities	690
11.2 On-site inspections	690
12. Quality assurance for the conduct of a clinical trial	690
13. Considerations for multicentre trials	691
References	692
Appendix 1 Declaration of Helsinki	693
Appendix 2 Model list of items to be included in a clinical trial protocol	697

Introduction

The purpose of these guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products is to set globally applicable standards for the conduct of such biomedical research on human subjects. They are based on provisions already promulgated in a number of countries, including Australia, Canada, European Community countries, Japan, Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) and the United States. These provisions inevitably vary somewhat in content and emphasis but all are consonant with regard to the prerequisites to be satisfied and the principles to be applied as a basis for assuring the ethical and scientific integrity of clinical trials. Indeed, they have provided a formal basis for mutual recognition of clinical data generated within the respective countries. Every care has been taken in developing the present guidelines as a practicable administrative tool for use by the World Health Organization's (WHO) Member States to assure their compatibility with existing national and other provisions. It is hoped, on the basis of further consultations, to seek formal acceptance of the guidelines by Member States as a contribution to harmonization of national standards and to facilitate the movement of pharmaceutical products internationally. No question arises, however, of challenging or replacing existing national regulations or requirements. The objective is to provide a complementary standard that can be applied worldwide. In countries where national regulations or requirements do not exist or require supplementation, relevant government officials may designate or adopt, in part or in whole, these guidelines as the basis on which clinical trials will be conducted.

The guidelines are addressed not only to investigators, but also to ethics review committees, pharmaceutical manufacturers and other sponsors of research, and drug regulatory authorities. By providing a basis both for the scientific and ethical integrity of research involving human subjects and for generating valid observations and sound documentation of the findings, these guidelines not only serve the interests of the parties actively involved in the research process, but protect the rights and safety of subjects, including patients, and ensure that the investigations are directed to the advancement of public health objectives.

The guidelines are intended specifically to be applied during all stages of drug development both prior to and subsequent to product registration and marketing but they are also applicable, in whole or in part, to biomedical research in general. They should also provide a resource for editors to determine the acceptability of reported research for publication and, specifically, of any study that could influence the use or the terms of registration of a pharmaceutical product. Not least, they provide an educational tool that should become familiar to everyone engaged in biomedical research and, in particular, to every newly trained doctor.

Glossary

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts.

adverse event

Any untoward medical occurrence in a clinical trial subject administered a pharmaceutical product; it does not necessarily have a causal relationship with the treatment.

adverse reaction

A response to a pharmaceutical product that is noxious and unintended and that occurs at doses normally used or tested in humans for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function. In clinical trials, injuries caused by overdosing, abuse or dependence and interactions with any other product should be considered adverse reactions.

audit of a trial

A systematic examination, carried out independently of those directly involved in the clinical trial, to determine whether the conduct of a trial complies with the agreed protocol and whether the data reported are consistent with the records on site; for example, whether data reported or recorded in the case report forms (CRFs) are consonant with those found in hospital files and other original records.

case report form (CRF)

A document that is used to record data on each trial subject during the course of the clinical trial, as defined by the protocol. The data should be collected by procedures that guarantee preservation, retention and retrieval of information and allow easy access for verification, audit and inspection.

clinical trial

A systematic study on pharmaceutical products in human subjects (including patients and other volunteers) in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the objective of ascertaining their efficacy and safety.

Clinical trials are generally classified into Phases I to IV. It is not possible to draw distinct lines between the phases and diverging opinions about details and methodology do exist. A brief description of the individual phases, based on their purposes as related to clinical development of pharmaceutical products, is given below:

Phase I

These are the first trials of a new active ingredient or new formulation in humans, often carried out in healthy volunteers. Their purpose is to establish

a preliminary evaluation of the safety, and the pharmacokinetic and, where possible, pharmacodynamic profile of the active ingredient in humans.

Phase II

These trials are performed in a limited number of subjects and are often, at a later stage, of a comparative (for example, placebo-controlled) design. Their purpose is to demonstrate therapeutic activity and to assess the short-term safety of the active ingredient in patients suffering from a disease or condition for which the active ingredient is intended. This phase also aims at the determination of appropriate dose ranges or regimens and (if possible) clarification of dose-response relationships in order to provide an optimal background for the design of extensive therapeutic trials.

Phase III

Trials in larger (and possibly varied) patient groups, with the purpose of determining the short- and long-term safety/efficacy balance of formulation(s) of the active ingredient, and of assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (for example, clinically relevant drug interactions, factors leading to differences in effect, such as age). These trials should preferably be of a randomized double-blind design but other designs may be acceptable (for example, long-term safety studies). Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use.

Phase IV

Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics for which the marketing authorization was granted and are normally in the form of post-marketing surveillance, or assessment of therapeutic value or treatment strategies. Although methods may differ, these studies should use the same scientific and ethical standards as applied in pre-marketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration, new combinations, etc. are normally considered as trials on new pharmaceutical products.

comparator product

A pharmaceutical or other product (which may be a placebo) used as a reference in a clinical trial.

confidentiality

Maintenance of the privacy of trial subjects, including their personal identity and all personal medical information.

contract

A document, dated and signed by the investigator, institution and sponsor, that sets out any agreements on financial matters and delegation or distribution of responsibilities. The protocol may also serve as a contract when it contains such information and is signed.

contract research organization (CRO)

A scientific organization (commercial, academic or other) to which a sponsor may transfer some of its tasks and obligations. Any such transfer should be defined in writing.

escape treatment

Any supplementary treatment provided to relieve a trial subject of symptoms caused by the investigated disease in the clinical trial. Escape treatment is often used in order to alleviate pain in placebo-controlled trials.

ethics committee

An independent body (a review board or an institutional, regional or national committee), constituted of medical professionals and nonmedical members, whose responsibility it is to verify that the safety, integrity and human rights of the subjects participating in a particular clinical trial are protected and to consider the general ethics of the trial, thereby providing public reassurance. Ethics committees should be constituted and operated so that their tasks can be executed free from bias and from any influence of those who are conducting the trial.

final report

A comprehensive description of the clinical trial after its completion, including a description of experimental methods (including statistical methods) and materials, a presentation and evaluation of the results, statistical analyses and a critical, ethical, statistical and clinical appraisal.

Good Clinical Practice (GCP)

A standard for clinical studies which encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies and which ensures that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented.

Good Manufacturing Practice (GMP)

That part of pharmaceutical quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. In these guidelines, GMP refers to the current GMP guidelines published by WHO (1).

informed consent

A subject's voluntary confirmation of willingness to participate in a particular clinical trial, and the documentation thereof. This consent should only be sought after all appropriate information has been given about the trial, including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative treatment that may be available, and of the subject's rights and responsibilities in accordance with the current revision of the Declaration of Helsinki (see Appendix 1).

inspection

An officially conducted examination (such as review of the conduct of the clinical trial, including quality assurance, personnel involved, any delegation of authority and audit) by relevant authorities at the site of the trial and/or the site of the sponsor in order to verify adherence to Good Clinical Practice as set out in these guidelines.

investigator

A person responsible for the clinical trial and for the rights, health and welfare of the subjects participating in the trial. The investigator should have qualifications and competence in accordance with local laws and regulations as evidenced by an up-to-date curriculum vitae and other credentials. Decisions relating to, and the provision of, medical or dental care must always be the responsibility of a clinically competent person legally allowed to practice medicine or dentistry.

investigational labelling

Labelling developed specifically for products involved in a clinical trial.

investigational product (synonym: study product)

Any pharmaceutical product or placebo being tested or used as a reference in a clinical trial.

investigator's brochure

A collection of data for the investigator consisting of all available relevant information on the investigational product(s), including chemical and pharmaceutical data, toxicological, pharmacokinetic and pharmacodynamic data obtained from studies in animals as well as in humans, and the results of earlier clinical trials. There should be adequate data to justify the nature, scale and duration of the proposed trial and to evaluate the potential safety and need for special precautions. If new data are generated, the investigator's brochure must be updated.

monitor

A person appointed by, and responsible to, the sponsor or contract research organization (CRO) for monitoring and reporting on the progress of the clinical trial and for verification of data.

patient/subject file

A collection of data consisting of all relevant information on the patient or subject (such as a hospital file, consultation record or special subject file) that permits the authenticity of the information presented in the case report form (CRF) to be verified and, where necessary, completed or corrected. The conditions regulating the use and consultation of such documents must be respected.

pharmaceutical product

Any substance or combination of substances that has a therapeutic, prophylactic or diagnostic use, or is intended to modify physiological functions, and is presented in a dosage form suitable for administration to humans.

principal investigator

The investigator serving as coordinator for certain kinds of clinical trials (for example, multicentre trials).

protocol

A document that states the background, rationale and objectives of the clinical trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. The protocol should be dated and signed by the investigator, the institution involved and the sponsor. It can also serve as a contract.

quality assurance relating to clinical trials

Systems and quality control procedures that are established to ensure that the trial is performed and the data are generated in compliance with Good Clinical Practice. These include procedures to be followed which apply to ethical and professional conduct, standard operating procedures (SOP), reporting procedures and professional or personnel qualifications.

raw data

All records or certified copies of original observations, clinical findings or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Such material includes laboratory notes, memoranda, calculations and documents, as well as all records of data from automated instruments or exact, verified copies in the form of photocopies, microfiches, etc. Raw data can also include photographic negatives, microfilm or magnetic media (for example, computer diskettes).

serious adverse event

An event that is associated with death, admission to hospital, prolongation of a hospital stay, persistent or significant disability or incapacity, or is otherwise life-threatening in connection with a clinical trial.

sponsor

An individual, a company, an institution or an organization which takes responsibility for the initiation, management and/or financing of a clinical trial. When an investigator initiates and takes full responsibility for a trial, the investigator then also assumes the role of the sponsor.

standard operating procedures (SOP)

Standard, detailed, written instructions for the management of clinical trials. They provide a general framework enabling the efficient implementation and performance of all the functions and activities for a particular trial as described in this document.

study product (synonym: investigational product)

Any pharmaceutical product or placebo being tested or used as a reference in a clinical trial.

trial subject

An individual who participates in a clinical trial, either as a recipient of the pharmaceutical product under investigation or as a control. The individual may be:

- a healthy person who volunteers to participate in a trial;
- a person with a condition unrelated to the use of the investigational product; and/or
- a person (usually a patient) whose condition is relevant to the use of the investigational product.

validation

The action of proving, in accordance with the principles of Good Clinical Practice, that any procedure, process, equipment (including the software or hardware used), material, activity or system actually leads to the expected results.

verification (validation) of data

The procedures carried out to ensure that the data contained in the final report match the original observations. These procedures may apply to raw data, data in case report forms (in hard copy or electronic form), computer printouts and statistical analyses and tables.

witness

A person who will not be influenced in any way by those who are involved in the clinical trial; who is present and may provide assistance, if required, when the subject's informed consent is obtained; and documents that this consent is given freely by signing and dating the informed consent form.

1. Provisions and prerequisites for a clinical trial

1.1 Justification for the trial

It is important for anyone preparing a trial of a medicinal product in humans that the specific aims, problems and risks or benefits of a particular clinical trial be thoroughly considered and that the chosen options be scientifically sound and ethically justified.

1.2 Ethical principles

All research involving human subjects should be conducted in accordance with the ethical principles contained in the current version of the Declaration of Helsinki (see Appendix 1). Three basic ethical principles should be respected, namely justice, respect for persons, and beneficence (maximizing benefits and minimizing harms and wrongs) or non-maleficence (doing no harm), as defined by the current revision of the International Ethical Guidelines for Biomedical Research Involving Human Subjects² or the laws and regulations of the country in which the research is conducted, whichever represents the greater protection for subjects. All individuals involved in the conduct of any clinical trial must be fully informed of and comply with these principles (see sections 3 and 4).

1.3 Supporting data for the investigational product

Pre-clinical studies that provide sufficient documentation of the potential safety of a pharmaceutical product for the intended investigational use are a prerequisite for a clinical trial. Information about manufacturing procedures and data from tests performed on the actual product should establish that it is of suitable quality for the intended investigational use. The pharmaceutical, pre-clinical and clinical data should be appropriate to the phase of the trial and the amount of supporting data should be appropriate to the size and duration of the proposed trial. In addition, a compilation of information on the safety and efficacy of the investigational product obtained in previous and ongoing clinical trials is required for planning and conducting subsequent trials.

1.4 Investigator and site(s) of investigation

Each investigator should have appropriate expertise, qualifications and competence to undertake the proposed study. Prior to the clinical trial, the investigator(s) and the sponsor should establish an agreement on the protocol, SOP, the monitoring and auditing of the trial, and the allocation of trial-related responsibilities. The trial site should be adequate to enable the trial to be conducted safely and efficiently (see section 4.7).

² These guidelines are updated regularly by the Council for International Organizations of Medical Sciences (CIOMS); the most recent update was published in 1993 (2).

1.5 Regulatory requirements

Countries in which clinical trials are performed should have regulations governing the way in which these studies can be conducted. The pre-trial agreement between the sponsor and investigator(s) should designate the parties responsible for meeting each applicable regulatory requirement (for example, application to or notification of the trial to the relevant authority, amendments to the trial protocol, reporting of adverse events and reactions, and notifications to the ethics committee). All parties involved in a clinical trial should comply fully with the existing national regulations or requirements. In countries where regulations do not exist or require supplementation, relevant government officials may designate, in part or in whole, these guidelines as the basis on which clinical trials will be conducted. The use of these guidelines should not prevent their eventual adaptation into national regulations or laws. Neither should they be used to supersede an existing national requirement in countries where the national requirement is more rigorous.

2. The protocol

The clinical trial should be carried out in accordance with a written protocol agreed upon and signed by the investigator and the sponsor. Any change(s) subsequently required must be similarly agreed on and signed by the investigator and sponsor and appended to the protocol as amendments.

The protocol, appendices and any other relevant documentation should state the aim of the trial and the procedures to be used; the reasons for proposing that the trial should be undertaken on humans; the nature and degree of any known risks; the groups from which it is proposed that trial subjects be selected; and the means for ensuring that they are adequately informed before they give their consent. Other important items to be included in a clinical trial protocol are listed in Appendix 2.

The protocol, appendices and other relevant documentation should be reviewed from a scientific and ethical standpoint by one or more (if required by local laws and regulations) review bodies (for example, institutional review board, peer review committee, ethics committee or drug regulatory authority), constituted appropriately for this purpose and independent of the investigator(s) and sponsor.

3. Protection of trial subjects

The personal integrity and welfare of the trial subject as defined in the Declaration of Helsinki should be the primary concern of all parties involved in the conduct of a clinical trial and the review of the protocol, but it is the ultimate responsibility of the investigator who must also take into consideration the scientific validity of the trial.

3.1 Declaration of Helsinki

The current revision of the Declaration of Helsinki (Appendix 1) is the accepted basis for clinical trial ethics and must be fully followed and respected by all parties involved in the conduct of such trials. Any departures from the Declaration must be justified and stated in the protocol. Independent assurance that subjects are protected can be provided only by an ethics committee and freely obtained informed consent.

3.2 Ethics committee

The role of the ethics committee (or other board responsible for reviewing the trial) is to ensure the protection of the rights and welfare of human subjects participating in clinical trials, as defined by the current revision of the Declaration of Helsinki and national and other relevant regulations, and to provide public reassurance, *inter alia*, by previewing trial protocols, etc. (see section 2).

The ethics committee should be constituted and operated so that its tasks can be executed free from bias and from any influence of those who are conducting the trial.

The ethics committee should have documented policies and procedures as a basis for its work which should be available to the public. These should set out the authority under which the committee is established, the number of members elected and their qualifications, a definition of what it will review, and its authority to intervene and maintain records of its activities. The documents should also state how frequently the committee will meet and how it will interact with the investigator and/or sponsor.

The investigator, or the investigator and the sponsor, must consult the relevant ethics committee(s) regarding the suitability of a proposed clinical trial protocol (including appendices and amendments) and of the methods and materials to be used in obtaining and documenting the informed consent of the subjects.

The ethics committee has an ongoing responsibility for the ethical conduct of research and therefore must be informed of all subsequent amendments to the protocol and of any serious adverse events occurring during the trial, or other new information likely to affect the safety of the subjects or the conduct of the trial. The ethics committee should be consulted if a re-evaluation of the ethical aspects of the trial appears to be required or if there is any doubt regarding the importance of a protocol change or new information.

Subjects must not be entered into the clinical trial until the relevant ethics committee(s) has issued its favourable opinion on the procedures. The ethics committee should give its opinion and advice in writing within a reasonable time, clearly identifying the trial protocol, itemizing the documents studied and stating the date of review. A list of those present at the committee meeting, including their professional status, should be attached.

When reviewing a clinical trial proposal, the ethics committee should consider the following:

- (a) The acceptability of the investigator for the proposed trial, on the basis of sufficient information made available to the committee, in terms of his or her qualifications, experience, availability for the duration of the trial, supporting staff and available facilities.
- (b) The suitability of the protocol, including the objectives of the study and the justification of predictable risks and inconveniences weighed against the anticipated benefits for the subjects and/or others, and the efficiency of its design (such as the potential for reaching sound conclusions with the smallest possible exposure of subjects).
- (c) The means by which trial subjects will be recruited, necessary or appropriate information will be given, and consent will be obtained. This is particularly important in the case of trials involving subjects who are members of a group with a hierarchical structure or another vulnerable group (see section 3.3, (e)-(f)).
- (d) The adequacy and completeness of the information, which should be written in a language and at a level of complexity understandable to everyone involved, to be given to the subjects, their relatives, guardians or, if necessary, legal representatives. All such written information must be submitted in its final form to the ethics committee.
- (e) Provision, if any, for compensation or treatment in the case of death or other loss or injury of a subject, if attributable to a clinical trial, and details of any insurance or indemnity (a source of legal and financial support) to cover the liability of the investigator(s) and sponsor (see section 5.9).
- (f) The appropriateness of the extent and form of payment through which the sponsor will remunerate or compensate the organization(s) and/or investigator(s) conducting the trial and the trial subjects, as required by local laws and regulations.
- (g) The acceptability of any proposed amendments to the protocol that are likely to affect the safety of the subjects or the conduct of the trial.

3.3 Informed consent

The principles of informed consent in the current revisions of the Declaration of Helsinki (Appendix 1) and the International Ethical Guidelines for Biomedical Research Involving Human Subjects (2) should be implemented in each clinical trial.

- (a) Information should be given in a language and at a level of complexity understandable to the subject in both oral and written form whenever possible. No subject should be obliged to participate in the trial. Subjects, their relatives, guardians or, if necessary, legal representatives must

be given ample opportunity to enquire about details of the trial. The information must make clear that the trial is a research procedure, that participation is voluntary, and that refusal to participate or withdrawal from the trial at any stage will not prejudice the subject's care, rights and welfare. Subjects must be allowed sufficient time, determined by their health condition and/or the illness, to enquire about details of the trial and to decide whether or not they wish to participate.

- (b) The subject must be made aware and consent that personal information may be scrutinized during the monitoring, auditing or inspection of the trial by authorized persons, the sponsor or relevant authorities, and that participation and personal information in the trial will be treated as confidential and will not be publicly available. This principle may be modified by national laws and regulations.
- (c) The subject must have access to information about insurance, if any, and other procedures for compensation and treatment should he or she be injured or disabled by participating in the trial.
- (d) If a subject consents to participate after a full and comprehensive explanation of the study, this consent should be appropriately recorded. The explanation should include the aim of the study; the expected benefits for the subjects and/or others; the possibility of allocation to a reference treatment or placebo; the risks and inconveniences (for example, invasive procedures); and, where appropriate, an explanation of alternative, recognized medical therapy. Consent must be documented either by the subject's dated signature or in agreement with local laws and regulations by the signature of an independent witness who records the subject's consent. In either case, the subject must be informed that signature confirms only that consent is based on the information provided and that the subject has freely chosen to participate, without prejudice, to legal and ethical rights, while reserving the right to withdraw from the study at his or her own initiative at any time, without having to give any reason. If, however, the reason for withdrawal relates to an adverse event(s), the investigator should be informed.
- (e) Careful consideration should be to ensuring the freedom of consent obtained from members of a group with a hierarchical structure, such as medical, pharmacy and nursing students, hospital and laboratory personnel, employees of the pharmaceutical industry, and members of the armed forces. In such cases, the willingness to volunteer may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of a retaliatory response from

senior members of the hierarchy in case of refusal to participate. Other vulnerable groups whose consent also needs special consideration include patients with incurable diseases, people in nursing homes, prisoners or detainees, the unemployed or people on a very low income, patients in emergency departments, some ethnic and racial minority groups, the homeless, nomads and refugees. If such categories are part of the population to be enrolled in a clinical trial, the ethics committee should consider carefully the appropriateness of the informed-consent process.

- (f) If the subject is incapable of giving personal consent (for example, in the case of children or adults who are unconscious or suffering from severe mental illness or disability), the inclusion of such subjects in a trial may be acceptable, provided it is permitted by local laws and regulations; the ethics committee is, in principle, in agreement; and the investigator thinks that participation will promote the welfare and be in the interest of the subject. The agreement of a legally acceptable representative that participation will promote the welfare and be in the interest of the subject should also be recorded by a dated signature. If the patient is incapable of giving either signed informed consent or witnessed signed verbal consent, this fact must be documented by the investigator, stating the reasons.
- (g) In a non-therapeutic study (such as when there is no direct clinical benefit to the subject), consent must always be given by the subject and documented by his or her dated signature.
- (h) The trial subjects should be informed that they have access to appropriate (identified) persons to obtain further information and medical advice or escape treatment, if necessary.
- (i) Any information that becomes available during the trial, which may be of relevance to the trial subjects, must be made known to them by the investigator.
- (j) The subjects should be informed of the circumstances under which the investigator or sponsor might terminate their participation in the study.

3.4 Confidentiality

The investigator must establish secure safeguards of confidentiality of research data as described in the current revision of the International Ethical Guidelines for Biomedical Research Involving Human Subjects (2) (see also section 3.3).

4. Responsibilities of the investigator

4.1 Medical care of trial subjects

The investigator is responsible for providing adequate and safe medical care (or dental care, where appropriate) of subjects during the clinical trial and for ensuring that appropriate medical care and relevant followup procedures are maintained after the trial for a period that is dependent upon the nature of the disease and the trial and the interventions made.

4.2 Qualifications

The investigator should:

- have qualifications and competence in accordance with local laws and regulations as evidenced by an up-to-date curriculum vitae and other credentials (decisions relating to, and the provision of, medical or dental care must always be the responsibility of a clinically competent person legally allowed to practise medicine or dentistry);
- have good knowledge and experience of the field of medicine or dentistry defined by the protocol;
- be experienced in clinical trial research methods or receive scientific support from an experienced colleague;
- be aware of available relevant data and literature and all information provided by the sponsor;
- have access to human and other resources to assume full responsibility for the proper conduct of the trial; and
- be aware of and comply with national regulatory and legal and ethical requirements.

4.3 Selection of trial subjects

The investigator is responsible for ensuring the unbiased selection of an adequate number of suitable subjects as defined by the protocol. It may be necessary to secure the cooperation of other physicians in order to obtain a sufficient number of subjects.

In order to assess the probability of recruiting an adequate number of subjects for the study, it may be useful to determine prospectively or to review retrospectively (for example, on the basis of the clinic's records) the availability of potential subjects. The investigator should check whether subjects so identified can or could be included according to the protocol.

The patient's own physician should, when relevant and with the patient's consent, be informed of the patient's participation in the clinical trial.

4.4 Compliance with the protocol

The investigator must agree with and sign the protocol (or another legally acceptable document mentioning the agreement with the protocol) with the sponsor, and confirm in writing that he or she has read, understands and will work according to the protocol and GCP.

The investigator is responsible for ensuring that the protocol is strictly followed. The investigator should not make any changes in the study without the agreement of the sponsor, except when necessary to eliminate an apparent immediate hazard or danger to a trial subject. Any change should be in the form of a protocol amendment, appended to the original protocol and signed by the investigator and the sponsor. Amendments which are likely to affect the safety of a subject or the conduct of the clinical trial should be submitted in writing to the ethics committee (see section 3.2) and drug regulatory authority and implemented only after approval has been received.

The investigator should take any steps judged necessary to protect the safety of the trial subject, whether specified in the protocol or not. Any such steps must be documented.

4.5 Information for subjects and informed consent

The investigator is responsible for giving adequate information to subjects about the clinical trial. The current version of the Declaration of Helsinki (Appendix 1) and the International Ethical Guidelines for Biomedical Research Involving Human Subjects (2) should be followed. The nature of the investigational pharmaceutical product, its stage of development and the complexity of the study, should be considered in determining the nature and extent of the information that should be provided.

Information should be given in both oral and written form in a language understandable to the subject. The protocol should state when and by whom such information will be provided and how the provision of information should be recorded.

Informed consent must be obtained according to the principles described in section 3.3.

The investigator should also supply subjects with, and encourage them to carry with them, information about their participation in the trial and information about the person(s) to contact in case of emergency.

4.6 The investigational product

The investigator must be thoroughly familiar with the properties, effects and safety of the investigational pharmaceutical product(s), including pre-trial data, as described in the investigator's brochure or in the literature. The investigator should be aware of all relevant new data on the product that appears during the course of the clinical trial.

4.7 The trial site

Clinical trials must be carried out under conditions which ensure adequate safety for the subjects. The site selected should be appropriate to the stage of development of the investigational product and the potential risks involved. The trial site must have adequate facilities, including laboratories, equipment and sufficient medical, paramedical and clerical staff to support the trial and to deal with all reasonably foreseeable emergencies. All laboratory assays must be validated and principles of Good Laboratory Practice (GLP) should be observed.

The investigator should ensure that he or she has sufficient time to conduct and complete the trial and that other commitments or trials do not divert essential subjects, resources or facilities away from the trial in hand.

The investigator must provide adequate information to all staff involved in the trial.

The investigator must notify or obtain approval for the trial from the relevant local hospital (medical, administrative) management in compliance with existing regulations.

4.8 Notification of the trial or submission to the drug regulatory authority

As governed by national regulations, the investigator, sponsor, or investigator jointly with the sponsor should give notification of the clinical trial to, or obtain approval from, the drug regulatory authority. Any submission to the drug regulatory authority should be in writing and dated, and contain sufficient information to identify the protocol.

4.9 Review by an ethics committee

Prior to its commencement, the investigator must ensure that the proposed clinical trial has been reviewed and accepted in writing by the relevant independent ethics committee(s) (see section 3.2). Any submission to and acceptance by the ethics committee should be in writing and dated, and contain sufficient information to identify the protocol or other submitted documents.

4.10 Serious adverse events or reactions

The investigator must take appropriate measures to ensure the safety of clinical trial subjects (see also section 7). The investigator is also responsible for notifying (with documentation) the relevant health authorities, the sponsor and, when applicable, the ethics committee immediately in the case of serious adverse events or reactions, as governed by national regulations.

4.11 Financing

The relationship between the investigator and the sponsor in matters such as financial support, fees and honorarium payments in kind must be stated in writing in the protocol or contract. The protocol or contract should be available to the drug regulatory authority and ethics committee on demand.

4.12 Monitoring, auditing and inspection

The investigator must be prepared to receive and be available for periodic visits by the monitor(s) and accept the implications of such visits (see also section 6). In addition, the investigator must accept auditing and/or inspection by the relevant health authorities and by persons appointed by the sponsor for quality assurance.

4.13 Record-keeping and handling of data

See section 8.

4.14 Handling of and accountability for pharmaceutical products for trial

See section 10.

4.15 Termination of the trial

In the case of premature termination of the clinical trial, the investigator must inform the drug regulatory authority, the ethics committee and, where applicable, the sponsor. Reasons for termination must be stated in writing.

4.16 Final report

After completion of the clinical trial, a final report must be drawn up and submitted to the drug regulatory authority. The report should be dated and signed by the investigator in accordance with local regulations to verify responsibility for the validity of the data.

4.17 Trials in which the investigator is the sponsor

In clinical trials in which the investigator is the sponsor, he or she is responsible for the corresponding functions (see section 5).

5. Responsibilities of the sponsor

The sponsor is often a pharmaceutical company, but may also be an individual, the investigator, or an independent institution or organization that initiates, funds, organizes and oversees the conduct of a clinical trial. When the sponsor is a foreign

company or organization, it should have a local representative to fulfil the appropriate local responsibilities as governed by national regulations.

The sponsor is responsible for providing the investigational and comparator (if any) products, as well as appropriate information to support the safe use of those products. In addition, the sponsor is responsible for ensuring that the trial is conducted in accordance with sound scientific principles and GCP standards by selecting qualified investigators, providing a protocol and ensuring protocol compliance, establishing the distribution of trial-related responsibilities, and providing facilities, equipment and staff for management of the trial, record-keeping, handling of data, monitoring, and quality assurance. The sponsor is also ultimately responsible for ensuring compliance with applicable legal, ethical and regulatory requirements (although local regulations may designate certain required activities as responsibilities of the investigator), and for providing compensation or indemnity in the event of trial-related injury or death, according to local laws and regulations.

5.1 Selection of the investigator(s)

The sponsor is responsible for selecting the investigator(s), taking into account the appropriateness and availability of the proposed trial site and facilities, and being assured of the investigator's qualifications and availability to conduct the study.

5.2 Delegation of responsibilities

The sponsor is responsible for agreeing with the investigator(s) on the allocation of protocol-related responsibilities, including data processing, breaking of the trial code, handling of statistics, preparation of trial reports, and preparation and submission of documentation to the ethics committee, the drug regulatory authority and any other required review bodies. This agreement should be confirmed in writing (protocol, contract or alternative document) prior to the trial.

The sponsor may transfer any or all clinical trial-related activities to a scientific body (commercial, academic or other), or to a CRO. Any such transfer should be documented in writing.

5.3 Compliance with the protocol and procedures

The sponsor is responsible for assuring the investigator's agreement to undertake the clinical trial as described in the protocol, and according to GCP, and to accept procedures for data recording (particularly in the CRF), monitoring, audits and inspections. The sponsor and the investigator must sign the protocol or an alternative document confirming this agreement.

Both the sponsor and the investigator should agree to any amendment to the protocol before it is implemented and this should be documented in writing.

Amendments which may affect the safety of the subjects or the conduct of the trial should be submitted in writing to the ethics committee (see section 3.2) through the investigator or, if applicable, directly by the sponsor. The sponsor should provide justification for the amendments. If required, the amendments should be submitted to the drug regulatory authority. The amendments should not be implemented until all the required approvals have been obtained, unless the delay caused by this process is likely to expose the subjects to an immediate hazard or danger.

5.4 Product information

As a prerequisite to planning the clinical trial, the sponsor is responsible for providing the investigator with available chemical/pharmaceutical, toxicological, pharmacological and clinical data (including data from previous and ongoing trials) regarding the investigational product and, where appropriate, the comparator product(s). This information should be accurate and adequate to justify the nature, scale and duration of the trial. In addition, the sponsor must bring any relevant new information arising during the trial to the attention of the investigator.

The sponsor is responsible for preparing and providing to investigators an investigator's brochure, which must include all relevant information about the product(s) and must be supplemented and/or updated whenever any relevant new information is available.

5.5 Safety information

The sponsor must inform the investigator(s) promptly of any relevant information on safety that becomes available during the clinical trial and ensure that the ethics committee and the drug regulatory authority are notified by the investigator(s), if required (see section 7).

5.6 Investigational product

The sponsor is responsible for supplying the investigational pharmaceutical product(s) and, if applicable, comparator products, prepared in accordance with the principles of GMP (see also section 10). The product(s) should be fully characterized, properly coded, and suitably packaged in such a way as to provide protection against deterioration and safeguard blinding procedures (if applicable); appropriate investigational labelling should be affixed.

Sufficient samples of each batch and a record of analyses and characteristics must be kept for reference so that, if necessary, an independent laboratory is able to re-check the investigational product(s) (for example, for quality control or bioequivalence).

Records of the quantities of investigational pharmaceutical products supplied must be maintained with batch or serial numbers. The sponsor must ensure that the

investigator is able to establish a system within his or her institution for the adequate and safe handling, storage, use, return (to the investigator or sponsor) and, if appropriate, destruction of the investigational product(s).

5.7 Trial management and handling of data

The sponsor should appoint appropriate individuals and/or committees for managing and supervising the clinical trial, handling and verifying the data obtained, statistical processing, and preparing the trial report (see section 8).

5.8 Standard operating procedures

Where warranted by the number or scale of clinical trials conducted, it is recommended that the sponsor establish written SOP to comply with GCP.

5.9 Compensation for subjects and investigators

As required by national law or regulations, the sponsor should provide adequate compensation or treatment for subjects in the event of trial-related injury or death and provide indemnity for the investigator, except in the case of claims resulting from malpractice and/or negligence (see section 3. 2, (e)-(f)).

5.10 Monitoring

The sponsor must appoint suitable and appropriately trained monitors and clinical research support personnel, and provide ongoing training to ensure that they are suitably qualified and to keep them up to date with new developments.

5.11 Quality assurance

The sponsor should establish a system or systems of quality assurance (including independent auditing) to ensure that the conduct of the clinical trial and the generation, documentation and reporting of data comply with the protocol, GCP standards and applicable regulatory requirements. The system should operate independently of those involved in conducting or monitoring the trial (see section 12).

5.12 Study reports

The sponsor is responsible for ensuring the preparation and appropriate approval(s) of a comprehensive final clinical study report suitable for regulatory purposes, whether or not the trial has been completed. The sponsor must also submit any relevant safety information (including safety updates) that becomes available during the trial and/or annual reports as required by the relevant health authorities.

5.13 Handling of adverse events

The sponsor should provide special forms for reporting any adverse events that occur during the clinical trial. The sponsor must investigate promptly, together with the investigator(s), all serious adverse events, take appropriate measures to ensure the safety of trial subjects, and report these events to appropriate authorities in accordance with applicable national requirements (see section 7).

5.14 Termination of the trial

If the sponsor elects or is required to terminate the clinical trial prematurely, then the investigator(s), ethics committee and relevant authorities must be notified of this decision and of the reasons for termination.

6. Responsibilities of the monitor

The monitor is the principal communication link between the sponsor and the investigator and is appointed by the sponsor. The number of monitors needed to ensure adequate monitoring of the clinical trial will depend on its complexity and the types of centres involved.

The main responsibility of the monitor is to oversee progress of the trial and to ensure that the study is conducted and data are handled in accordance with the protocol, GCP, and applicable ethical and regulatory requirements. The monitor is responsible for controlling adherence to the protocol, ensuring that data are correctly and completely recorded and reported, and confirming that informed consent is being obtained and recorded for all subjects prior to their participation in the trial. Any unwarranted deviation from the protocol or any transgression of the principles embodied in GCP should be reported promptly to the sponsor and the relevant ethics committee(s).

The monitor should follow a predetermined written set of SOP. A written record should be kept of all visits, telephone calls and letters to the investigator.

6.1 Qualifications

The monitor should be appropriately trained and fully aware of all aspects of the drug under investigation and the requirements of the protocol, including any annexes and amendments. The monitor should have adequate medical, pharmaceutical and/or scientific qualifications, and clinical trial experience. The qualifications most appropriate for a monitor will depend on the type of trial and nature of the product under investigation.

6.2 Assessment of the trial site

The monitor should assess the trial site prior to the clinical trial to ensure that the facilities (including laboratories, equipment and staff) are adequate, and that an

adequate number of trial subjects is likely to be available for the duration of the trial. The monitor should also assess the trial site during and after the trial to ensure that the investigator complies with the protocol and that data are handled in accordance with the predetermined set of SOP.

6.3 Staff education and compliance

The monitor should ensure that all staff assisting the investigator in the clinical trial have been adequately informed about and will comply with the details of the trial protocol.

6.4 Data management

The monitor should assist the investigator in reporting the data and results of the clinical trial to the sponsor (for example, by providing guidance on correct procedures for completion of CRFs) and by verifying the accuracy of the data obtained (see also section 8).

6.5 Case report forms

The monitor is responsible for ensuring that all CRFs are correctly filled out in accordance with original observations. Any errors or omissions should be clarified with the investigator, corrected and explained on the CRF. Procedures should be established for the investigator's certification of the accuracy of CRFs by a signature, initials or a similar method. All procedures for ensuring accuracy of CRFs must be maintained throughout the course of the clinical trial.

6.6 Investigational product

The monitor should confirm that procedures for the storage, dispensing and return of investigational product(s) are safe, adequate and properly documented in accordance with local regulations and the trial protocol (see also section 10.4).

6.7 Communication

The monitor should facilitate communication between the investigator and sponsor. The monitor (or some other responsible person designated by the sponsor and known to the investigator) should be available to the investigator at all times for reporting of adverse events or consultation on other trial-related matters.

6.8 Notification of the trial or submission to the drug regulatory authority

The monitor should assist the investigator in notifying the drug regulatory authority of the clinical trial and submitting any necessary documentation.

6.9 Reports

The monitor should submit a written report to the sponsor after each site visit and after all relevant telephone calls, letters and other contacts with the investigator. The report should include details of the findings and any actions taken.

7. Monitoring of safety

7.1 Handling of and recording adverse events

In accordance with sections 4.1 and 4.4 of these guidelines, the investigator must ensure the safety of the trial subjects. This includes providing the best possible care for subjects experiencing any trial-related adverse events and conducting a thorough investigation to determine causality.

The occurrence of adverse events must be monitored carefully and recorded in detail during the course of the clinical trial.

The trial protocol should clearly state the method(s) by which adverse events will be monitored. Provisions should be included to ensure prompt dose reduction or withdrawal of therapy for patients experiencing unacceptable toxic effects. The protocol should describe how information relating to adverse events is to be handled and analysed by the investigator and the sponsor, and their responsibilities to report to each other and to the drug regulatory authority. The sponsor should provide special forms for reporting trial-related adverse events.

Consideration should be given to establishing a special committee to monitor adverse events (see also section 13).

7.2 Reporting adverse events

Regulations

National regulations vary considerably in their requirements for reporting adverse events. For serious events, however, accelerated reporting is required.

National regulations may require the sponsor and/or the investigator to report certain types of adverse events or reactions (for example, serious, previously unknown) to the drug regulatory authority and ethics committee. If required, all such reports should be accompanied by an assessment of causality and possible impact on the clinical trial and on the future use of the product. In reporting, measures should be taken to avoid unnecessary duplication.

The investigator

The investigator must report serious adverse events to the sponsor immediately and to the drug regulatory authority and the ethics committee as specified in the protocol and in accordance with national regulations. Normally, adverse events associated with the

use of the product must be reported to the drug regulatory authority within a specified time limit.

Reports on adverse events submitted by the investigator to the drug regulatory authority should contain both subject and trial identification data (such as the unique code number assigned to each subject in the trial).

When reporting adverse events to the sponsor, the investigator should protect confidentiality by excluding the names of individual subjects, personal identification numbers (for example, social security numbers) or addresses. The unique code number assigned to the trial subject should be used in the report and the investigator should retain the code to facilitate verification of data by the sponsor or drug regulatory authority and any medical follow-up which may be warranted. The name of the investigator reporting the adverse events should be stated.

After the trial has been completed or terminated, all recorded adverse events should be listed, evaluated and discussed in the final report.

The sponsor

During the trial, the sponsor is responsible for reporting any trial-related adverse events or reactions associated with the use of the investigational product to the local health authority as required by national regulations and to other investigators involved in clinical trials of the same product.

The sponsor should also report as soon as possible to the investigator as well as to the drug regulatory authority and relevant authorities in other countries any trial with the same product that has been stopped due to action taken by a regulatory authority, or any other withdrawals of the product from the market for safety reasons. The sponsor should amend the investigator's brochure as required to keep the description of adverse events updated and to include any other significant new safety information.

8. Record-keeping and handling of data

The aim of record-keeping and handling of data is to record, store, transfer and, where necessary, convert efficiently and accurately the information gathered on each trial subject into data that can be used in the report.

All steps involved in data management should be documented in order to allow step-by-step retrospective assessment of the quality of the data and the performance of the clinical trial ("the audit paper trail concept"). Documentation is facilitated by methods such as the use of checklists and forms giving details of action taken, dates, the individuals responsible, etc.

The allocation of responsibilities for record-keeping and handling of data should be specified in the protocol or other written agreement(s) between the sponsor and investigator(s).

A basic aspect of the integrity of data is the safeguarding of “blinding” with regard to treatment assignment. It starts with the randomization of patients into treatment groups and is maintained through all steps of data processing up to the moment when the decision to break the code is formally taken.

In the event of electronic handling of data, confidentiality of the database must be secured by safety procedures such as passwords and written assurances from all staff involved. Provision must be made for the satisfactory maintenance of the database and for back-up procedures.

8.1 Responsibilities of the investigator

- (a) The investigator has overall responsibility for ensuring the accuracy and completeness of data entry. The investigator must ensure that the observations and findings are recorded correctly and completely on the CRFs and signed by the responsible person designated in the protocol.
When conducting a study and using CRFs to report clinical trial data to the sponsor, the investigator must also ensure that the routine requirements for recording of data in the source documents (for example, hospital and laboratory records, consultation files) are met, particularly those relating to the treatment given to the subject and adverse events.
- (b) If trial data are entered directly into a computer, there must always be an adequate safeguard to ensure validation, including a signed and dated printout and back-up records. Computerized systems should be validated and a detailed description for their use should be produced and kept up to date.
- (c) All corrections to CRFs and to raw data must be made in a way which does not obscure the original entry. The correct data must be inserted with the reason for the correction (if not obvious), the date, and the initials of the investigator or authorized person. For electronic data processing, only authorized persons should be permitted to enter or modify data in the computer and there should be a record of changes and deletions. If data are altered during processing, the alteration must be documented.
- (d) Laboratory values with normal reference ranges, preferably together with the specificity and sensitivity of the methods used, should always be recorded on the CRF or be attached to it. Values outside a clinically accepted reference range or values that differ significantly from previous values must be evaluated and commented upon by the investigator.
- (e) Data other than those required by the protocol may appear on the CRF, provided they are clearly marked as additional or optional findings, with an explanation of their significance.

- (f) Units of measurement must always be stated and conversion of units must always be indicated and documented.
- (g) The final report of the trial should be drawn up as defined in the protocol. The report should be signed by the sponsor, monitor and investigator(s), as well as by the responsible statistician, in accordance with the applicable regulations.
- (h) For a period of time defined by national regulations, the investigator should maintain a confidential record to allow the translation of the code used to conceal the identity of the individual subjects in the trial (subject identification code). The investigator may submit the subject identification code list to the drug regulatory authority after the trial, together with the final report, according to national regulations.
- (i) The investigator should ensure that the subject's participation in the clinical trial is clearly marked in his or her medical records.

8.2 Responsibilities of the sponsor and the monitor

- (a) When electronic data handling or remote electronic data entry systems are employed, the sponsor must use validated data processing programs with adequate user documentation. A predetermined set of SOP for such systems must be available. Such systems should be designed to allow correction after loading and the corrections made must appear in an audit file.
- (b) Appropriate measures should be taken by the monitor to avoid overlooking missing data or including inconsistencies. If a computer assigns values automatically when data are missing, this should be made clear.
- (c) The sponsor must ensure the greatest possible accuracy when processing data. If data are transformed during processing, the transformation must be documented and the method validated. It should always be possible to compare the data printout with the original observations and findings.
- (d) The sponsor must be able to identify all data entered pertaining to each subject by means of an unambiguous code.
- (e) The sponsor must maintain a list of persons authorized to make corrections and prevent unauthorized access to the data by appropriate security systems.

8.3 Archiving of data

As required by national regulations, the investigator must arrange for the retention of the subject identification codes for a sufficient period of time to permit any medical

follow-up which may be warranted, including follow-up for delayed toxic reactions. It must be possible to identify each trial subject by name against the subject and product container identification codes, treatment assignment and the CRFs. Subject files and other supporting data must be kept for a period of time as required by local regulations. The sponsor or supplier of the product must make appropriate arrangements for the retention of all other essential documentation pertaining to the clinical trial in a form which can be retrieved for future reference. Archived data may be kept on microfiche or electronic or optical record (for example, compact disc), provided that a hard copy can be made available on request.

The protocol, documentation, approvals and all other essential documents related to the trial, including certificates that satisfactory audit and inspection procedures have been carried out, must be retained by the sponsor. Data on adverse events must always be included.

All data and documents should be made available if requested by relevant authorities.

9. Statistics and calculations

The use of qualified biostatistical expertise is necessary before and throughout the entire clinical trial procedure, commencing with the design of the protocol and CRFs and ending with completion of the final report and/or publication of the results.

The sponsor and the investigator should agree where and by whom the statistical work should be carried out. This information and the name of the responsible statistician should be recorded in the protocol.

9.1 Experimental design

The scientific integrity of a clinical trial and the credibility of the data produced depend primarily on the design of the trial. In the case of comparative trials, the protocol should therefore describe:

- an *a priori* rationale for the difference between treatments that the trial is designed to detect, and the statistical power to detect that difference, taking into account clinical and scientific information and professional judgement on the clinical significance of statistical differences; and
- measures taken to avoid bias, particularly with regard to the randomization, when relevant, and selection of patients.

9.2 Randomization and blinding

In the case of a randomized clinical trial, the randomization procedure must be documented. Where a sealed code for each individual treatment has been supplied in

a blinded, randomized study, it should be kept both at the site of the investigation and with the sponsor.

In the case of a blinded trial, the protocol must state the conditions under which the code may be broken and by whom. A system is also required to enable immediate access to the information about treatment received by individual subjects in the case of an emergency. The system must only permit access to the treatment schedule of one trial subject at a time. If the code is broken, this must be justified and documented in the CRF.

9.3 Statistical analysis

The type(s) of statistical analyses to be used must be specified in the protocol, and any other subsequent deviations from this plan should be justified and described in the final report of the clinical trial. The statistical analysis should be planned and carried out or verified by an identified, appropriately qualified and experienced statistician. The possibility and circumstances of interim analyses must also be specified in the protocol.

The investigator and the monitor must ensure that the data are of the highest quality possible at the point of collection and the statistician must ensure the integrity of the data during processing.

The results of statistical analyses should be presented in such a manner as to facilitate interpretation of their clinical importance (for example, as estimates of the magnitude of the treatment effect, the difference between treatments and confidence intervals) rather than in a form that relies solely on significance testing.

An account must be made of missing, unused or spurious data excluded during statistical analyses. All such exclusions must be documented so that they can be reviewed if necessary.

10. Handling of and accountability for pharmaceutical products

The sponsor is responsible for ensuring that the investigational pharmaceutical product(s) and, if applicable, comparator products supplied for the clinical trial are of appropriate quality and subject to quality assurance procedures (see section 5. 11).

If significant changes are made in the formulation of the investigational or comparator product during the course of the trial, the results of additional studies (for example, on the stability, comparative dissolution rate or, as appropriate, comparative bioavailability) should be made available before the new formulation is used in the trial. The studies should demonstrate that the changes would not be expected to alter the pharmacokinetic profile or other clinical characteristics of the product.

10.1 Supply and storage

The arrangements made by the sponsor to supply the investigator with pharmaceutical products for the clinical trial should be described in the protocol. The manner in which the study products are to be recorded, delivered, dispensed and stored should be detailed.

The principles of GMP (1) should be applied not only by the supplier of the pharmaceutical product(s), but also by any intermediaries responsible for storing the product(s) temporarily.

Records must be kept of information about the shipment, delivery, receipt, storage, return and destruction of any remaining pharmaceutical products. The investigator should not supply the investigational product to any person not targeted to receive it. Preferably a local pharmacy or the pharmacy department of the local hospital should assume responsibility for storage, delivery, return and keeping records of the investigational and, when appropriate, comparator product(s). If so, these procedures must be documented to make auditing possible.

10.2 Investigational labelling and packaging

The sponsor is responsible for the proper packaging and investigational labelling of the pharmaceutical products used. Study products should be labelled in compliance with the protocol and any applicable national regulations. The investigational label should state that the product is for clinical research purposes only. Investigational label information should be accurate and in a language that is understandable to the subject.

In blinded trials, the package should be labelled in a way that does not reveal the identity of the product. A coding system should be used to allow for the proper identification of the blinded products given to individual subjects (in case of emergency). In addition, all study products, including comparator products, should be indistinguishable by appearance, taste, smell, weight and other physical characteristics.

10.3 Responsibilities of the investigator

The investigator is responsible for ensuring:

- proper and safe handling of the investigational and, when appropriate, comparator products during and after the clinical trial, preferably in cooperation with a pharmacy (see section 10. 1);
- that the investigational product is used in accordance with the protocol, which implies use only for subjects included in the trial and by designated staff responsible to the investigator, and that this use is documented in such a way as to ensure appropriate dosage;
- that the dosage and instructions for use are correct and that every subject involved understands them properly; and

- that unused investigational and, when appropriate, comparator products are returned in accordance with the protocol to the pharmacy or sponsor or destroyed, and that proper records of these activities are kept.

10.4 Responsibilities of the sponsor and the monitor³

The sponsor is responsible for:

- supplying the investigational and, when appropriate, comparator product(s), prepared in accordance with principles of GMP. The products should be fully characterized, properly coded, and suitably packaged in such a way as to provide protection against deterioration during transport and storage at intermediate destinations; appropriate investigational labelling should be affixed (see section 10.2);
- ensuring that the package of investigational product(s) is of a size suitable for the clinical trial and adequate for the trial subjects;
- keeping sufficient samples from each batch used in the trial as a reference for control tests and validation of data, as required by national regulations; and
- providing information about the expiry date (month/year) or retest date in a manner understandable to all staff involved in the trial.

During the visits to the clinical trial site, the monitor should check:

- that all study products for the trial are used exclusively within the limits defined by the protocol;
- that inventory records of study products are in order and that there are sufficient supplies;
- that the expiry dates of the products are not likely to be, or have not been, exceeded;
- that the storage conditions for study products are adequate; and
- procedures for and records of returned and/or unused study products.

11. Role of the drug regulatory authority

The role of governments is to provide the legal framework for clinical trials. The aim should be twofold: (i) to protect the safety and rights of the subjects participating in a trial, and (ii) to ensure that trials are adequately designed to meet scientifically sound

³ See also sections 5 and 6.

objectives. These aims may be met by several means, including the specification of the investigator's qualifications and requirement for review and approval of the protocol by relevant scientific and/or ethics committees.

Drug regulatory authorities should have a mandate to review protocols and, where necessary to protect the safety of subjects, to require protocol revisions and/or termination of trials.

Regulations should allow for on-site inspections of the quality and reliability of the data obtained, with due concern for confidentiality.

11.1 General responsibilities

The national drug regulatory authority should ensure that the protocols for clinical trials are submitted in advance for review and are in accordance with existing national regulations. On the basis of its review of clinical trial protocols and/or reports, the regulatory authority may propose revisions to a protocol, request additional data or terminate a trial.

The drug regulatory authority should evaluate the adequacy of supervision of the trial by reviewing the monitor's reports to the sponsor (see section 6.9). In addition, the authority should be able to conduct on-site inspections of the reliability and quality of reported results.

National regulations should specify the procedures for reporting and handling cases of misconduct discovered in connection with clinical trials.

11.2 On-site inspections

As permitted by national regulations, the drug regulatory authority may carry out on-site inspections of the clinical trial site. Such inspections may be carried out routinely, randomly and/or for specific reasons, and should consist of a comparison of the procedures and practices of the investigator with those set out in the protocol and reports submitted to the regulatory authority by the investigator or the sponsor.

The inspection should determine whether the investigator has custody of the required records or, if not, who has assumed this responsibility. The data archives should be tested for ease of retrieval.

Inspections may include data audit. The drug regulatory authority should have easy access to all patient files and raw data used for and generated during the trial.

12. Quality assurance for the conduct of a clinical trial

The sponsor is responsible for implementing a system of quality assurance to ensure that the trial is performed and the data are generated, recorded and reported in compliance with the protocol, GCP and national regulations.

All clinical trial sites, data and documents must be available for verification. All observations and findings should be verifiable in order to ensure the credibility of

data and to assure that the conclusions presented are derived correctly from the raw data. The verification processes must be specified and scientifically justified. Statistically controlled sampling may be used to verify data obtained in a trial.

Quality control procedures must be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

The sponsor, investigational sites, facilities and laboratories, and all relevant data (including raw data) and documentation and reports concerning the data (including subject files) must be available for an audit and for inspection by relevant health authorities. The audit should be conducted by a nominated person(s) or organization(s) independent of those carrying out the clinical trial.

13. Considerations for multicentre trials

Because a multicentre clinical trial is conducted simultaneously by several investigators at different sites following the same protocol, some special administrative arrangements are normally needed. Ideally, the trial should begin and end simultaneously at all sites.

A number of aspects are rendered more complex in multicentre trials, such as:

- the elaboration, discussion and written acceptance of the protocol and its annexes by all investigators;
- submission of the proposed protocol or protocol amendments to the ethics committee(s) and the number of committees to be consulted;
- the organization of initial and intermediary meetings of parties involved in the trial;
- implementation of the trial;
- the procedure(s) used for the randomization of trial subjects;
- ensuring that the quality of the investigational and comparator products, if used, is maintained during distribution and storage in different locations;
- the training of investigators to follow the same protocol;
- standardization of methods for evaluating and analysing laboratory and diagnostic data (for example, establishment of an external quality-control system for laboratory assays);
- control of adherence to the protocol, including measures to terminate participation of trial sites if necessary;
- the role of the monitor(s);
- centralized data management and analysis;
- drafting of the final report and clearances required; and
- publication of the trial results.

A multicentre trial therefore may require a special administrative system, the scale of which will depend on the number of trial sites involved, study end-points and knowledge of the investigational pharmaceutical product. One or several committees may be set up for this purpose or the necessary functions may be performed by one or more designated person(s). The functions, responsibilities and mandate of the committee(s) or person(s) should be described in the trial protocol, as should the procedure for nomination.

For example, a committee or an individual could be responsible for overseeing the initiation and overall performance of the trial. Similarly, a second committee or person could be appointed to provide advice on policy matters and data collection. A third committee or person could be made responsible for the accuracy and verification of the data obtained. This committee or person would therefore require access to the results obtained in the trial, including adverse events. It should be stated in the protocol under what circumstances and how this committee or person can break the trial code. Collaboration between these committee(s) or person(s) is necessary.

A coordinating committee could also be set up or a coordinator appointed with responsibility for the control of the performance and progress of the trial and maintaining contacts with the drug regulatory authorities and ethics committees.

These administrative arrangements will provide adequate assurance that the study will be planned and conducted according to generally accepted scientific principles and GCP.

References

1. Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-second report*. Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823; https://iris.who.int/bitstream/handle/10665/39645/WHO_TRS_823.pdf?sequence=1&isAllowed=y)
2. Council for International Organizations of Medical Sciences. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva, CIOMS, 1993, Annex 1.

Appendix 1

Declaration of Helsinki¹

Recommendations guiding physicians in biomedical research involving human subjects

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, “The health of my patient will be my first consideration”, and the International Code of Medical Ethics declares that “A physician shall act only in the patient’s interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient.”

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice, most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research, a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under

¹ Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983 and the 41st World Medical Assembly, China, Hong Kong Special Administrative Region (SAR), September 1989. World Medical Association. *Handbook of declarations*. Ferney-Voltaire, 1992 (unpublished document; available on request from the World Medical Association, 28 avenue des Alpes, 01210 Ferney Voltaire, France).

review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor, provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.
Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with professional care (clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic biomedical research involving human subjects (non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

Appendix 2

Model list of items to be included in a clinical trial protocol

The clinical trial protocol should, where relevant, be required to cover the following points:

1. Title and justification for the trial.
2. Statement of the rationale, objectives and purpose of the trial.
3. Brief description of the site(s) where the trial is to be conducted.
4. Name and address of the sponsor.
5. Name, address and qualifications of each investigator.
6. Detailed description of the type of trial (randomized, blinded, open), trial design (parallel groups, cross-over technique), blinding technique (double-blind, single-blind), and method of and procedure(s) for randomization.
7. Description of the trial subjects (criteria for inclusion and exclusion of potential subjects), process of recruitment, and method(s) and timing of allocation of subjects into investigational groups.
8. Number of trial subjects needed to achieve the trial objective, based on statistical considerations.
9. Description of and justification for the route of administration, dosage, dosage interval and treatment period for the investigational and comparator products, if used. Dose-response relationships should be considered.
10. Any other treatment that may be given or permitted concomitantly.
11. Clinical and laboratory tests, pharmacokinetic analyses, etc. that are to be carried out.
12. Description of how responses are to be recorded (description and evaluation of methods and frequency of measurement), follow-up procedures, and measures to determine the extent of compliance with the treatment among trial subjects.
13. Discontinuation criteria for trial subjects and instructions on terminating the whole study or a part of the study.
14. Methods for recording and reporting adverse events or reactions, and provisions for dealing with complications.
15. Procedures for the maintenance of subject identification code lists, treatment records, lists for the randomization of subjects and/or case report forms (CRFs). Records should permit identification of individual patients or participants as well as auditing and reconstruction of data.

16. Information about how the trial code is established, where it will be kept, and when, how and by whom it can be broken in the event of an emergency.
17. Measures to be implemented to ensure the safe handling and storage of the investigational and comparator products, if used, and to promote and determine the extent of compliance with the prescribed treatment and other instructions.
18. Description of the methodology to be used to evaluate the results (including statistical methods) and to report on patients or participants withdrawn from the trial.
19. Time schedule for completion of the trial.
20. Information to be presented to the trial subjects, including how they will be informed about the trial, and how and when their consent will be obtained.
21. Instructions for staff involved in the trial, including how they are to be informed about the way the trial is to be conducted and about the procedures for drug usage and administration.
22. Ethical considerations and measures relating to the trial.
23. Medical care to be provided after the trial, and modalities of posttrial treatment.
24. When the protocol serves as a contract, statements regarding financing, insurance, liability, delegation or distribution of responsibilities, and publication policy.
25. List of literature referred to in the protocol.

6. Prequalification

6.1 Guidelines on submission of documentation for a multisource (generic) finished product. General format: preparation of product dossiers in common technical document format

Annex 15, WHO Technical Report Series, 961, 2011

1. Introduction	700
1.1 Background	700
1.2 Objectives	700
1.3 Scope	700
1.4 General principles	701
2. Glossary	702
3. Organization of a product dossier for a multisource product in common technical document format	703
4. Modules (including Module 1) of a product dossier for a multisource pharmaceutical product	705
5. Module 3 – quality	707
6. Module 5 of a product dossier for a multisource pharmaceutical product	708
7. Guidance on format and presentation of a product dossier in common technical document format	709
7.1 Guidance on format	709
7.2 Guidance on presentation	709
8. Variations	710
References	710

1. Introduction

1.1 Background

In its forty-fifth report, the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations published the *Procedure for prequalification of pharmaceutical products (1)* which outlines the procedure and considerations for the process undertaken by WHO in providing United Nations agencies with advice on the acceptability in principle of pharmaceutical products for procurement by such agencies. The above-mentioned report states:

“This activity of WHO aims to facilitate access to priority essential medicines that meet WHO-recommended norms and standards of acceptable quality”.

As mentioned in this report, when submitting an Expression of Interest (EOI) for product evaluation, the applicant should send to the WHO focal point (together with the other data requirements) a *product dossier* (PD), in the format specified in the WHO guidance documents on submitting product data and information.

Through the International Conference on Harmonisation (ICH) process, considerable harmonization has been achieved in the organization of the registration documents with the issuance of the common technical document (CTD) guideline (2-5). This recommended format in the CTD guideline for registration applications has become widely accepted by regulatory authorities both within and beyond the ICH Regions.

This document provides recommendations on the format and presentation for these types of PDs.

1.2 Objectives

These guidelines are intended to:

- assist applicants in the preparation of PDs for multisource products by providing clear general guidance on the format of these dossiers;
- fully adopt the modular format of the CTD as developed by ICH; and
- provide guidance on the location of regional information (Module 1) and other general data requirements.

These measures are intended to promote effective and efficient processes for the development of these PDs and the subsequent assessment procedures.

1.3 Scope

These guidelines apply to PDs for multisource pharmaceutical products containing existing active pharmaceutical ingredients (APIs) of synthetic or semi-synthetic origin

and their corresponding finished pharmaceutical products (FPPs). For the purposes of these guidelines, an existing API is one that has been previously authorized through a finished product by a stringent regulatory authority (SRA).¹ APIs from fermentation, biological, biotechnological or herbal origin are covered by other guidelines.

These guidelines primarily addresses the organization of the information to be presented in PDs for multisource products. They are not intended to indicate what studies are required. They merely indicate an appropriate format for the data that have been acquired. Applicants should not modify the overall organization of the CTD as outlined in the guidelines.

1.4 General principles

These guidelines present the agreed-upon common format for the preparation of a well-structured CTD for PDs that will be submitted to WHO. A common format for the technical documentation will significantly reduce the time and resources needed to compile PDs for the prequalification of multisource pharmaceutical products and will ease the preparation of electronic submissions. Assessments and communication with the applicant will be facilitated by a standard document containing common elements. In addition, exchange of regulatory information between national medicine regulatory authorities (NMRAs) and with WHO will be simplified.

Ultimately, this is intended to support the objectives of the WHO-managed Prequalification of Medicines Programme in listing pharmaceutical products of acceptable safety, efficacy and quality in the interest of public health.

These *general filing guidelines* should be read in conjunction with other applicable WHO and ICH reference documents and guidelines that provide further guidance and recommendations on the topic-specific content requirements for multisource products, notably:

- *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (6);
- *Bioequivalence trial information form (BTIF)* (7);
- *Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part* (8);
- *Quality overall summary — product dossier (QOS–PD)* (9).

¹ Stringent regulatory authority (SRA): a regulatory authority which is:

- a member of the International Conference on Harmonisation (ICH) (as specified on www.ich.org); or
- an ICH observer, being the European Free Trade Association (EFTA), as represented by Swissmedic, Health Canada and World Health Organization (WHO), and may be updated from time to time); or
- a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (may be updated from time to time).

Together, these guidelines, templates and reference documents mentioned within them are intended to assist applicants and WHO by harmonizing with international approaches and facilitating the preparation and subsequent assessment procedures for PDs through the integration of the internationally accepted CTD format and, where possible, terminology.

Once implemented these guidelines will supersede the following guidelines and template which were in use previously:

- *Guideline on submission of documentation for prequalification of multi-source (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis;*
 - Supplement 1 — Dissolution testing;
 - Supplement 2 — Extension of the WHO List of Stable (not easily degradable ARV) APIs;
- *Pharmaceutical Quality Information Form (PQIF).*

2. Glossary

active pharmaceutical ingredient (API)

Any substance or combination of substances used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings (1).

applicant

The person or entity who, by the deadline mentioned in the invitation, submits an expression of interest (EOI) to participate in this procedure in respect of the product(s) listed in the invitation, together with the required documentation on such product(s) (1).

finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labelling (1).

manufacturer

A company that produces, packages, repackages, labels and/or relabels pharmaceutical products (1).

multisource (generic) pharmaceutical products

Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable (6).

3. Organization of a product dossier for a multisource product in common technical document format

The CTD is organized into five *modules*. Module 1 is region-specific. Modules 2, 3, 4 and 5 are intended to be common for all regions. Conformance with these guidelines should ensure that Modules 2, 3, 4 and 5 are provided in a format acceptable to WHO and to regulatory authorities.

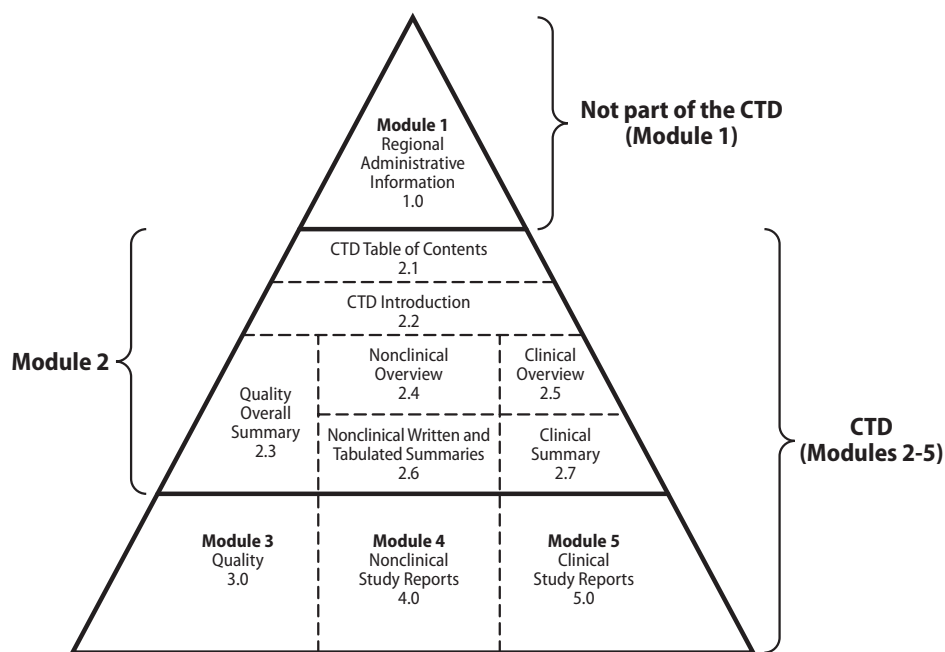
This section provides an overview of module contents for a multisource product in greater detail.

- Module 1: Administrative information and prescribing information
 - This module should contain documents specific to WHO and each region; for example, application forms or the proposed label for use in the region. The content and format of this module can be specified by WHO and the relevant regulatory authorities.
 - A summary of the bioequivalence/bioavailability information should be provided according to WHO's *Bioequivalence Trial Information Form (BTIF)* (7).
 - Quality information summary (QIS): see WHO's *Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part* for instructions (8).
- Module 2: CTD summaries
 - This Module should begin with a general introduction to the pharmaceutical, including its pharmacological class, mode of action and proposed clinical use. In general, the Introduction should not exceed one page.
 - A summary of the quality information should be provided according to WHO's *Quality overall summary — product dossier (QOS-PD)* template (9).
 - The organization of these summaries is described in Guidelines for ICH M4, M4Q and M4S (3-5).
- Module 3: Quality
 - Information on quality should be presented in the structured format described in ICH M4Q and WHO's *Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part* (8).

- Module 4: Nonclinical study reports
 - Generally not applicable for multisource products (some exceptions may apply).
- Module 5: Clinical study reports
 - The human study reports and related information should be presented in the order described in ICH M4E (3) and WHO's *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (6).

The overall organization of the CTD is presented in Figure 1.

Figure 1
Organization of the CTD



This figure is reproduced with the kind permission of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

In preparing PDs for multisource products, it is acknowledged that certain modules or sections of the CTD would generally *not be applicable* (e.g. Module 4 — nonclinical study reports, although some exceptions may apply) and should be marked as such.

4. Modules (including Module 1) of a product dossier for a multisource pharmaceutical product

This section outlines filing considerations for PDs in the CTD format. Table 1 provides an overview of the presentation of the PD, including modular structure and main headings.

Table 1
Modular format of PDs for multisource products in CTD format

Module 1 – Administrative information and prescribing information	
1.0	Cover letter
1.1	Table of contents of the application including Module 1 (Modules 1–5)
1.2	Application information:
1.2.1	Copy of the expression of interest (EOI)
1.2.2	Manufacturing and marketing authorization(s)/international registration status and/or the WHO certificate of pharmaceutical product (CPP)
1.2.3	Copy of certificate(s) of suitability of the <i>European Pharmacopoeia</i> (CEP) (including any annexes)
1.2.4	Letters of access for active pharmaceutical ingredient master files (APIMFs)
1.2.5	Good manufacturing practices (GMP) information
1.2.6	Biowaiver requests in relation to conducting a comparative bioavailability study
1.3	Product information:
1.3.1	Summary of product characteristics (SmPC)
1.3.2	Labelling (outer and inner labels)
1.3.3	Package leaflet (also known as patient information leaflet or PIL)
1.4	Regional summaries:
1.4.1	Bioequivalence trial information form (BTIF)
1.4.2	Quality information summary (QIS)
1.5	Electronic review documents (e.g. product information, BTIF, QIS, QOS–PD)
1.6	Samples (e.g. FPP, device(s), certificates of analysis)
Module 2 – Common technical document (CTD) summaries	
2.1	CTD Table of contents (Modules 2–5)
2.2	CTD Introduction
2.3	Quality overall summary – product dossier (QOS–PD)
2.4	Nonclinical overview – generally not applicable for multisource products (some exceptions may apply)

Table 1 *continued*

Module 2 – Common technical document (CTD) summaries
2.5 Clinical overview
2.6 Nonclinical written and tabulated summaries – generally not applicable for multisource products (some exceptions may apply)
2.7 Clinical summary
Module 3 – Quality
3.1 Table of contents of Module 3
3.2 Body of data
3.3 Literature references
Module 4 – Nonclinical study reports – generally not applicable for multisource products (some exceptions may apply)
4.1 Table of contents of Module 4
4.2 Study reports
4.3 Literature references
Module 5 – Clinical study reports
5.1 Table of contents of Module 5
5.2 Tabular listing of all clinical studies
5.3 Clinical study reports
5.3.1 Reports of biopharmaceutical studies
5.3.7 Case-report forms and individual patient listings
5.4 Literature references

Additional guidance for some of the sections to be included in Module 1 is provided below:

1.0 Cover letter

The cover letter submitted with the PD should include a clear statement by the responsible person submitting the PD, indicating that the information submitted is true and correct.

1.2.2 Manufacturing and marketing authorization(s)/ international registration status

List the countries in which:

- the FPP (or set of FPPs) has been granted a marketing authorization;

- the FPP (or one or more of the set of FPPs) has been withdrawn from the market; and
- an application for the marketing of the FPP (or one or more of the set of FPPs) has been rejected, deferred or withdrawn.

For further guidance see section 3.2.P3.1 of the *Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part* (8).

1.4 Regional summaries

The regional summaries should be prepared in accordance with the available WHO templates, which are available on the WHO Prequalification web site.

1.5 Electronic review documents

Electronic submission of documentation (CD or DVD) should be submitted in Microsoft Word (required for templates/summaries, e.g. QOS–PD, QIS, BTIF) or text-selectable PDF format (other documentation).

1.6 Samples (e.g. FPP, device(s))

A sample and certificate of analysis of the FPP(s) and devices(s) should be provided to enable visual inspection of the pharmaceutical product, the packaging materials and the label as well as comparison of the data with those in the SmPC, labelling and the package leaflet.

Draft labelling may be submitted at the time of dossier submission when labelling for marketing has not been finalized. For guidance regarding labelling, refer to the information on WHO public assessment reports (WHOPARs) available on the Prequalification web site under Information for Applicants (Prequalification Guidelines).

5. Module 3 – quality

For Module 3.2.S Drug substance (or active pharmaceutical ingredient (API)), there are three options to satisfy the information requirements for APIs within the Prequalification Programme. In brief these are:

- Option 1: certificate of suitability of the *European Pharmacopoeia* (CEP) procedure;
- Option 2: active pharmaceutical ingredient master file (APIMF) procedure; or
- Option 3: full details in the PD.

All options require the submission of information in CTD format (3.2.S), although the content may differ in places. The *Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part* (8) provides detailed guidance on this issue and on the preparation of the FPP information by the applicant.

6. Module 5 of a product dossier for a multisource pharmaceutical product

The majority of PDs for multisource products are supported by one or more pivotal comparative bioavailability studies. When filing a PD in the CTD format, it is anticipated that only the following relevant sections of Module 5 will normally be required.

Module 5: Clinical study reports

- 5.1 Table of contents for Module 5
- 5.2 Tabular listing of all clinical studies
- 5.3 Clinical study reports
 - 5.3.1 Reports of biopharmaceutical studies
 - 5.3.1.2 Comparative bioavailability and bioequivalence study reports
 - 5.3.1.3 In vitro–in vivo correlation study reports if available
 - 5.3.1.4 Reports of bioanalytical and analytical method for human studies²
 - 5.3.7 Case-report forms (CRFs) and individual patient listings: only CRFs for subjects who experienced serious adverse events should be included. All CRFs should be available upon request.
- 5.4 Literature references

For guidance regarding biowaivers, refer to the biowaiver implementation documents available on the Prequalification web site. For guidance regarding comparator products, refer to the information available under Guidance on bioequivalence studies on the Prequalification web site.

² Bioanalytical or analytical methods for BA/BE or in vitro dissolution studies should ordinarily be provided in the individual clinical study reports. However, where a method is used in multiple studies, the method and its validation should only be included once in section 5.3.1.4 and referenced in the appropriate individual clinical study reports.

7. Guidance on format and presentation of a product dossier in common technical document format

7.1 Guidance on format

Throughout the CTD, the information should be displayed in an unambiguous and transparent manner. Text and tables should be prepared using margins that allow the document to be printed on both A4-sized paper (European Union and Japan) and 8.5 × 11-inch paper (US). The left-hand margin should be sufficiently large that information is not obscured whatever the method of binding. Fonts for text and tables should be of a style and size large enough to be easily legible, even after photocopying. Times New Roman, 12-point font is recommended for narrative text.

Acronyms and abbreviations should be defined the first time they are used in each module.

References should be cited in accordance with the current edition of the *Uniform requirements for manuscripts submitted to biomedical journals*, International Committee of Medical Journal Editors (ICMJE).³ Copies of relevant pages of references should be provided, with a copy of the full article in the case of a publication. English translations should be provided as necessary.

7.2 Guidance on presentation

The paper copies of the application should be bound for easy access to information.

Each binder should be labelled with the proprietary name (if applicable) and the non-proprietary name of the FPP (e.g. “Name ABC” Abacavir (as sulfate) 300 mg tablets) and the company name of the applicant. For ease of reference, the following information could also be included on the label of each binder (space permitting): the volume number for that binder (out of the total number of volumes *for that module*), the section(s) contained within each volume and the date of the application (month and year), e.g.:

FPP “Name ABC”
Nonproprietary name
Applicant “XYZ”
Module 3 — Quality
Volume 1 of 3
Module 3.1 — 3.2.S.3
Month/year

³ The first edition of the *Uniform requirements for manuscripts submitted to biomedical journals* was conceived by the Vancouver Group and was published in 1979.

8. Variations

All variation applications should be submitted using the CTD format, regardless of the original PD format.

In the case of the filing of a variation, applicants would normally provide only the relevant modules or sections affected by the change. For example, if the variation was for a change in the shelf-life of the FPP, only those sections affected by the change would need to be submitted (10).

An updated and annotated QIS should be provided with each variation application.

References

1. Procedure for prequalification of pharmaceutical products. Revision. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth report*. Geneva, World Health Organization, 2011, Annex 10 (WHO Technical Report Series, No. 961; https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1).
2. Common Technical Document for the Registration of Pharmaceuticals for Human Use: Efficacy (ICH M4E) together with the complementary ICH Questions and Answers documents for the above mentioned guidelines.
3. Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use (ICH M4) (2003): Efficacy.
4. Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality (ICH M4Q) (2003): Quality.
5. Common Technical Document for the Registration of Pharmaceuticals for Human Use: Safety (ICH M4S) (2003): Safety.
6. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization, 2006, Annex 7 (WHO Technical Report Series, No. 937; https://apps.who.int/iris/bitstream/handle/10665/43443/WHO_TRS_937_eng.pdf?sequence=1).
7. Bioequivalence trial information form (BTIF) on: <http://apps.who.int/prequal/>.
8. Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part: on: https://iris.who.int/bitstream/handle/10665/112733/WHO_TRS_986_eng.pdf?sequence=1.
9. Quality overall summary - product dossier (QOS-PD): on: <http://apps.who.int/prequal/>.
10. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2009, Annex 2 (WHO Technical Report Series, No. 953; https://iris.who.int/bitstream/handle/10665/44553/WHO_TRS_953_eng.pdf?sequence=1&isAllowed=y).

6.2 Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products

Annex 4, WHO Technical Report Series, 953, 2009

1. Introduction

A significant part of the quality of a finished pharmaceutical product (FPP) is dependent on the quality of the active pharmaceutical ingredients (APIs) used for its production. Under the World Health Organization (WHO) guidelines on good manufacturing practices (GMP), it is the manufacturer of the FPP who is responsible for the overall quality of the product, i.e. including the choice of the suppliers and manufacturers of the ingredients.

However, in the context of globalization, APIs are sourced in a worldwide market and the risk of sourcing substandard or contaminated products is high. A proper system of qualification of suppliers can promote the constant sourcing of active ingredients of appropriate quality and thereby safeguard public health interests.

Full evaluation of suppliers of APIs, however, is a cost-intensive and resource-demanding activity, which only a few national medicines regulatory authorities (NMRAs) can afford. As a result, API assessment is not often part of granting marketing authorizations to FPPs, a situation which can undermine the quality and safety of marketed pharmaceutical products.

The need for quality assurance of APIs was noted in the resolutions of the 12th International Conference of Drug Regulatory Authorities in 2006. If adopted and implemented, this procedure would assist procurement agencies in validating the quality of the pharmaceutical products they are purchasing and facilitate product evaluation by NMRAs of WHO Member States as part of the marketing authorization procedures.

The purpose of this procedure is to provide relevant United Nations agencies and relevant authorities of WHO Member States, such as NMRAs, with advice on the acceptability, in principle, of APIs which are found to meet WHO-recommended quality standards.

Those APIs and their specified manufacturing sites which are found to meet the quality standards recommended by WHO are included in a list of APIs, as manufactured at the specified manufacturing sites, which have – at the time of their evaluation and inspection by WHO – been found to be acceptable, in principle, for use in the production of pharmaceutical products. It remains the ultimate responsibility of

the manufacturer of the FPP to ensure that the API, as accepted in principle, is suitable for the manufacture of the specific pharmaceutical product, for example in a sterile or a fixed-dose combination product.

Inclusion in the list does not imply any approval by WHO of the APIs and manufacturing sites in question. Moreover, inclusion in the list does not constitute a WHO endorsement or warranty of the fitness of any API for a particular purpose, including its use in a particular pharmaceutical product and the safety and/or efficacy of that pharmaceutical product in the treatment of specific diseases.

2. Glossary

The definitions given below apply to the terms used in this procedure. They may have different meanings in other contexts.

active pharmaceutical ingredient (API)

Any substance or combination of substances used in a finished product, intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings.

finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling.

manufacture or production

All operations of purchase of materials and starting materials, preparation of the API and of the pharmaceutical product, including packaging and repackaging, labelling and re-labelling, quality control, release, storage and distribution and the related controls. The terms “manufacture” and “production” are used interchangeably in this document.

manufacturer of active pharmaceutical ingredient (API)

A company that produces, packages and labels active pharmaceutical ingredients (APIs).

3. Purpose and principles

The purpose of this quality assessment procedure is to evaluate whether the APIs meet the requirements recommended by WHO, including that they are manufactured in compliance with WHO current good manufacturing practices (current good manufacturing practices being hereinafter referred to as GMP) (1, 2). This will be done through standardized quality assessment and inspection procedures.

The quality assessment procedure established by WHO is based on the following principles:

- a general understanding of the production and quality control activities of the manufacturer of the API;
- assessment of data and information on the API, submitted by the manufacturer, which includes the manufacturing process, material specifications, test data and results, including changes and variations;
- assessment of the API manufacturing site(s) for consistency in production and quality control of raw materials, with specific emphasis on key starting materials or intermediates and the final APIs during and after purification through compliance with WHO GMP;
- random sampling and testing of APIs;
- control of storage and distribution;
- handling of complaints and recalls; and
- monitoring of complaints from relevant United Nations agencies and national medicines regulatory authorities of WHO Member States.

WHO will collaborate with NMRAs and other organizations on quality assessment and site inspections. WHO recommends that manufacturers of APIs expressing interest in participating in the prequalification of APIs should inform and ask the relevant NMRA to collaborate with WHO in the quality assessment process. It is recommended that the manufacturers provide the national medicines regulatory authority with the necessary authorization to discuss the product files with WHO representatives during inspections where relevant or required (subject to appropriate confidentiality provisions, if necessary).

4. Steps of the procedure

WHO undertakes a comprehensive evaluation of the quality of APIs, based on information submitted by the applicants, and inspection of the relevant manufacturing site(s).

At regular intervals WHO will publish an invitation to interested parties, asking them to voluntarily participate in this procedure in respect of the substances mentioned in the invitation. By submitting an expression of interest (EOI), the applicant undertakes to share information with WHO on all relevant aspects of manufacture and control of the specified APIs together with any changes carried out and/or planned.

Interested applicants provide the necessary information to WHO by submitting an API dossier and other information as requested. Assessment will normally include evaluation of:

- API dossiers, which must include data and information as specified in the guidelines for submission (the guidelines are available on the WHO web site (<https://extranet.who.int/prequal/medicines/>); and

- manufacturing sites of APIs, which must adhere to WHO GMP.

If evaluation demonstrates that an API and its corresponding manufacturing site(s) meet the standards recommended by WHO, it will be included in the list of APIs which have – at the time of their assessment and inspection – been found to be acceptable, in principle, for use in production of pharmaceutical products.

WHO reserves the right to terminate the procedure of quality assessment of a specific API if the applicant is not able to provide the required information, and/or the applicant is unable to implement any corrective actions, which WHO may require, within a specified time period, or when the information supplied is inadequate to complete the quality assessment process.

WHO recognizes the evaluation of relevant APIs by competent authorities which apply stringent standards for quality, similar to those recommended by WHO, such as, for example, but not limited to, the US Food and Drug Administration (USFDA), the European Medicines Agency (EMA), and the European Directorate for the Quality of Medicines & HealthCare (EDQM).

Provided that the competent authority applying stringent standards is willing to share certain information with WHO on the API in question, WHO will consider this information for possible inclusion of the API in the list of WHO prequalified APIs. It will do so as and when information about such APIs becomes available to WHO. These products can be added to the list of APIs prequalified by WHO, on the basis of the scientific assessment and inspections conducted by the competent authority concerned, and the exchange of relevant information between the concerned authority and WHO.

5. Invitation for expression of interest

WHO will, at regular intervals, publish an invitation to manufacturers of specific APIs as identified in the invitation to submit an API dossier for evaluation in accordance with this procedure and the relevant guidelines.

The APIs listed in an invitation for expressions of interest (EOI) will generally be APIs for pharmaceutical products which:

- are considered by WHO to be vital for the effective treatment and prevention of the specified diseases, for example, but not limited to, the treatment of HIV/AIDS, malaria or tuberculosis; and which
- the WHO Expert Committee on Specifications for Pharmaceutical Preparations has identified as being of highest concern in relation to quality.

Each invitation will be open and transparent, inviting all relevant parties to submit an EOI for the APIs listed. Such an invitation will normally be published on the WHO web site and possibly also through other media, such as the international press.

Guidelines developed for the submission of the API dossier are available on the WHO web site at <https://extranet.who.int/prequal/medicines/> and will be sent to interested manufacturers upon request.

6. Data and information to be submitted

Interested manufacturers are expected to submit documentation on the APIs as called for in the invitation for EOI. Applicants should submit their API dossiers, with the required information, to the WHO focal point, before the deadline specified in the invitation. Guidance and instructions developed for the submission of the dossiers shall be made available on the WHO web site. Data and information to be submitted in the API dossier should include the following:

General information

- nomenclature
- structure
- general properties

Manufacture

- site(s) of manufacture
- description of manufacturing process and process controls
- control of materials
- control of critical steps and intermediates
- process validation and/or evaluation
- manufacturing process development

Characterization

- elucidation of structure and other characteristics
- impurities

Control of the API

- specification
- analytical procedures
- validation of analytical procedures
- batch analysis
- justification of specification

Reference standards or materials

Container closure system

Stability

- stability summary and conclusion
- post-approval stability protocol and stability commitment
- stability data.

The above-listed content of the API dossier is the same as the common technical documentation (CTD) content for the API section and is in line with the content of the API master file (APIMF) dossier, open and restricted parts together, as established for the purposes of WHO prequalification of pharmaceutical products (3).

Holders of APIMFs whose dossiers as per the CTD have been assessed with a positive notified outcome by WHO as part of the prequalification procedure for a pharmaceutical product, and whose product has subsequently been included in the list of WHO prequalified pharmaceutical products can, in response to an invitation for EOI, apply in writing for evaluation under this API prequalification procedure without dossier assessment. WHO, however, reserves the right to assess those issues which are required to be evaluated under the present procedure, but which were not covered by the assessment of the APIMF dossier as part of the prequalification of a pharmaceutical product.

Alternatively, a drug master file, as prepared for or submitted to the NMRA of an ICH¹ region, can be submitted provided that it contains the information required. In such cases a covering letter cross-referencing the information should be provided by the manufacturer. In this regard, the WHO Pharmaceutical Starting Materials Certification Scheme (SMACS) can be used in support of the relevant data which are covered by the Scheme (4).

Changes in the manufacture of an API should be documented in the API dossier through appropriate change control procedures and communicated to WHO.

7. Screening of dossiers submitted

Each API dossier submitted by an applicant will be screened for completeness prior to being evaluated. Dossiers submitted for APIs, which are not listed in an invitation for EOI or which have not otherwise been invited by WHO, will not be accepted for evaluation.

¹ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Similarly, WHO will not consider dossiers that are incomplete. The applicant will be informed that an incomplete dossier has been received and will be requested to complete the dossier within a specified time period. In the event of non-compliance the dossier may be rejected on grounds of incompleteness and returned to the applicant. Dossiers that are considered complete as the result of the administrative screening will be retained by WHO for evaluation purposes.

8. Assessment of API dossiers

The information on the API submitted in the dossier will be evaluated by teams of experts (assessors) appointed by WHO. The assessors involved in dossier assessment must have the relevant qualifications and experience in the fields of pharmacy, organic and analytical chemistry, quality assessment, quality assurance and other relevant fields.

The assessors will be appointed in accordance with a standard operating procedure (SOP) established by WHO. The assessors should preferably be from NMRAs and they will act as temporary advisers to WHO. The assessors must comply with the confidentiality and conflict of interest rules of WHO, as laid down in the relevant sections of this procedure.

The assessment of product dossiers will be done in accordance with SOPs established by WHO for that purpose so as to ensure uniformity in evaluation and timeliness of assessment activities. If needed, WHO may provide training to these experts.

9. Site inspection

Dependent on the outcome of the evaluation of the API dossier, the planning of inspections should take into account the types of API and the results and reports of inspections conducted by regulatory authorities or other competent organizations.

WHO will plan and coordinate the performance of inspections at the manufacturing site(s) of APIs and that of the key intermediate (if relevant) to assess compliance with the relevant sections of WHO GMP guidelines, and will compare the technical information on the manufacturing process given in the API dossier submitted to WHO with the manufacturing process actually carried out on site.

The inspections will be performed by a team of inspectors consisting of experts appointed by WHO, preferably from NMRA inspectorates, who will act as temporary advisers to WHO. The inspectors must have the relevant qualifications and experience to perform such inspections, be competent in areas such as production and quality control of pharmaceuticals, and have appropriate experience in WHO GMP. The inspectors must comply with the confidentiality and conflict of interest rules of WHO, as laid down in the relevant sections of this procedure. If needed, WHO may provide training to these experts.

A WHO staff member will coordinate the team. Each team will perform the inspections and report on its findings to WHO in accordance with SOPs established by

WHO for that purpose so as to ensure a standard harmonized approach. A representative of the NMRA of the country of manufacture would normally be expected to accompany the team to the manufacturing facilities to assess the compliance with GMP.

10. Reporting and communication of results of the evaluation

Each assessment and inspection team will finalize its reports according to the established WHO SOP and format, describing the findings and including recommendations to the applicant.

The findings from the dossier assessment, including, but not limited to, deficiencies of the documentation and data submitted, shall be communicated in writing to the applicant and will request submission of the missing data and information and for corrective actions, as appropriate.

The inspection report will be communicated to the applicant. If any additional information is required, or corrective action has to be taken by the manufacturer of the API and/or manufacturer of the key intermediate, WHO will postpone its decision of the acceptability of the respective site(s), until such information has been evaluated, or the corrective action has been taken and found satisfactory in light of the specified standards.

WHO reserves the right to terminate the procedure of quality assessment of a specific API if the applicant is not able to provide the required information or implement the corrective actions within a specified time period, or if the information supplied is inadequate to complete the quality assessment process.

In the event of any disagreement between an applicant and WHO, an SOP established by WHO for the handling of appeals and complaints will be followed to discuss and resolve the issue.

As WHO is responsible for the quality assessment, the ownership of the reports lies with WHO. Thus, WHO shall be entitled to use and publish such reports, subject always, however, to the protection of any commercially sensitive confidential information of the manufacturer. “Confidential information” means:

- confidential intellectual property, “know-how” and trade secrets (including, e.g. programmes, manufacturing processes or information contained or embodied in an API dossier, unpublished aspects of trademarks, and patents); and
- commercial confidences (e.g. structures and development plans of a company).

Provisions of confidentiality will be contained in an exchange of letters between WHO and each applicant, to be concluded before the assessment of the API dossier or inspection of the manufacturing sites.

Notwithstanding the foregoing, WHO reserves the right to share the full evaluation and inspection reports with the relevant authorities of any interested Member State of the Organization and United Nations agencies.

11. Outcome of quality assessment procedure

Once WHO is satisfied that the quality assessment process is complete for the relevant API, and that the WHO-recommended standards are met, the API, as produced at the specified manufacturing site(s), will be included in the list of prequalified APIs. The list of prequalified APIs will be compiled in accordance with an SOP established by WHO for final decision-making on inclusion in the list. The list will be published on the WHO web site and will specify the characteristics of the prequalified APIs, as follows:

- API application WHO reference number;
- International Nonproprietary Name (INN) of active ingredient;
- name of API manufacturer, physical address of manufacturing site(s);
- applicant reference to pharmacopoeial or in-house standards;
- primary and secondary packaging material(s);
- retest period;
- storage conditions stated on labelling.

Each applicant will receive a letter from WHO informing it of the outcome of the quality assessment process regarding the submitted API applications. Once the APIs are included in the list of prequalified APIs, the applicant shall be held to keep WHO continuously updated on all relevant aspects of the manufacture and control of such APIs and to meet any requirements, as agreed with WHO.

In accordance with World Health Assembly Resolution WHA57.14 of 22 May 2004, WHO will, subject always to the protection of commercially sensitive confidential information, publish WHO Public Inspection Reports (WHOPIR(s)) on the manufacturers that were found to be in compliance with WHO-recommended guidelines and standards. These reports will be published on the WHO web site. WHO shall also be entitled to publish negative evaluation outcomes.

The decision to list an API is made based upon information available to WHO at that time, i.e. information in the submitted API dossier, and on the status of GMP at the facilities used in the manufacture and control of the API at the time of the site inspection(s) conducted by WHO.

This decision is subject to change on the basis of new information that may become available to WHO. If serious safety and/or quality concerns arise in relation to a prequalified API, WHO may delist the API or suspend the API until results of further investigations become available and are evaluated by WHO.

12. Procurement, sourcing and supply

All APIs included in the list should hold a certificate granted pursuant to the WHO SMACS prior to moving in international commerce (4).

Procuring United Nations agencies should be aware that manufacturers purchasing APIs from the sources included in the WHO list should still perform the relevant qualification of the manufacturer and quality control of the API with regard to the physicochemical characteristics and other aspects of the API that have an impact on the quality, safety and efficacy of the FPP (5).

Manufacturers of APIs, in turn, should be aware that inclusion in the list does not exclude their duties to communicate to buyers the necessary technical data.

13. Maintenance of prequalification status

Applicants are required to communicate details to WHO of any changes (variations) in manufacture and control that may have an impact on the safety, efficacy and quality of the API. It is the applicant's responsibility to provide WHO with the appropriate documentation (referring to relevant parts of the dossier) to prove that any intended or implemented variation will not have an impact on the quality of the API that has been prequalified. WHO will undertake an evaluation of variations according to the established WHO guidelines and SOPs and communicate the outcome to the applicant.

Adherence to the reporting requirements will be verified during the inspections carried out by WHO.

Random samples of APIs supplied to manufacturers of FPPs may be taken by WHO or by the NMRA of a Member State and submitted to WHO for independent testing. Certificates of analysis released by the manufacturer and specifications for test methods should be provided by the manufacturer to WHO for review upon request. In the event of failure to meet the established criteria for testing, WHO will investigate the problem and communicate this to the manufacturer concerned.

Complaints concerning prequalified APIs, communicated to WHO, will be investigated in accordance with an SOP established by WHO for that purpose. After investigation WHO will provide a written report of the problem and include recommendations for action where relevant. WHO will make the report available to the applicant, and to the NMRA of the country where the manufacturing site is located. Subject always to considerations of commercially sensitive information as referred to above, WHO also reserves the right to make such reports public if it considers this to be of public health concern. In addition, WHO reserves the right to share the full report with relevant authorities of interested Member States of the Organization and United Nations agencies.

WHO will at regular intervals arrange for the APIs and manufacturing sites included in the list to be re-evaluated. If, as a result of this re-evaluation, it is found

that an API and/or specified manufacturing site no longer complies with the WHO-recommended standards, such APIs and manufacturing sites will be removed from the list. Failure of a manufacturer to participate in the reassessment procedure will also lead to removal from the list.

Re-evaluation, including reinspections of manufacturing sites, will be done at regular intervals based on risk assessment, but at least once every five years.

Re-evaluation, including reinspections, shall also be performed:

- if any fraud or omissions by the applicant/manufacturer of APIs in the initial assessment procedure or during the follow-up activities becomes evident; and
- if WHO or any of the relevant United Nations agencies or NMRAs of WHO Member States consider that a batch or batches of prequalified APIs supplied are not in compliance with the specifications which were found to be applicable upon prequalification.

14. Cost recovery

WHO reserves the right to charge for the quality assessment procedure on a cost recovery basis.

15. Confidentiality undertaking

The assessors and inspectors will treat all information to which they will gain access during the evaluations and inspections, or otherwise in connection with the discharge of their responsibilities in regard to the above-mentioned activities, as confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set forth below.

Assessors and inspectors will take all reasonable measures to ensure:

- that confidential information is not used for any purpose other than the evaluation/inspection activities described in this document; and
- that it is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

Assessors and inspectors will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

- was known to them prior to any disclosure by or on behalf of WHO (including by manufacturers); or
- was in the public domain at the time of disclosure by or on behalf of WHO (including by manufacturers); or

- has become part of the public domain through no fault of theirs; or
- has become available to them from a third party not in breach of any legal obligations of confidentiality.

16. Conflict of interest

Before undertaking the work, each assessor and inspector will also (in addition to the above-mentioned confidentiality undertaking) be required to sign a declaration of interest. If, based on this declaration of interest, it is felt that there is no risk of a real or perceived conflict of interest (or it is felt that there is only an insignificant and/or irrelevant conflict of interest), and it is thus deemed appropriate for the evaluator or inspector in question to undertake this work, he/she will discharge his/her functions exclusively as adviser to WHO. In this connection, each assessor and inspector is required to confirm that the information disclosed by him/her in the declaration of interest is correct and complete, and that he/she will immediately notify WHO of any change in this information.

All inspectors furthermore agree, that at the manufacturer's request, WHO will advise the manufacturer in advance of the identity of each inspector and composition of the team performing the site inspection, and provide curricula vitae of the inspectors. The manufacturer then has the opportunity to express possible concerns regarding any of the inspectors to WHO prior to the visit. If such concerns cannot be resolved in consultation with WHO, the manufacturer may object to a team member's participation in the site visit. Such an objection must be made known to WHO by the manufacturer within 10 days of receipt of the proposed team composition. In the event of such an objection, WHO reserves the right to cancel all or part of its agreement with, and the activities to be undertaken by, that inspector.

References

1. WHO good manufacturing practices: main principles for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003, Annex 4 (WHO Technical Report Series, No. 908; https://iris.who.int/bitstream/handle/10665/42613/WHO_TRS_908.pdf?sequence=1&isAllowed=y); and related in: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials*. Volume 2, 2nd updated edition. *Good manufacturing practices and inspection*. Geneva, World Health Organization, 2007.
2. WHO good manufacturing practices: guidelines on active pharmaceutical ingredients. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report*. Geneva, World Health Organization, 1999, Annex 5 (WHO Technical Report Series, No. 885; https://iris.who.int/bitstream/handle/10665/42145/WHO_TRS_885.pdf?sequence=1&isAllowed=y); and related in: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials*. Volume 2, 2nd updated edition. *Good manufacturing practices and inspection*. Geneva, World Health Organization, 2007.

3. Guidelines on Active Pharmaceutical Ingredient Master File Procedure. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-second report*. Geneva, World Health Organization, 2008, Annex 4 (WHO Technical Report Series, No. 948; https://iris.who.int/bitstream/handle/10665/43852/WHO_TRS_948_eng.pdf?sequence=1&isAllowed=y).
4. WHO Pharmaceutical Starting Materials Certification Scheme (SMACS): guidelines on implementation. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report*. Geneva, World Health Organization, 2004, Annex 3 (WHO Technical Report Series, No. 917; https://iris.who.int/bitstream/handle/10665/42851/WHO_TRS_917.pdf?sequence=1&isAllowed=y).
5. Good trade and distribution practices for pharmaceutical active pharmaceutical ingredients. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report*. Geneva, World Health Organization, 2004, Annex 2 (WHO Technical Report Series, No. 917; https://iris.who.int/bitstream/handle/10665/42851/WHO_TRS_917.pdf?sequence=1&isAllowed=y).

6.3 Guidelines on active pharmaceutical ingredient master file procedure^{1,2}

Annex 4, WHO Technical Report Series, 948, 2008

1. Introduction	725
2. Scope	725
3. Content of the active pharmaceutical ingredient master file	725
3.1 Open part of APIMF	726
3.2 Restricted part of APIMF	727
4. Use of the APIMF procedure	728
5. Steps of the APIMF procedure	729
6. Content of the product dossier when the APIMF procedure is used	730
7. Changes and updates to the APIMF	731
Appendix 1 Template letter of access	732
Appendix 2 Part of covering letter to be submitted by the APIMF holder to WHO	733

¹ These guidelines are based on the approach described in the *Consultation draft guideline on active substance master file procedure*. London, European Medicines Agency, 2005 (document CPMP/QWP/227/02 Rev 2).

² The APIMF procedure guidelines do not apply to biological APIs.

1. Introduction

The main objective of the Active Pharmaceutical Ingredient Master File (APIMF) procedure is to allow valuable confidential intellectual property or “know-how” of the manufacturer of the active pharmaceutical ingredient (API) to be protected, while at the same time allowing the applicant for prequalification or prequalification variation (from now on named in the text as the applicant) to take full responsibility for the finished pharmaceutical product (FPP) and the quality and quality control of the API. The WHO Prequalification Programme thus has access to all the information necessary for an evaluation of the suitability of the use of the API in the FPP.

The APIMF procedure is a possibility offered to applicants for WHO prequalification of medicinal products and the manufacturers of their APIs. Other means of submission of scientific data on the API include:

- a valid certificate of suitability of pharmacopoeial monographs with which the API complies with all appendices, and adding information which is not covered by the certificate;
- by submitting scientific information on the API to the extent available and organized according to the current guidance documents, available on the WHO Prequalification web site (<https://extranet.who.int/prequal/medicines/>). In this case, the API manufacturer should provide a signed declaration that the synthesis and subsequent purification is conducted in accordance with what is presented in the dossier.

In addition, the WHO pharmaceutical starting materials certification scheme (SMACS) can be used to attest the relevant data as covered in the scheme. (*WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report. Geneva, World Health Organization, 2004. WHO Technical Report Series, No. 917, Annex 3.*)

2. Scope

These guidelines are intended to assist applicants in the compilation of the information on APIs in their dossiers for prequalification or when submitting a variation to a dossier on a prequalified product (named in the text from now on as product dossier) when the APIMF procedure is used. It is also intended to help APIMF holders in the compilation of their APIMFs.

3. Content of the active pharmaceutical ingredient master file

The APIMF should contain detailed scientific information as indicated in Section 2. Active pharmaceutical ingredient(s) of the “Guideline on Submission of Documentation

for Prequalification of Multi-source (Generic) Finished Pharmaceutical Products (FPPs) Used in the Treatment of HIV/AIDS, Malaria and Tuberculosis”, available on the WHO Prequalification web site at: <https://extranet.who.int/prequal/medicines/>.

The information required should be organized and presented in the structure and format described in these guidelines, which follows that of the Common Technical Document (CTD), agreed in November 2000 within the framework of the International Conference on Harmonisation (ICH, see web site: www.ich.org).

The scientific information in the APIMF should be physically divided into two separate parts, namely the open part (OP) and the restricted part (RP). In addition to the OP and RP, the APIMF should contain a table of contents and a separate quality summary for the OP and the RP. The OP and RP should each have a version number given by the APIMF holder. The structure of the version numbers should be unique and the following structure is suggested:

Name APIMF holder / Name active pharmaceutical ingredient / OP or RP / version number / date in yyyy-mm-dd.

3.1 Open part of APIMF

The OP contains the information that the APIMF holder regards as non-confidential to the applicant, whereas the RP contains the information that the APIMF holder regards as confidential. It is emphasized that the OP is still a confidential document that cannot be submitted to third parties without the written consent of the APIMF holder. In all cases the OP should contain sufficient information to enable the applicant to take full responsibility for an evaluation of the suitability of the specifications for the API to control the quality of this API for use in the manufacture of a specified FPP.

For the OP, at least those aspects listed below must be covered by appropriate documentation in the APIMF.

General information

- nomenclature
- structure
- general properties.

Manufacture

- manufacturer(s)/site of manufacture
- description of the manufacturing process and process controls
A flow chart and brief outline of the manufacturing process is regarded as sufficient, if detailed information is presented in the RP. However, full validation data on the sterilization process may be requested in the OP (in cases where there is no further sterilization of the final product).

- control of critical steps and intermediates
in so far as the information is also relevant for the applicant to prequalification.

Characterization

- elucidation of structure and other characteristics
- impurities.

Control of API

- specification
- analytical procedures
- validation of analytical procedures
- batch analysis
- justification of specification.

Reference standards or materials

Container closure system

Stability

- stability summary and conclusion
- post-approval stability protocol and stability commitment
- stability data.

3.2 Restricted part of APIMF

The RP should contain the remaining information, such as a detailed description of the individual steps of the manufacturing method (reaction operating conditions, data on validation and evaluation of critical steps) and the quality control during the manufacturing method of the API. Information relevant to the applicant such as that on impurities should be discussed in the RP, but it may be also submitted in the OP if considered necessary to enable the applicant to take full responsibility for its product.

For the RP, at least those aspects listed below must be covered by appropriate documentation in the APIMF.

Manufacture

- manufacturer(s)/site of manufacture
- detailed description of the manufacturing process and process controls

- control of materials
- control of critical steps and intermediates
in so far as the information is related to the detailed description of the manufacturing process and in so far as this information is not relevant for the applicant;
- process validation and/or evaluation
- manufacturing process development.

Characterization

- impurities
in so far as the information is related to the detailed description of the manufacturing process and in so far as the APIMF holder sufficiently justifies that there is no need to control these impurities in the final API.

Control of API

- justification of specification
in so far as the information is related to the detailed description of the manufacturing process, control of materials and process validation.

4. Use of the APIMF procedure

An APIMF can only be submitted in support of a product dossier or a variation to a product dossier and is only reviewed in connection with that product dossier. An APIMF is never approved as such, it can be only accepted in relation to an FPP dossier.

The relationship between the quality of the API and its use in the FPP needs to be justified in the relevant product dossier. Although the APIMF procedure is developed to keep the intellectual property relating to the API confidential, it is also permissible to use the procedure when there is no confidentiality issue between the applicant and the API manufacturer, e.g. when the applicant for prequalification manufactures the API itself.

Preferably, the API manufacturer should be the holder of the APIMF. It is, however, permissible for the APIMF to be submitted by another party, considered as the holder. In this case, a formal letter of authorization should be available from the manufacturer of the API.

The APIMF procedure should be used for APIs where a professed standard is declared, i.e. where no monograph exists in *The International Pharmacopoeia*, *European Pharmacopoeia*, *United States Pharmacopoeia* or *Japanese Pharmacopoeia*, or where a monograph exists but a manufacturer's in-house standard is declared. The APIMF procedure can also be used when APIs are described in *The International Pharmacopoeia*, *European Pharmacopoeia*, *United States Pharmacopoeia* or *Japanese Pharmacopoeia*.

A Drug Master File (DMF) of an API (active substance) assessed by a drug regulatory authority in the International Conference on Harmonisation (ICH)-participating and associated countries can be accepted without further evaluation provided that:

- the complete drug master file is submitted to the WHO Prequalification Programme;

and

- the corresponding assessment report from ICH or the associated authorities is made available through a mechanism of sharing of information;

or

- the manufacturer is able to prove that the API is used in an FPP-approved, in an ICH-participating, or associated country. In this respect, a certificate according to the WHO pharmaceutical starting materials certification scheme (SMACS) issued by a competent regulatory authority can be submitted, if available.

The holder of the DMF should also declare in writing that there have been no changes to the manufacture of batches of API to be supplied for WHO prequalification and to the DMF content since its acceptance by the ICH- participating or associated countries.

5. Steps of the APIMF procedure

The APIMF holder (manufacturer of the API or its authorized representative) should provide the APIMF to WHO only once, independently of the number of applicants and the number of FPP dossiers submitted. The submission of the relevant documentation by the APIMF holder to WHO must be synchronized to arrive at approximately the same time as the first product dossier is received from the FPP manufacturer that refers to the APIMF.

Where the APIMF procedure is used, the applicant for prequalification should submit to WHO the product dossier together with the “letter of access”. The APIMF holder should give permission to WHO, in the form of a “letter of access”, to assess the data in the APIMF in relation to a specific product dossier (see Appendix 1).

The APIMF holder should submit to WHO:

- the APIMF accompanied by a covering letter (see Appendix 2);
- quality summaries on the RP and the OP;
- the letter of access (see Appendix 1).

In addition, the APIMF holder should submit to the relevant FPP applicant(s):

- a copy of the latest version of the OP;
- a copy of the quality summary on the latest version of the OP;
- the letter of access.

WHO requires that any APIMF updates made in relation to one prequalification dossier should apply to all other FPP dossiers referencing that specific APIME. It is the responsibility of the APIMF holder to notify the applicants and WHO about any changes to the OP and/or RP, so that the applicants can update all affected prequalification dossiers accordingly and file the appropriate variation(s) with WHO as necessary.

6. Content of the product dossier when the APIMF procedure is used

The applicant for prequalification is responsible for ensuring that he or she has access to the relevant information concerning the current manufacture of the API.

The specifications used by the applicant to control the quality of the API should be unambiguously laid down in the product dossier. The applicant for prequalification should quote the *OP version number / date in yyyy-mm-dd*, or should include a copy of the OP in the prequalification dossier. The version of the OP in the prequalification dossier should be the most recent and it should be identical to the OP as supplied by the APIMF holder to WHO as part of the APIME.

The applicant should include all relevant details from the OP in the Quality summary of the product dossier. Aspects of the APIMF that are specifically relevant to the FPP under consideration should be highlighted in this summary.

In the case of a single supplier/manufacturer of the API, and where the APIME, a valid certificate of suitability of pharmacopoeial monographs or the WHO API prequalification procedure is used, the specifications of the applicant for the API in the product dossier should in principle be identical to those of the APIME, the certificate of suitability or the prequalified API. The applicant does not, however, need to accept redundant specifications, unnecessarily tight specification limits or outdated analytical methods. In cases where the applicant uses a different analytical method to the one described in the APIME, both methods should be validated. Technical specifications relevant to the FPP, which are normally not part of the specifications in the APIME (e.g. particle size), should be part of the API specifications submitted by the applicant for prequalification in its product dossier.

In cases where there is more than one supplier/manufacturer of API using one of the APIME, certificate of suitability or API prequalification procedures, there should be a core of one single set of specifications for the API presented by the applicant for prequalification that is identical for each supplier. It is acceptable to lay down in the specification more than one acceptance criterion and/or analytical method for a specific single parameter with the statement “for API from supplier X” (e.g. in the case of residual solvents).

7. Changes and updates to the APIMF

As for FPPs, APIMF holders should keep their APIMFs up to date on the actual synthesis or manufacturing process. The quality control methods should be kept in line with the current regulatory and scientific requirements. APIMF holders should not modify the contents of their APIMF (e.g. manufacturing process or specifications) without informing each applicant and WHO when a change introduced requires the filing of a variation to the product dossier. Changes in the RP of an APIMF not requiring filing of a variation, should, however, be notified to WHO. Before implementation, any change to the APIMF should be reported to WHO by every applicant by means of an appropriate variation procedure. A covering letter should be provided. In cases where the contents of the APIMF cannot be changed for a certain period of time, the APIMF holder should still provide the aforementioned data to the applicant and to WHO, making reference to this reason and requesting a later date of implementation.

The covering letter sent by the APIMF holder to WHO should contain the following information:

- a tabular list summarizing the changes carried out since the the APIMF was first compiled;
- an overview comparing the old and new content of the APIMF;
- information as to whether the change has already been accepted, rejected or withdrawn by another drug regulatory authority in the ICH-participating and associated countries;
- the names of the relevant applicants;
- the new OP and/or RP with each new version number;
- an updated Quality summary, if relevant;
- a discussion of the potential impact on the quality of the API as a result of the change(s).

Appendix 1

Template letter of access

Letter of access

Reference number of active pharmaceutical ingredient master file (given by WHO Prequalification, if known):

Manufacturing site: *(name and physical address; specify the unit, block or plot (if applicable))*

Active pharmaceutical ingredient master file holder: *(name and address)*

The aforementioned active pharmaceutical ingredient master file holder hereby authorizes the (WHO relevant staff members and external experts) to refer to and review the above-mentioned active pharmaceutical ingredient master file in support of the following Prequalification application(s) or Variation application(s) submitted by *(name of the applicant)* on *(planned date of submission)*; *(name of FPP product and prequalification code/ reference number, if known)* *(name of applicant)*

The aforementioned active pharmaceutical ingredient master file holder is committed to ensuring batch-to-batch consistency and to informing *(name of the applicant to prequalification)* and WHO of any change in the OP or RP parts of the active pharmaceutical ingredient master file.

Signature for the active pharmaceutical ingredient master file holder *(Date, name and address)*

Appendix 2

Part of covering letter to be submitted by the APIMF holder to WHO

This active pharmaceutical ingredient master file is submitted in relation to the product dossier:

(Name of the FPP in WHO Prequalification Programme for medicinal products)

(Name of applicant for Prequalification for the application concerned)

and describes (changes to) the manufacturing process and specifications of the (or one of the) active pharmaceutical ingredient(s) of this product dossier.

(Name active pharmaceutical ingredient)

The version number *(given by the APIMF holder)* of this active pharmaceutical ingredient master file is:

Open part: version *(version number)*

Restricted part: version *(version number)*

This active pharmaceutical ingredient master file has previously been submitted for assessment in relation to a product dossier for an FPP within the WHO Prequalification Programme.

(Refer to the prequalification code/reference number and name of the FPP and the FPP manufacturer.)

6.4 Procedure for prequalification of pharmaceutical products

Annex 10, WHO Technical Report Series, 961, 2011

1. Introduction	735
2. Glossary	735
3. Purpose and principles	737
4. Steps of the procedure	738
5. Invitation for expressions of interest	739
6. Data and information to be submitted	740
7. Screening of dossiers submitted	741
8. Dossier assessment	742
9. Site inspection	742
10. Reporting and communication of the results of the evaluation	744
11. Outcome of the prequalification procedure	745
12. Maintenance of prequalification status	745
13. Cost recovery	747
14. Confidentiality undertaking	747
15. Conflict of interest	748
Appendix 1 Flowchart of WHO prequalification of pharmaceutical products	749
Appendix 2 Characteristics of the prequalified pharmaceutical product to be made available for public access on the WHO web site	750

1. Introduction

The World Health Organization (WHO) provides United Nations agencies with advice on the acceptability, in principle, of pharmaceutical products for procurement by such agencies.

This activity of WHO aims to facilitate access to priority essential medicines that meet WHO-recommended norms and standards of acceptable quality. WHO undertakes a comprehensive evaluation of the quality of pharmaceutical products, based on information submitted by the manufacturers of such products or other applicants, and on an inspection of the corresponding manufacturing facilities and clinical sites. This is done through a standardized procedure which is based on WHO-recommended quality standards. The quality of pharmaceutical products is obviously crucial for the safety and efficacy of such products.

The pharmaceutical products found to meet the WHO-recommended quality standards are included in the list of medicines, as manufactured at the specified manufacturing sites, which are considered to be acceptable, in principle, for procurement by United Nations agencies. The list of prequalified pharmaceutical products is principally intended for use by United Nations agencies — including the Joint United Nations Programme on HIV/AIDS (UNAIDS), United Nations Children's Fund (UNICEF) and United Nations Population Fund (UNFPA) — to guide their procurement decisions. The growing list of pharmaceutical products that have been found to meet WHO-recommended standards may, however, also be of interest to other organizations and countries wishing to engage in the bulk procurement of pharmaceutical products.

Inclusion in the list does not imply any approval by WHO of the pharmaceutical products and manufacturing sites in question (which is the sole prerogative of national authorities). Moreover, inclusion in the list does not constitute an endorsement or warranty by WHO of the fitness of any product for a particular purpose, including its safety and/or efficacy in the treatment of specific diseases.

2. Glossary

The definitions given below apply to the terms used in this procedure. They may have different meanings in other contexts.

active pharmaceutical ingredient (API)

A substance used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings.

applicant

The person or entity who, by the deadline mentioned in the invitation, submits an expression of interest (EOI) to participate in this procedure in respect of the product(s) listed in the invitation, together with the required documentation on such product(s).

contract research organization (CRO)

An organization (commercial, academic or other) to which an applicant may have transferred some of its tasks and obligations in relation to the conduct of clinical studies with the product submitted to WHO for assessment under the current procedure.

finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labelling.

invitation for expressions of interest (EOIs) or invitation

Invitation calling upon interested parties (e.g. manufacturers or other applicants) to submit an expression of interest (EOI) to WHO by a specified deadline for the purpose of participating in the WHO prequalification procedure in respect of the product(s) listed in the invitation. Such an EOI should be accompanied by the required documentation on the product(s) in question.

manufacturer

A company that produces, packages, repackages, labels and/or relabels pharmaceutical products.

pharmaceutical product

Any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in human beings, or with a view to making a medical diagnosis in human beings, or to restoring, correcting or modifying physiological functions in human beings.

prequalification

Standardized quality assessment procedure of WHO to evaluate the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies. Agencies using information resulting from the prequalification procedure should perform additional steps of qualification prior to purchasing, such as ensuring financial stability and standing of the supplier, ability to supply the required quantities, security of the supply chain, preshipment quality control and other related aspects.

stringent regulatory authority (SRA)

For the purpose of this procedure, a stringent regulatory authority (SRA) is:

- the medicines regulatory authority in a country which is: (a) a member of the International Conference on Harmonisation (ICH) (European Union (EU) Japan and the United States); or (b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by SwissMedic and Health Canada (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time); and
- only in relation to good manufacturing practices (GMP) inspections: a medicine regulatory authority that is a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) as specified at <http://www.picscheme.org>.

3. Purpose and principles

The purpose of this WHO procedure is to evaluate whether certain pharmaceutical products (considered by WHO to be vital for the prevention and treatment of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), tuberculosis, malaria and other diseases, or for reproductive health) meet the requirements recommended by WHO and are manufactured in compliance with current good manufacturing practices (hereinafter referred to as GMP).

This procedure established by WHO is based on the following principles:

- the medicines eligible for prequalification are listed in invitations for EOI published on the WHO web site (<https://extranet.who.int/prequal/medicines/fpps-apis-eligible-prequalification-eois>);
- a general understanding of the production and quality control activities of the manufacturer;
- assessment of pharmaceutical product data and information on safety, efficacy and quality submitted by the manufacturer, including product formulation, manufacture and test data and results;
- inspection of finished pharmaceutical product (FPP) and active pharmaceutical ingredient (API) manufacturing site(s) for compliance with GMP;
- inspection of clinical testing units or contract research organizations (CROs) performing clinical trials for compliance with current good clinical practices (hereinafter referred to as GCP) and current good laboratory practices (hereinafter referred to as GLP);
- reliance on the information supplied by stringent national medicines regulatory authorities;

- random sampling and testing of pharmaceutical products supplied;
- handling of complaints and recalls reported to WHO; and
- monitoring of complaints from agencies and countries.

WHO may collaborate with national medicines regulatory authorities (NMRAs) regarding dossier assessments and inspections. Subject to the terms of section 4 below, the prequalification of a product may also be based on approval by a stringent regulatory authority (SRA).

WHO recommends that applicants expressing interest in participation in the prequalification procedure inform the NMRAs in the country of manufacture of their intention and request them to collaborate with WHO in the quality assessment process. It is recommended that applicants provide the NMRAs with the necessary authorization to discuss the relevant product files with WHO representatives during dossier assessment and site inspections (subject to appropriate confidentiality provisions, if necessary).

4. Steps of the procedure

WHO undertakes a comprehensive evaluation of the quality of pharmaceutical products, based on information submitted by the applicants, and inspection of the relevant manufacturing and clinical sites. (A flowchart showing the prequalification process is provided in Appendix 1.)

At regular intervals, and also taking into consideration pertinent input received from relevant United Nations agencies, WHO will publish an invitation to interested parties, requesting them to voluntarily participate in this procedure in respect of the products mentioned in the invitation.

By submitting an EOI, the applicant undertakes to share information with WHO on all relevant aspects of manufacture and control of the specified products along with changes made and/or planned. Interested applicants provide the necessary information to WHO by submitting a product dossier in the prescribed format, and other information as requested.

The procedure will normally include:

- assessment of product dossiers, which must include product data and information as specified in the guidelines for submission, available on the WHO web site (<http://apps.who.int/prequal/>);
- inspection of manufacturing sites of FPPs and active pharmaceutical ingredients (APIs), to assess compliance with GMP;
- inspection of clinical sites (if applicable), to assess compliance with GCP and GLP as appropriate.

If the evaluation above demonstrates that a product and its corresponding manufacturing (and clinical) site(s) meet WHO-recommended standards, the product

will be included in the list of pharmaceutical products that are considered to be acceptable, in principle, for procurement by United Nations agencies.

WHO reserves the right to terminate the evaluation of a specific product if the applicant is not able to provide the required information, and/or is unable to implement any corrective actions which WHO may require within a specified time period, or when the information supplied is inadequate to complete this procedure.

WHO recognizes the evaluation of relevant products by SRAs which apply standards for quality equivalent to those recommended by WHO. Provided that the NMRA is willing to share certain information with WHO on the products in question, WHO will consider such products for inclusion in the list of WHO-prequalified products. It will do so as and when information about such products becomes available to WHO and when the holders of the regulatory approval of such products express their interest in having these products prequalified by WHO. These products will be added to the list of products prequalified by WHO, on the basis of the scientific assessment and inspections conducted by the regulatory authority concerned, and the exchange of relevant information between the regulatory authority and WHO.

An inspection of a manufacturer or CRO may not be required if:

1. There has been an inspection by an SRA; and
2. The inspection was conducted within the last three years; and
3. Information on the inspection (including inspection report and responses to any deficiencies) is available for review by WHO; and
4. Based on this and other available information, it is determined¹ that the site(s) in question meet(s) the applicable WHO-recommended standards.

With a view to coordinating inspection activities, avoiding duplication and promoting information sharing without prejudice to the protection of any confidential and or proprietary information of the applicants and manufacturers in accordance with the terms of this procedure, WHO may disclose inspection related information to regulatory authorities of WHO Member States as well as to regulatory authorities that are members of the PIC/S.

5. Invitation for expressions of interest

The pharmaceutical products listed in an invitation for EOIs are considered by WHO to be vital for the effective treatment and prevention of the specified diseases (including

¹ Taking into account any known specific risk(s) associated with the product(s), the results of previous inspections conducted by WHO or an SRA, any complaints (if known), the scope and detail of the inspection report, the number and type of any GMP deficiencies reported, the comprehensiveness of the manufacturer's response and the timelines for implementation of corrective action(s).

HIV/AIDS, malaria and tuberculosis) or for reproductive health. These products are normally included in either the WHO Model List of Essential Medicines or the relevant WHO treatment guidelines and recommendations (or both).

The products included in the WHO Model List of Essential Medicines are those that satisfy the priority health-care needs of a population. They are selected, among other criteria, on the basis of disease prevalence, evidence on efficacy and safety, and analysis of comparative cost-effectiveness. Products included in WHO treatment guidelines are selected on the basis of an assessment of the evidence for benefits, risks, costs and appropriateness for use in a variety of situations, taking into account the needs of special populations and the values and preferences of the groups (professional and patient) using them.

Each invitation will be open and transparent, inviting all relevant parties to submit an EOI for the pharmaceutical products listed. Such an invitation will normally be published on the WHO web site and possibly also through other media, such as the international press.

In situations of high public health concern as determined by WHO, the Organization may also directly invite relevant parties to submit specified product dossiers for evaluation by WHO under this procedure without publication of an invitation for EOI.

6. Data and information to be submitted

Interested parties are expected to submit documentation on the pharmaceutical products as called for in the invitation for EOIs. Applicants should submit their product dossiers with the required information to the WHO focal point, before the deadline specified in the invitation. Guidance and instructions developed for the submission of the dossiers are made available on the WHO web site.

Normally the applicants who participate in the WHO prequalification scheme for pharmaceutical products are the manufacturers of the FPPs, as specified in the invitations for EOIs. In the case that an applicant is not the manufacturer of the FPP, all relevant documentation, including (but not limited to) contract manufacturing documentation, should be submitted, demonstrating that the applicant is in full control of the manufacturing process for, and quality assurance of, the products submitted for prequalification.

In submitting an EOI for product evaluation, the applicant should send the following to the WHO focal point:

- a covering letter, expressing interest in participating in the WHO prequalification procedure and confirming that the information submitted in the product dossier is complete and correct;
- a product dossier, in the format specified in the WHO guidance documents on submitting product data and information;

- product samples, to enable visual examination and chemical and pharmaceutical analysis;
- a site master file (SMF) for each manufacturing site listed in the product dossier, in the format specified in the WHO guidance documents for submitting an SMF; and
- a contract research organization master file (CROMF) for each clinical site listed in the dossier, in the format specified in the WHO guidance documents for submitting a CROMF.

All documentation should be submitted in English.

For the purposes of this procedure, different requirements for documentation to be submitted apply to the following categories of products:

- multisource (generic) FPPs to be assessed by WHO;
- innovator FPPs approved by SRAs; and
- multisource (generic) FPPs approved by SRAs.

The documentation requirements for each of the above categories can be found on the WHO web site at: <https://extranet.who.int/prequal/medicines/guidance-documents>. These requirements may be revised from time to time.

Multisource generic products must be shown, either directly or indirectly, to be therapeutically equivalent to the comparator product if they are to be considered interchangeable. WHO will maintain and make public the list of comparator products for this purpose. The WHO web site provides guidance on the evidence needed for a product to be considered equivalent without the need for in vivo equivalence studies (i.e. application of biowaiver).

If considered necessary or desirable by either party, and before the actual evaluation process starts, a discussion may be held between the manufacturer and WHO. This meeting should be scheduled as early as possible with a predefined agenda to address questions sent in advance to WHO by the manufacturer.

7. Screening of dossiers submitted

Each product dossier submitted by an applicant will be screened for completeness before being evaluated. Dossiers submitted for products which are not listed in an invitation for EOIs or have not otherwise been invited by WHO will not be accepted for assessment.

Similarly WHO will not consider dossiers that are incomplete. The applicant will be informed that an incomplete dossier has been received and will be requested to complete the dossier within a specified time period. In the event of non-compliance, the dossier may be rejected on grounds of incompleteness and returned to the applicant. Dossiers that are considered complete as the result of the screening will be retained by WHO for assessment.

After screening, if the dossier is accepted for assessment the applicant will be informed of this, including the dossier reference number, by letter. This letter will serve as an agreement between WHO and the applicant for the participation in prequalification and a commitment to comply with the provisions of the prequalification procedure.

8. Dossier assessment

The product information submitted in the dossiers will be assessed by teams of experts (assessors) appointed by WHO. The assessors involved in dossier assessment must have the relevant qualifications and experience in the fields of pharmaceutical development, quality assessment of pharmaceutical products, quality assurance, biopharmaceutics and other relevant fields. The assessors will be appointed in accordance with a standard operating procedure (SOP) established by WHO. The assessors should preferably be from NMRA and they will act as temporary advisers to WHO. The assessors must comply with the confidentiality and conflict of interest rules of WHO, as laid down in the relevant sections of this procedure.

The assessment of product dossiers will be done in accordance with SOPs established by WHO for that purpose so as to ensure uniformity in evaluation and timeliness of assessment activities. If needed, WHO may provide training to these experts.

Following the assessment of each part of the dossier, a report will be provided to the applicant. Applicants are expected to submit responses to comments and any additional information that may be requested as soon as possible. Within one month, the applicant should inform WHO of the estimated time frame required to address and respond to all queries. The procedure is usually suspended (i.e. WHO will not undertake any further action) until all required responses and any additional information is received by WHO.

Each applicant may request a hearing or meeting with the WHO experts involved in the assessment of this applicant's dossier to clarify issues identified by the WHO experts. WHO may provide technical assistance to applicants regarding appropriate product information to be submitted as well as production and control requirements.

9. Site inspection

WHO will plan and coordinate, in accordance with SOPs established by WHO and based on quality risk management (QRM) principles, the performance of inspections of the site(s) of manufacture of the API(s) and the FPP, and of the clinical testing units or CROs.

The following factors will be taken into account when planning inspections:

- the results of previous inspection(s) by WHO or an SRA, and history of compliance of the company or facility with GMP, GCP and or GLP as appropriate;

- the outcome of the assessment of data submitted to WHO;
- complexity of the site, processes and product;
- number and significance of known quality defects (e.g. complaints, recalls);
- major changes to, e.g. buildings, equipment, processes, key personnel;
- site experience with manufacturing and testing of a product; and
- test results of official control laboratories.

The inspections of the manufacturing site(s) are conducted to assess compliance with GMP as recommended by WHO and include data verification. SMFs submitted by the applicant will be reviewed before an inspection is performed.

The inspections of clinical testing units or CROs are carried out to assess compliance with GCP and GLP, and to perform data verification.

The WHO norms and standards applicable to inspections of APIs and FPPs, and of clinical testing units or CROs, can be found on the WHO web site at <https://extranet.who.int/prequal/inspection-services/medicines>. These requirements may be revised from time to time.

The inspections will be performed by a team of inspectors usually including experts appointed by WHO, preferably from NMRA inspectorates, who will act as temporary advisers to WHO. The inspectors must have the relevant qualifications and experience to perform such inspections, be competent in areas such as production and quality control of pharmaceuticals, and have appropriate experience in GMP and GCP or GLP. The inspectors must comply with the confidentiality and conflict of interest rules of WHO, as laid down in the relevant sections of this procedure. If needed, WHO may provide training to these experts.

A WHO staff member will coordinate the team and will normally lead the inspection team. Each team will perform the inspections and report its findings to WHO in accordance with SOPs established by WHO for that purpose so as to ensure a standard harmonized approach. A representative of the NMRA of the country of manufacture would normally be expected to accompany the team to the manufacturing and testing facilities to assess the compliance with GMP and GCP or GLP.

In accordance with SOPs established by WHO and based on QRM principles, an on-site inspection by a WHO inspection team may be waived provided that the site in question is found to meet the applicable WHO- recommended standards following a desk review of requested inspection reports, the manufacturers response(s) to the relevant inspectorate describing corrective actions to any deficiencies identified in the inspection reports and an acceptable product quality review report for the identified product(s).

10. Reporting and communication of the results of the evaluation

Each assessment and inspection team will finalize its reports according to the established WHO SOP and format, describing the findings and including recommendations to the applicant, manufacturer(s) and/or CROs where relevant.

The findings from the dossier assessment including, but not limited to, deficiencies of the documentation and data submitted, shall be communicated in writing to the applicant requesting submission of the missing data and information, as appropriate.

The inspection report will be communicated to the manufacturer or CRO as applicable. With the written agreement of the manufacturer or CRO, a copy of the inspection report may also be provided to the applicant (if other than the manufacturer or CRO). If any additional information is required, or corrective action has to be taken by the manufacturer or CRO, WHO will postpone its decision on the acceptability of the site(s) concerned until such information has been evaluated or the corrective action has been taken and found satisfactory in light of the specified standards.

WHO reserves the right to terminate this procedure for a specific product if the applicant is not able to provide the required information or implement the corrective actions within a specified time period, or if the information supplied is inadequate to complete this procedure.

In the event of any disagreement between an applicant and WHO, an SOP established by WHO for the handling of such disagreements will be followed to discuss and resolve the issue.

As WHO is responsible for the prequalification procedure, the ownership of the reports lies with WHO. Thus, WHO shall be entitled to use and publish such reports subject always, however, to the protection of any commercially sensitive confidential information of the applicant, manufacturer(s) and/or testing organization(s). “Confidential information” in this context means:

- confidential intellectual property, know-how and trade secrets (including, e.g. formulas, processes or information contained or embodied in a product, unpublished aspects of trade marks, patents, etc.); and
- commercial confidences (e.g. structures and development plans of a company).

Provisions of confidentiality will be contained in the exchange of letters, to be concluded before the assessment of the product dossier or inspection of the manufacturing and clinical sites, between WHO and each applicant, manufacturer or CRO.

Notwithstanding the foregoing, WHO reserves the right to share the full assessment and inspection reports with the relevant authorities of any interested Member State of the Organization and interested United Nations agencies.

11. Outcome of the prequalification procedure

Once WHO is satisfied that this procedure is complete for the relevant product, and that the WHO-recommended standards are met, the product, as manufactured at the specified manufacturing site(s), will be included in the list of prequalified pharmaceutical products. The list of prequalified pharmaceutical products will be compiled in accordance with an SOP established by WHO for final decision-making on inclusion in the list. The list will be published on the WHO web site and will specify the characteristics of the prequalified pharmaceutical products, as described in Appendix 2 to this procedure.

Each applicant will receive a letter of prequalification from WHO informing it of the outcome of the quality assessment process in regard of the submitted product(s). Once the product(s) are included in the list of prequalified pharmaceutical products, the applicant shall be responsible for keeping WHO continuously updated on all relevant aspects of the manufacture and control of such product(s) and to meet any requirements, as agreed with WHO.

In accordance with World Health Assembly Resolution WHA57.14 of 22 May 2004, WHO will — subject to the protection of any commercially sensitive confidential information — publish WHO Public Assessment Reports (WHOPAR(s)) on the product dossier assessments and WHO Public Inspection Reports (WHOPIR(s)) on the manufacturers and CROs, that were found to be in compliance with WHO-recommended guidelines and standards. These reports will be published on the WHO web site. Subject always to the protection of commercially sensitive confidential information, WHO shall also be entitled to publish negative evaluation outcomes in accordance with SOPs established by WHO. These include notices of concern as well as notices of suspension.

The decision to list a pharmaceutical product is made based upon information available to WHO at that time, i.e. information in the submitted dossier and on the status of GMP, GLP and GCP at the facilities used in the manufacture and testing of the product at the time of the site inspection(s) conducted by WHO or at the time of the site inspection(s) conducted by an SRA, the outcome of which has been determined by WHO to meet the applicable WHO-recommended standards, in accordance with the terms of this procedure. This decision is subject to change on the basis of new information that may become available to WHO. If serious safety and/ or quality concerns arise in relation to a prequalified product, WHO may delist the product after evaluation of the new evidence and a risk–benefit assessment, or may suspend the product until results of further investigations become available and are evaluated by WHO.

12. Maintenance of prequalification status

Applicants are required to communicate details to WHO of any changes (variations) in manufacture and control that may have an impact on the safety, efficacy and quality of the product.

Guidance on variations to prequalified dossiers as can be found on the WHO web site at <https://extranet.who.int/prequal/medicines/guidance-documents>. These requirements may be revised from time to time.

It is the applicant's responsibility to provide WHO with the appropriate documentation (referring to relevant parts of the dossier) to prove that any intended or implemented variation will not have a negative impact on the quality of the product that has been prequalified. WHO will undertake an evaluation of variations according to the established WHO guidelines and SOPs and communicate the outcome to the applicant within the prescribed time lines. Adherence to the reporting requirements will be verified during the inspections carried out by WHO.

Random samples of prequalified products supplied by listed manufacturers or applicants will be taken for independent testing of final product characteristics. Certificates of analysis of final products released by the manufacturer and specifications for test methods should be provided by the manufacturer or applicant to WHO for review upon request. In the event of failure to meet the established criteria for testing, WHO will investigate the problem and communicate the outcome of this investigation to the manufacturer and applicant, if other than the manufacturer.

Complaints concerning prequalified pharmaceutical products communicated to WHO will be investigated in accordance with an SOP established by WHO for that purpose. After investigation, WHO will provide a written report of the problem and include recommendations for action where relevant. WHO will make the report available to the applicant/manufacturer, and to the NMRA of the country where the manufacturing site is located. Subject always to the protection of commercially sensitive information as referred to above, WHO shall be entitled to make such reports public. In addition, WHO reserves the right to share the full report with the relevant authorities of interested Member States of the Organization and interested United Nations agencies.

Manufacturers of prequalified pharmaceutical products and associated API manufacturers will be re-inspected at regular intervals as determined by WHO, but normally at least once every three years. Re-inspections are conducted to verify compliance with GMP as recommended by WHO and include data verification.

Furthermore, in order to maintain their prequalification status, WHO will arrange for prequalified pharmaceutical products to be requalified at regular intervals.

Every five years from the date of prequalification, or when requested to do so by the WHO Prequalification of Medicines Programme, the holder of a prequalified product is required to submit data and information in relation to the product to WHO for assessment. The purpose of this assessment is to verify that the product conforms to information and data submitted in relation to prequalification, conforms to current norms and standards, and to verify the consistency of the quality of the product and its manufacturing process(es) over the identified period.

The procedure and guidelines on the requalification of prequalified products can be found on the WHO web site at <https://extranet.who.int/prequal/medicines/guidance->

documents. These requirements may be revised from time to time. Re-inspection and/or requalification may also be performed:

- if any fraud or omissions by the applicant, manufacturer(s) of an FPP or API, or CROs in the initial assessment procedure or during the follow-up activities, become evident; and
- if WHO or any United Nations agency considers that a batch or batches of supplied prequalified pharmaceutical products are not in compliance with the specifications which were found to be applicable upon prequalification

If, as a result of re-inspection or requalification, it is found that a product and/or specified manufacturing site no longer complies with the WHO-recommended standards, such products and manufacturing sites may be suspended or removed from the list of prequalified pharmaceutical products. Failure of a manufacturer or applicant to participate in re-inspection or requalification (as applicable) may also lead to suspension or removal from this list.

13. Cost recovery

WHO reserves the right to charge for this procedure on a cost-recovery basis.

14. Confidentiality undertaking

The assessors and inspectors will treat all information to which they will gain access during the assessments and inspections, or otherwise in connection with the discharge of their responsibilities in regard to the above-mentioned project, as confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set forth below.

Assessors and inspectors will take all reasonable measures to ensure that confidential information:

- is not used for any purpose other than the assessment/inspection activities described in this document; and
- is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

Assessors and inspectors will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

- was known to them prior to any disclosure by or on behalf of WHO (including by manufacturers); or

- was in the public domain at the time of disclosure by or on behalf of WHO (including by manufacturers); or
- has become part of the public domain through no fault of theirs; or
- has become available to them from a third party not in breach of any legal obligations of confidentiality.

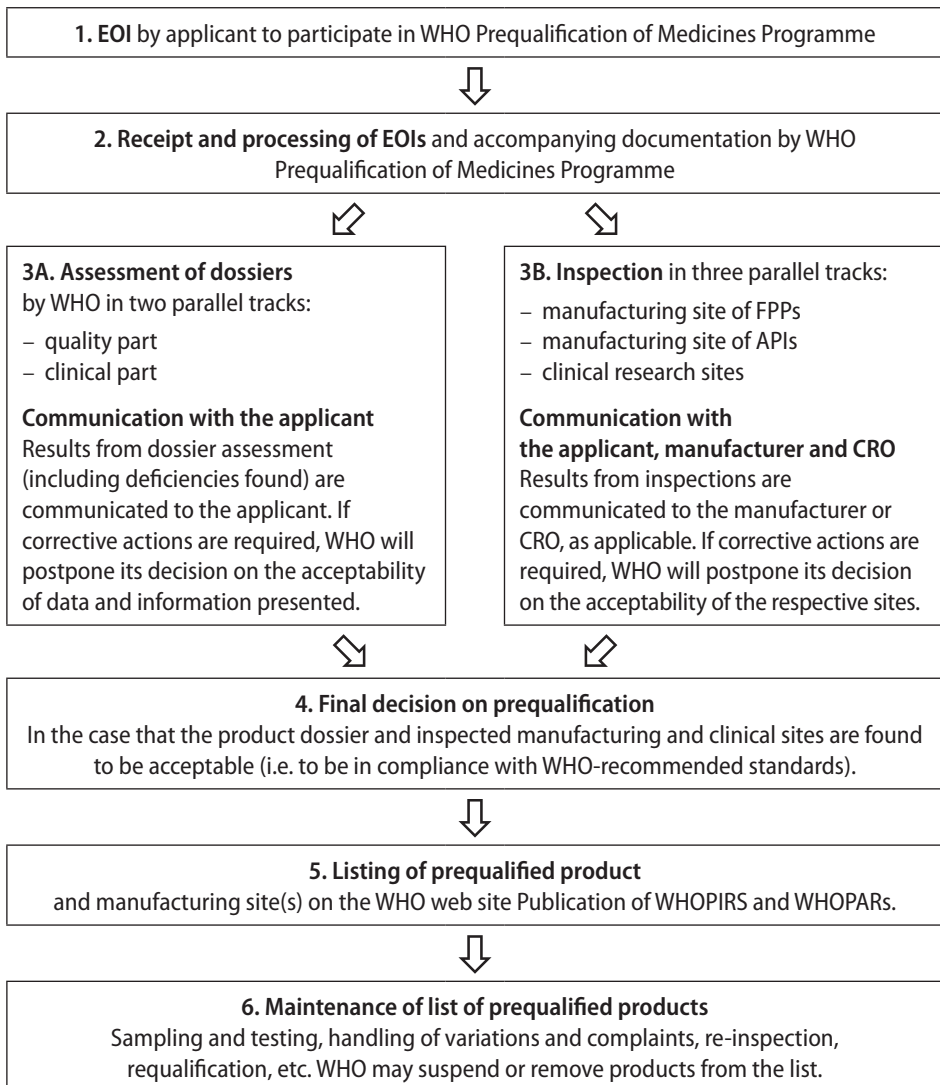
15. Conflict of interest

Before undertaking the work, each assessor and inspector will also (in addition to the above-mentioned confidentiality undertaking) be required to sign a declaration of interest. If, based on this declaration of interest, it is felt that there is no risk of a real or perceived conflict of interest (or it is felt that there is only an insignificant and/or irrelevant conflict of interest), and it is thus deemed appropriate for the assessor or inspector in question to undertake this work, he/she will discharge his/her functions exclusively as adviser to WHO. In this connection, each assessor and inspector is required to confirm that the information disclosed by him/her in the declaration of interest is correct and complete, and that he/she will immediately notify WHO of any change in this information.

All inspectors furthermore agree that, at the manufacturer's or CRO's request, WHO will advise the manufacturer or CRO, in advance, of the identity of each inspector and the composition of the team performing the site inspection, and provide curricula vitae of the inspectors. The manufacturer or CRO then has the opportunity to express possible concerns regarding any of the inspectors to WHO before the visit. If such concerns cannot be resolved in consultation with WHO, the manufacturer or CRO may object to a team member's participation in the site visit. Such an objection must be made known to WHO by the manufacturer or CRO within 10 days of receipt of the proposed team composition. In the event of such an objection, WHO reserves the right to cancel all or part of its agreement with, and the activities to be undertaken by, that inspector.

Appendix 1

Flowchart of WHO prequalification of pharmaceutical products



EOI, expression of interest; FPP, finished pharmaceutical product; API, active pharmaceutical ingredient; CRO, contract research organization; WHOPIR, public inspection report; WHOPAR, public assessment report.

Appendix 2

Characteristics of the prequalified pharmaceutical product to be made available for public access on the WHO web site

- WHO product reference number
- International Nonproprietary Name (INN) of active pharmaceutical ingredient(s) (API(s))
- dosage form and strength
- trade name(s) of the product (if applicable)
- name of applicant and official address
- name of manufacturer of finished pharmaceutical product (FPP)
- physical address of manufacturing site(s) (and unit, if applicable)
- name of API manufacturer, physical address of manufacturing site(s) (and unit, if applicable)
- product description (as in FPP specifications, i.e. coated, scored, etc.)
- pack size(s), primary and secondary packaging material(s)
- storage conditions
- shelf-life (provisional, if applicable)
- summary of product characteristics
- package leaflet
- labelling

6.5 Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality parts

Annex 4, WHO Technical Report Series, 970, 2012

1. Introduction	752
1.1 Background	752
1.2 Objectives	752
1.3 Scope	753
1.4 General principles	753
1.5 Guidance on format	754
2. Glossary	755
3. Quality summaries	757
3.1 Module 2.3: Quality overall summary – product dossiers (QOS-PD)	757
3.2 Module 1.4.2: Quality information summary (QIS)	758
4. Module 3: Quality	759
4.1 Table of contents of Module 3	759
4.2 Body of data	759
3.2.S Drug substance (or active pharmaceutical ingredient, API)	759
3.2.P Drug product (or finished pharmaceutical product (FPP))	785
3.2.A Appendices	811
3.2.R Regional information	812
4.3 Literature references	813
References	813
Appendix 1 Recommendations for conducting and assessing comparative dissolution profiles	818
Appendix 2 Product quality review requirements for <i>established multisource products</i>	820

1. Introduction

1.1 Background

The *Procedure for prequalification of pharmaceutical products* (1) outlines the procedure and considerations for the process undertaken by WHO in providing United Nations agencies with advice on the acceptability, in principle, of pharmaceutical products for procurement by such agencies. It states:

“This activity of WHO aims to facilitate access to priority essential medicines that meet WHO-recommended norms and standards of acceptable quality.”

As mentioned in WHO Technical Report Series, No. 961 (1), in submitting an expression of interest (EOI) for product evaluation, the applicant should send a product dossier (PD) to the WHO focal point (together with the other data required), in the format specified in the WHO guidance documents on submitting product data and information.

Through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) process, considerable harmonization has been achieved on the organization for the Quality module of the registration documents with the issuance of the *Common technical document (CTD) – quality (ICH M4Q)* guideline (2). This format, recommended in the M4Q guideline for the quality information of registration applications, has become widely accepted by regulatory authorities both within and beyond the ICH regions.

The current document provides recommendations on the quality information for active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs) that should be submitted to WHO to support PDs.

Alternative approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. It is also important to note that the WHO Prequalification of Medicines Programme may request information or material, or define conditions not specifically described in this guidance, in order to adequately assess the quality of a pharmaceutical product.

1.2 Objectives

These guidelines are intended to:

- assist applicants in the preparation of the Quality Module of PDs for multisource products by providing clear general guidance on the format of these dossiers;
- fully adopt the modular format of the *Common technical document – quality (M4Q)* (2) as developed by ICH;

- provide guidance on the technical and other general data requirements.

These measures are intended to promote effective and efficient processes for the development of these PDs by applicants and for the subsequent assessment procedures by WHO.

1.3 Scope

These guidelines apply to PDs for multisource pharmaceutical products containing existing APIs of synthetic or semi-synthetic origin. For the purposes of these guidelines, an existing API is one that has been previously approved through a finished product by a stringent regulatory authority (SRA)¹ or by WHO. Fermentation, biological, biotechnological and herbal APIs are covered by other guidelines.

1.4 General principles

To facilitate the preparation of the PD, these guidelines are organized in accordance with the structure of the ICH *Common technical document – quality (M4Q)* guideline (2).

The text of the M4Q (CTD-Q) guideline (2) has been restated verbatim in these guidelines in **bold text**, with minor modifications to accommodate WHO terminology and to include certain text that would be appropriate for multisource pharmaceutical products, notably:

- “Drug substance” is replaced with “active pharmaceutical ingredient” or “API”.
- “Drug product” is replaced with “finished pharmaceutical product” or “FPP”.
- “Application” is replaced with “product dossier” or “PD”.
- “Combination product” is replaced with “fixed-dose combination” or “FDC”.
- “Clinical batches” is replaced with “comparative bioavailability” or “biowaiver batches”.

Additional guidance by WHO, following the **bold text** reproduced from the M4Q (CTD-Q) guideline (2), is printed in plain text to make it easily distinguishable from the ICH text and is included to provide further clarity on WHO’s expectations for the content of PDs. This approach is intended to facilitate the identification and origin of the text in these guidelines (i.e. from ICH or from WHO).

¹ A stringent regulatory authority (SRA): a regulatory authority which is:

- a member of the International Conference on Harmonisation (ICH) (as specified on www.ich.org); or
- an ICH observer, being the European Free Trade Association (EFTA), as represented by SwissMedic, and Health Canada (as may be updated from time to time); or
- a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

The content of these guidelines should be read in conjunction with relevant information described in other existing WHO or ICH reference documents and guidelines. The quality of existing APIs and corresponding multisource products should not be inferior to new APIs and innovator (comparator) FPPs. Therefore, the principles of the ICH guidelines that are referenced throughout this document and in other WHO guidelines may equally apply to existing APIs and multisource products.

Scientific literature may be appropriate to fulfil the requirements for some of the information or parameters outlined in these guidelines (e.g. qualification of specified identified impurities). Furthermore, the requirements outlined in certain sections may not be applicable to the proposed API or FPP. In these situations, either a summary and the full reference to the scientific literature should be provided, or the non-applicability of the requested information should be clearly indicated with an accompanying explanatory note.

1.5 Guidance on format

The recommendations outlined in the WHO general filing guideline *Guidelines on submission of documentation for a multisource (generic) finished product: general format: preparation of product dossiers in common technical document format* (3) should be followed for the format and presentation of the PD.

There may be a number of instances where repetition of sections can be considered appropriate. Whenever a section is repeated, it should be made clear what the section refers to by creating a distinguishing title in parentheses following the M4Q (CTD-Q) guideline heading, e.g. 3.2.S Drug substance (or API) (name, Manufacturer A).

The following are recommendations for the presentation of the information in the Quality module for different scenarios that may be encountered:

- The Open part (non-proprietary information) of each APIMF should always be included *in its entirety* in the PD, as an annex to 3.2.S.
- For an FPP containing more than one API, one complete “3.2.S” section should be provided for one API, *followed by* another complete “3.2.S” section for each of the other APIs.
- For an API from multiple manufacturers, one complete “3.2.S” section should be provided for the API from one manufacturer, *followed by* another complete “3.2.S” section for the API from each of the other API manufacturers.
- For an FPP with multiple strengths (e.g. 10, 50, 100 mg) one complete “3.2.P” section should be provided with the information for the different strengths provided *within* the subsections. One complete copy of the PD should be provided for each FPP strength.

- For an FPP with multiple container-closure systems (e.g. bottles and unit dose blisters) one complete “3.2.P” section should be provided with the information for the different presentations provided *within* the subsections.
- For multiple FPPs (e.g. tablets and a parenteral product) a separate dossier is required for each FPP.
- For an FPP supplied with reconstitution diluent(s) one complete “3.2.P” section should be provided for the FPP, *followed by* the information on the diluent(s) in a separate part “3.2.P”, as appropriate.
- For a co-blistered FPP one complete “3.2.P” section should be provided for each product.

2. Glossary

The definitions provided below apply to the words and phrases used in these guidelines. Although an effort has been made to use standard definitions as far as possible, they may have different meanings in other contexts and documents. The following definitions are provided to facilitate interpretation of the guidelines.

active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form, and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

active pharmaceutical ingredient (API) starting material

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house (ICH Q7). See also *starting materials for synthesis*.

applicant

The person or entity who, by the deadline mentioned in the invitation, submits an expression of interest (EOI) to participate in this procedure in respect of the product(s) listed in the invitation, together with the required documentation on such product(s).

Biopharmaceutics Classification System (BCS) highly soluble

An API for which the highest dose recommended by WHO (if the API appears on the WHO Model list of essential medicines) or highest dose strength available on the market as an oral solid dosage form (if the API does not appear on the WHO Model list of

essential medicines) is soluble in 250 ml or less of aqueous media over the pH range of 1.2–6.8 at 37 °C.

commitment batches

Production batches of an API or FPP for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application.

comparator product

A pharmaceutical product with which the generic product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established. For the Prequalification of Medicines Programme, the selection of the comparator product is based on the information presented under Guidance on bioequivalence studies available on the Prequalification web site.

established multisource (generic) product

A multisource product that has been marketed by the applicant or manufacturer associated with the dossier for at least five years and for which at least 10 production batches were produced over the previous year, or, if less than 10 batches were produced in the previous year, not less than 25 batches were produced in the previous three years.

existing API

An API that is not considered a new active substance, which has been previously approved through a finished product by a stringent regulatory authority or by WHO, but requires the filing of a dossier. This would include, for example, new PDs and variations to multisource products.

finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product which has undergone all stages of manufacture, including packaging in its final container and labelling.

innovator pharmaceutical product

Generally the pharmaceutical product that was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality.

manufacturer

A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals.

multisource (generic) pharmaceutical products

Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

officially recognized pharmacopoeia (or compendium)

Those pharmacopoeias recognized in the WHO Prequalification of Medicines Programme (i.e. *British Pharmacopoeia* (BP), *European Pharmacopoeia* (Ph.Eur.), *The International Pharmacopoeia* (Ph.Int.), *Japanese Pharmacopoeia* (JP) and *United States Pharmacopoeia* (USP)).

ongoing stability study

The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected retest period (or shelf-life) of the API, or confirm or extend the shelf-life of the FPP.

pilot-scale batch

A batch of an API or FPP manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger; unless otherwise adequately justified.

primary batch

A batch of an API or FPP used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf-life. For the WHO Prequalification of Medicines Programme, primary batch requirements are outlined in 3.2.S.7.1 and 3.2.P.8.1 for the API and FPP, respectively.

production batch

A batch of an API or FPP manufactured at production scale by using production equipment in a production facility as specified in the application.

starting materials for synthesis

Materials that mark the beginning of the manufacturing process as described in an application or in an API master file (APIMF). A starting material for a synthetic API is a chemical compound of defined molecular structure that contributes to the structure of the API. See also *API starting material*.

3. Quality summaries

3.1 Module 2.3: Quality overall summary – product dossiers (QOS-PD)

The Quality overall summary (QOS) is a summary that follows the scope and the outline of the Body of data in Module 3. The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the CTD.

The QOS should include sufficient information from each section to provide the Quality assessor with an overview of Module 3. The QOS should also emphasize critical key parameters of the product and provide, for instance, justification in cases where guidelines were not followed. The QOS should include a discussion of key issues that integrates information from sections in the Quality module and supporting information from other Modules (e.g. qualification of impurities via toxicological studies), including cross-referencing to volume and page number in other Modules.

The WHO *Quality overall summary – product dossiers (QOS-PD)* template should be completed for multisource pharmaceutical products containing APIs of synthetic or semi-synthetic origin (see 1.3 Scope for further clarification) and their corresponding FPPs.

All sections and fields in the QOS-PD template that would be applicable should be completed. It is understood that certain sections and fields may not apply and should be indicated as such by reporting “not applicable” in the appropriate area with an accompanying explanatory note.

The use of tables to summarize the information is encouraged where possible. The tables included in the template may need to be expanded or duplicated (e.g. for multiple strengths). These tables are included as illustrative examples of how to summarize information. Other approaches can be used to summarize the information if they fulfil the same purpose.

3.2 Module 1.4.2: Quality information summary (QIS)

The QIS template should be completed to provide a condensed summary of the key quality information for the PD and constitutes part of the submission package. The QIS provides an accurate record of technical data in the PD at the time of prequalification. The QIS is a condensed version of the QOS-PD and represents the final agreed-upon key information on the API and FPP from the PD assessment (including, but not limited to, identification of the manufacturer(s), site addresses, API/FPP specifications, stability conclusions and relevant commitments).

The QIS template is structured according to the numbering and section headings of the ICH M4Q (CTD-Q) guideline to permit the rapid assembly of the QIS by copying the requisite information from the corresponding portions of the QOS-PD filed with the PD. It is acknowledged that the numbering of the sections in the QIS may not be entirely sequential. Those sections not considered necessary for inclusion in the QIS have been removed (e.g. 2.3.S.5 Reference standards or materials) and the remaining sections have retained their original numbering to maintain consistency with the original PD.

The QIS will serve as an official reference document in the course of good manufacturing practices (GMP) inspections, variation assessments and requalification assessments as performed by WHO.

4. Module 3: Quality

4.1 Table of contents of Module 3

A Table of contents for the filed product dossier should be provided.

4.2 Body of data

3.2.S Drug substance (or active pharmaceutical ingredient, API)

There are four options for submitting the API information to WHO:

- Option 1: confirmation of API prequalification document;
- Option 2: Certificate of Suitability of the *European Pharmacopoeia* (Ph.Eur.) (CEP); or
- Option 3: active pharmaceutical ingredient master file (APIMF) procedure; or
- Option 4: full details in the PD.

The applicant should clearly indicate at the beginning of the API section (in the PD and in the QOS-PD) how the information on the API for each API manufacturer is being submitted. The API information submitted by the applicant or FPP manufacturer should include the following according to the options used.

- *Option 1: Confirmation of API prequalification document.*

A complete copy of the Confirmation of API prequalification document should be provided in Module 1, together with the duly filled out authorization box in the name of the FPP manufacturer or applicant.

The applicant should supply the following information in the dossier, with data summarized in the QOS-PD.

- 3.2.S.1.3 *General properties* – discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the API manufacturer's specifications, e.g. solubilities and polymorphs according to the guidance in this section.
- 3.2.S.2 – if the sterility of the FPP is based upon the sterile manufacture of the API then data on the sterilization process together with full validation data should be provided.
- 3.2.S.3.1 *Elucidation of structure and other characteristics* – studies to identify polymorphs and particle size distribution, where applicable, according to the guidance in this section.
- 3.2.S.4.1 *Specification* – the specifications of the FPP manufacturer including all tests and limits of the API manufacturer's specifications

and any additional tests and acceptance criteria that are not controlled by the API manufacturer's specifications such as polymorphs and/or particle size distribution.

- 3.2.S.4.2/3.2.S.4.3 *Analytical procedures and validation* – any methods used by the FPP manufacturer in addition to those in the API manufacturer's specifications.
- 3.2.S.4.4 *Batch analysis* – results from two batches of at least pilot-scale, demonstrating compliance with the FPP manufacturer's API specifications.
- 3.2.S.5 *Reference standards or materials* – information on the FPP manufacturer's reference standards.
- 3.2.S.7 *Stability* – data to support the retest period if either the proposed retest period is longer or the proposed storage conditions are at a higher temperature or humidity to that of the prequalified API.

■ *Option 2: Certificate of Suitability of the European Pharmacopoeia (CEP)*

A complete copy of the CEP (including any annexes) should be provided in Module 1. The declaration of access for the CEP should be duly filled out by the CEP holder on behalf of the FPP manufacturer or applicant to the WHO Prequalification of Medicines Programme who refers to the CEP. In addition, a written commitment should be included that the applicant will inform WHO in the event that the CEP is withdrawn. It should also be acknowledged by the applicant that withdrawal of the CEP will require additional consideration of the API data requirements to support the PD. The written commitment should accompany the copy of the CEP in Module 1.

Together with the CEP, the applicant should supply the following information in the dossier, with data summarized in the QOS-PD.

- 3.2.S.1.3 *General properties* – discussions on any additional applicable physicochemical and other relevant properties of the API that are not controlled by the CEP and Ph.Eur. monograph, e.g. solubilities and polymorphs according to the guidance in this section.
- 3.2.S.3.1 *Elucidation of structure and other characteristics* – studies to identify polymorphs (except where the CEP specifies a polymorphic form) and particle size distribution, where applicable, according to the guidance in this section.
- 3.2.S.4.1 *Specification* – the specifications of the FPP manufacturer including all tests and limits of the CEP and Ph.Eur. monograph and

any additional tests and acceptance criteria that are not controlled in the CEP and Ph.Eur. monograph, such as polymorphs and/or particle size distribution.

- 3.2.S.4.2/3.2.S.4.3 *Analytical procedures and validation* – for any methods used by the FPP manufacturer in addition to those in the CEP and Ph.Eur. monograph.
- 3.2.S.4.4 *Batch analysis* – results from two batches of at least pilot-scale, demonstrating compliance with the FPP manufacturer's API specifications.
- 3.2.S.5 *Reference standards or materials* – information on the FPP manufacturer's reference standards.
- 3.2.S.6 *Container-closure system* – specifications including descriptions and identification of primary packaging components except where the CEP specifies a container-closure system and the applicant declares the intent to use the same container-closure system.
- 3.2.S.7 *Stability* – except where the CEP specifies a retest period that is the same as or longer than that proposed by the applicant, and storage conditions are the same or at a higher temperature and humidity than those proposed by the applicant.

In the case of sterile APIs, data on the process for sterilization of the API including validation data should be included in the PD.

■ *Option 3: Active pharmaceutical ingredient master file (APIMF) procedure*

Full details of the chemistry, manufacturing process, quality controls during manufacturing and process validation for the API may be submitted as an APIMF by the API manufacturer as outlined in WHO's *Guidelines on active pharmaceutical ingredient master file procedure* (4).

In such cases, the Open part (non-proprietary information) needs to be included in its entirety in the PD as an annex to 3.2.S. In addition, the applicant or FPP manufacturer should complete the following sections in the PD and QOS-PD in full according to the guidance provided unless otherwise indicated in the respective sections:

General information S.1.1–S.1.3

Manufacture S.2

Manufacturer(s) S.2.1

Description of manufacturing process and process controls S.2.2

Controls of critical steps and intermediates S.2.4

Elucidation of structure and other characteristics S.3.1

*Impurities S.3.2**Control of the API S.4.1–S.4.5**Reference standards or materials S.5**Container-closure system S.6**Stability S.7.1–S.7.3*

It is the responsibility of the applicant to ensure that the complete APIMF (i.e. both the applicant's Open part and the API manufacturer's Restricted part) is supplied to WHO directly by the API manufacturer and that the applicant has access to the relevant information in the APIMF concerning the current manufacture of the API.

A copy of the letter of access should be provided in the PD Module 1. APIMF holders can use the guidance provided for the option "Full details in the PD" for preparation of the relevant sections of the Open and Restricted parts of their APIMFs. Reference should also be made to the APIMF guidelines in WHO Technical Report Series, No. 948, Annex 4 (4).

- *Option 4: Full details in the PD*
Information on the 3.2.S *Active pharmaceutical ingredient* sections, including full details of chemistry, manufacturing process, quality controls during manufacturing and process validation for the API, should be submitted in the PD as outlined in the subsequent sections of these guidelines. The QOS-PD should be completed according to section 3.1 of these guidelines.

3.2.S.1 General information (name, manufacturer)**3.2.S.1.1 Nomenclature (name, manufacturer)**

Information on the nomenclature of the API should be provided. For example:

- (recommended) International Nonproprietary Name (INN);
- compendial name, if relevant;
- chemical name(s);
- company or laboratory code;
- other nonproprietary name(s) (e.g. national name, United States Adopted Name (USAN), British Approved Name (BAN));
- Chemical Abstracts Service (CAS) registry number.

The chemical names listed should be consistent with those appearing in the scientific literature and those appearing on the product labelling information (e.g. in the summary of product characteristics (SmPC) and package leaflet, also known as the patient information leaflet (PIL)). Where several names exist the preferred name should be indicated.

3.2.S.1.2 *Structure (name, manufacturer)*

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

This information should be consistent with that provided in section 3.2.S.1.1. For APIs existing as salts the molecular mass of the free base or acid should also be provided.

3.2.S.1.3 *General properties (name, manufacturer)*

A list should be provided of physicochemical and other relevant properties of the API.

This information can be used in developing the specifications, in formulating FPPs and in the testing for release and stability purposes.

The physical and chemical properties of the API should be discussed, including the physical description, solubilities in common solvents (e.g. water, alcohols, dichloromethane and acetone), quantitative aqueous pH solubility profile (e.g. pH 1.2–6.8, dose/solubility volume), polymorphism, pH and pKa values, ultraviolet (UV) absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity and partition coefficient (see table in the QOS-PD). This list is not intended to be exhaustive but provides an indication as to the type of information that could be included.

Some of the most relevant properties to be considered for APIs are discussed below in greater detail.

Physical description

The physical description should include appearance, colour and physical state. Solid forms should be identified as being crystalline or amorphous (see 3.2.S.3.1 for further information on API solid forms).

Solubilities and quantitative aqueous pH solubility profile

The following should be provided for all options for the submission of API data.

The solubilities in a number of common solvents should be provided (e.g. in water, alcohols, dichloromethane and acetone).

The solubilities over the physiological pH range (pH 1.2–6.8) in several buffered media should be provided in mg/ml. If this information is not readily available (e.g. from literature references), it should be generated in-house.

For solid oral dosage forms, the dose/solubility volume should be provided as determined according to the formula:

$$\text{dose/solubility volume} = \frac{\text{largest dosage strength (mg)}}{\text{the minimum concentration of the drug (mg/ml)}^*}$$

* corresponding to the lowest solubility determined over the physiological pH range (pH 1.2–6.8) and temperature (37 ± 0.5 °C).

According to the Biopharmaceutics Classification System (BCS), highly soluble (or highly water soluble) APIs are those with a dose/solubility volume of ≤ 250 ml.

For example, compound A has as its lowest solubility at $37 \pm 0.5^\circ\text{C}$, 1.0 mg/ml at pH 6.8 and is available in 100 mg, 200 mg and 400 mg strengths. This API would not be considered a BCS *highly soluble* API as its dose/solubility volume is greater than 250 ml ($400 \text{ mg}/1.0 \text{ mg/ml} = 400 \text{ ml}$).

Polymorphism

As recommended in ICH's *CTD-Q Questions and answers/location issues* document (5) the following list explains where specific data should be located in the PD:

- The polymorphic form(s) present in the proposed API should be listed in section 3.2.S.1.3.
- The description of manufacturing process and process controls (3.2.S.2.2) should indicate which polymorphic form is manufactured, where relevant.
- The literature references or studies performed to identify the potential polymorphic forms of the API, including the study results, should be provided in section 3.2.S.3.1.
- If a polymorphic form is to be defined or limited (e.g. for APIs that are not BCS *highly soluble* and/or where polymorphism has been identified as an issue), details should be included in 3.2.S.4.1– 3.2.S.4.5.

Additional information is included in the referenced sections of these guidelines.

Particle size distribution

As recommended in ICH's *CTD-Q Questions and answers/location issues* document (5), the studies performed to determine the particle size distribution of the API should be provided in section 3.2.S.3.1 (refer to this section of these guidelines for additional information).

Information from the literature

Supportive data and results from specific studies or published literature can be included within or attached to this section.

Reference documents: ICH Q6A (6).

3.2.S.2 Manufacture (name, manufacturer)

3.2.S.2.1 Manufacturer(s) (name, manufacturer)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

The facilities involved in the manufacturing, packaging, labelling, testing and storage of the API should be listed. If certain companies are responsible only for specific steps (e.g. milling of the API) this should be clearly indicated.

The list of manufacturers or companies should specify the *actual addresses* of the production or manufacturing site(s) involved (including block(s) and units(s)), rather than the administrative offices. Telephone number(s), fax number(s) and e-mail address(es) should be provided.

A valid manufacturing authorization should be provided for the production of APIs. If available, a certificate of compliance with GMP should be provided in the PD in Module 1.

3.2.S.2.2 Description of manufacturing process and process controls (name, manufacturer)

The description of the API manufacturing process represents the applicant's commitment for the manufacture of the API. Information should be provided to adequately describe the manufacturing process and process controls. For example:

A flow diagram of the synthetic process(es) should be provided that includes molecular formulas, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and API reflecting stereochemistry, and identifies operating conditions and solvents.

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g. temperature, pressure, pH, time).

Alternative processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or filed in 3.2.S.2.5.

Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF may be indicated for confidential information. In this case, if detailed information is presented in the Restricted part, the information to be provided for this section of the PD includes a flow chart (including molecular structures and all reagents and solvents) and a brief outline of the manufacturing process, with special emphasis on the final steps, including purification procedures. However, for sterile APIs, full validation data on the sterilization process should be provided in the Open part (in cases where there is no further sterilization of the final product).

The following requirements apply to the fourth option for submission of API information, where full details are provided in the dossier.

As discussed in ICH Q7 (7) and *WHO Technical Report Series*, No. 957, Annex 2 (8), the point at which the *API starting material* is introduced into the manufacturing process is the starting point for the application of GMP requirements. The API starting material itself needs to be proposed and its choice justified by the manufacturer and

accepted as such by assessors. The API starting material should be proposed taking into account the complexity of the molecule, the proximity of the API starting material to the final API, the availability of the API starting material as a commercial chemical and the quality controls placed upon the API starting material. This justification should be documented in the dossier and be available for review by WHO GMP inspectors.

In situations where the API starting material is a complex molecule and only a minimal number of synthetic steps from the final API, a further molecule called the starting material for synthesis should be proposed and its choice justified by the applicant. The starting material for synthesis defines the starting point in the manufacturing process for an API to be described in an application. The applicant should propose and justify which substances should be considered as starting materials for synthesis (see section 3.2.S.2.3 for further guidance). In the case where the precursor to the API is obtained by fermentation, or is of plant or animal origin, such a molecule can be considered the API starting material regardless of complexity.

A one-step synthesis may be accepted in exceptional cases, for example, where the API starting material is covered by a CEP, or where the API starting material is an API accepted through the APIMF or API prequalification procedure within the WHO Prequalification of Medicines Programme, or when the structure of the API is so simple that a one-step synthesis can be justified, e.g. ethambutol or ethionamide.

In addition to the detailed description of the manufacturing process as per ICH M4Q, the recovery of materials, if any, should be described in detail with the step in which they are introduced into the process. Recovery operations should be adequately controlled such that impurity levels do not increase over time. For recovery of solvents, any processing to improve the quality of the recovered solvent should be described. Regarding recycling of filtrates (mother liquors) to obtain second crops, information should be available on maximum holding times of mother liquors and maximum number of times the material can be recycled. Data on impurity levels should be provided to justify recycling of filtrates.

Where there are multiple manufacturing sites being used by one API manufacturer, a comprehensive list in tabular form should be provided comparing the processes at each of the sites and highlighting any differences.

All solvents used in the manufacture (including purification and/or crystallization step(s)) should be clearly identified. Solvents used in the final steps should be of high purity. Use of recovered solvents in the final steps of purification and/or crystallization is not recommended; however their use can be justified on presentation of sufficient data demonstrating that recovered solvents meet appropriate standards as outlined in ICH Q7 (7).

Where polymorphic or amorphous forms have been identified, the form resulting from the synthesis should be stated.

Where particle size is considered a critical attribute (see 3.2.S.3.1 for details) the particle size reduction method(s) (e.g. milling or micronization) should be described.

Justification should be provided for use of alternative manufacturing processes. Alternative processes should be explained with the same level of detail as for the primary process. It should be demonstrated that batches obtained by the alternative processes have the same impurity profile as obtained by the principal process. If the impurity profile obtained is different it should be demonstrated to be acceptable according to the requirements described under S.3.2.

It is acceptable to provide information on pilot-scale manufacture, provided it is representative of production scale and scale-up is reported immediately to WHO according to the requirements of the WHO variation guidelines (9).

3.2.S.2.3 Control of materials (name, manufacturer)

Materials used in the manufacture of the API (e.g. raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials meet standards appropriate for their intended use should be provided, as appropriate (details in 3.2.A.2).

Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF is considered sufficient for this section.

The following requirements apply to the fourth option for submission of API information, where full details are provided in the dossier.

The API starting material should be fully characterized and suitable specifications proposed and justified, including, at a minimum, control for identity, assay, impurity content and any other critical attribute of the material. For each API starting material, the name and address of the manufacturing site(s) of the manufacturer(s) should be indicated. A brief description of the preparation of the API starting material should be provided for each manufacturer, including the solvents, catalysts and reagents used. A single set of specifications should be proposed for the starting material that applies to material from all sources. Any future changes to the API starting material manufacturers, mode of preparation or specifications should be notified.

As indicated in section 3.2.S.2 there are occasions where a starting material for synthesis may also need to be defined. In general, the starting material for synthesis described in the PD should:

- be a synthetic precursor of one or more synthesis steps prior to the final API intermediate. Acids, bases, salts, esters and similar derivatives of the API, as well as the racemate of a single enantiomer API, are not considered final intermediates;
- be a well characterized, isolated and purified substance with its structure fully elucidated including its stereochemistry (when applicable);
- have well-defined specifications that include among others one or more specific identity tests and tests and limits for assay and specified, unspecified and total impurities;

- be incorporated as a significant structural fragment into the structure of the API.

Copies of the specifications for the materials used in the synthesis, extraction, isolation and purification steps should be provided in the PD, including starting materials, reagents, solvents, catalysts and recovered materials. Confirmation should be provided that the specifications apply to materials used at each manufacturing site. A certificate of analysis of the starting material for synthesis should be provided. A summary of the information on starting materials should be provided in the QOS-PD.

The carry-over of impurities of the starting materials for synthesis into the final API should be considered and discussed.

A letter of attestation should be provided confirming that the API and the starting materials and reagents used to manufacture the API are without risk of transmitting agents of animal spongiform encephalopathies.

When available a CEP demonstrating compliance with recommendations on transmissible spongiform encephalopathy (TSE) should be provided. A complete copy of the CEP (including any annexes) should be provided in Module 1.

Reference documents: ICH Q6A (6).

3.2.S.2.4 Controls of critical steps and intermediates (name, manufacturer)

Critical steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled should be provided.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF is considered sufficient for this section of the PD, with the exception of information that is also relevant for the applicant (4).

The following requirements apply to the fourth option for submission of API information where full details are provided in the dossier.

The critical steps should be identified. These can include: steps where significant impurities are removed or introduced; steps introducing an essential molecular structural element such as a chiral centre or resulting in a major chemical transformation; steps having an impact on solid-state properties and homogeneity of the API that may be relevant for use in solid dosage forms.

Specifications for isolated intermediates should be provided and should include tests and acceptance criteria for identity, purity and assay, where applicable.

Reference documents: ICH Q6A (6).

3.2.S.2.5 Process validation and/or evaluation (name, manufacturer)

Process validation and/or evaluation studies for aseptic processing and sterilization should be included.

Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF is considered sufficient for this section of the PD.

The following requirements apply to the fourth option for submission of API information where full details are provided in the dossier.

It is expected that the manufacturing processes for all APIs are properly controlled. If the API is prepared as sterile a complete description should be provided of the aseptic processing and/or sterilization methods. A description of the controls used to maintain the sterility of the API during storage and transportation should also be provided. Alternative processes should be justified and described (see guidance in 3.2.S.2.2 for the level of detail expected).

3.2.S.2.6 *Manufacturing process development (name, manufacturer)*

A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the API used in producing comparative bioavailability or biowaiver, scale-up, pilot, and, if available, production scale batches.

Reference should be made to the API data provided in Section 3.2.S.4.4.

Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF is considered sufficient for this section of the PD.

3.2.S.3 Characterization (name, manufacturer)

3.2.S.3.1 *Elucidation of structure and other characteristics (name, manufacturer)*

Confirmation of structure based on, e.g. synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should also be included.

Elucidation of structure

The PD should include quality assurance (QA) certified copies of the spectra, peak assignments and a detailed interpretation of the data from the studies performed to elucidate and/or confirm the structure of the API. The QOS-PD should include a list of the studies performed and a conclusion from the studies (e.g. whether the results support the proposed structure).

For APIs that are not described in an officially recognized pharmacopoeia, the studies carried out to elucidate and/or confirm the chemical structure normally include elemental analysis, infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR) and mass spectra (MS) studies. Other tests could include X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC).

For APIs that are described in an officially recognized pharmacopoeia it is generally sufficient to provide copies of the IR spectrum of the API from each of the proposed manufacturer(s) run concomitantly with an officially recognized pharmacopoeial reference standard. See section 3.2.S.5 for details on acceptable reference standards or materials.

Isomerism/stereochemistry

When an API is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the comparative biostudies, and information should be given as to the stereoisomer of the API that is to be used in the FPP.

Where the potential for stereoisomerism exists, a discussion should be included of the possible isomers that can result from the manufacturing process and the steps where chirality was introduced. The identity of the isomeric composition of the API to that of the API in the comparator product should be established. Information on the physical and chemical properties of the isomeric mixture or single enantiomer should be provided, as appropriate. The API specification should include a test to ensure isomeric identity and purity.

The potential for interconversion of the isomers in the isomeric mixture, or racemization of the single enantiomer should be discussed.

When a single enantiomer of the API is claimed for non-pharmacopoeial APIs, unequivocal proof of absolute configuration of asymmetric centres should be provided, such as determined by X-ray of a single crystal.

If, based on the structure of the API, there is not a potential for stereoisomerism, it is sufficient to include a statement to this effect.

Polymorphism

Many APIs can exist in different physical forms in the solid state. Polymorphism is characterized as the ability of an API to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice. Solvates are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent. If the incorporated solvent is water the solvates are also commonly known as hydrates.

Polymorphic forms of the same chemical compound differ in internal solid-state structure and, therefore, may possess different chemical and physical properties, including packing, thermodynamic, spectroscopic, kinetic, interfacial and mechanical properties. These properties can have a direct impact on API processability, pharmaceutical product manufacturability and product quality and performance, including stability, dissolution and bioavailability. The unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences.

Applicants to the WHO Prequalification of Medicines Programme and API manufacturers are expected to have adequate knowledge about the polymorphism of the APIs used and/or produced. Information on polymorphism can come from the scientific literature, patents, compendia or other references to determine if polymorphism is a concern, e.g. for APIs that are not *BCS highly soluble*. In the absence of published data for APIs that are not *BSC highly soluble*, polymorphic screening will be necessary to

determine if the API can exist in more than one crystalline form. Polymorphic screening is generally accomplished via crystallization studies using different solvents and conditions.

A number of methods can be used to characterize the polymorphic forms of an API. Demonstration of a non-equivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism. XRPD can also be used to provide unequivocal proof of polymorphism. Other methods, including microscopy, thermal analysis (e.g. DSC, thermal gravimetric analysis and hot-stage microscopy) and spectroscopy (e.g. IR, Raman, and solid-state nuclear magnetic resonance (ssNMR)) are helpful for further characterization of polymorphic forms. Where polymorphism is a concern, the applicants or manufacturers of APIs should demonstrate that a suitable method, capable of distinguishing different polymorphs, is available to them.

Decision tree 4(1) of ICH Q6A (6) can be used where screening is necessary and 4(2) can be used to investigate if different polymorphic forms have different properties that may affect performance, bioavailability and stability of the FPP and to decide whether a preferred polymorph should be monitored at release and on storage of the API. Where there is a preferred polymorph, acceptance criteria should be incorporated into the API specification to ensure polymorphic equivalence of the commercial material and that of the API batches used in the comparative bioavailability or biowaiver studies. The polymorphic characterization of the API batches used in comparative bioavailability or biowaiver studies by the above-mentioned methods should be provided. The method used to control polymorphic form should be demonstrated to be specific for the preferred form.

Polymorphism can also include solvation or hydration products (also known as pseudopolymorphs). If the API is used in a solvated form, the following information should be provided:

- specifications for the solvent-free API in 3.2.S.2.4, if that compound is a synthetic precursor;
- specifications for the solvated API including appropriate limits on the weight ratio of API to solvent (with data to support the proposed limits);
- a description of the method used to prepare the solvate in 3.2.S.2.2.

Particle size distribution

For APIs that are not *BCS highly soluble* contained in solid FPPs, or liquid FPPs containing undissolved API, the particle size distribution of the material can have an effect on the in vitro and/or in vivo behaviour of the FPP. Particle size distribution can also be important in dosage form performance (e.g. delivery of inhalation products), achieving uniformity of content in low-dose tablets (e.g. 2 mg or less), desired smoothness in ophthalmic preparations and stability of suspensions.

If particle size distribution is an important parameter (e.g. as in the above cases), results from an investigation of several batches of the API should be provided, including characterization of the batch(es) used in the comparative bioavailability or biowaiver studies. API specifications should include controls on the particle size distribution to ensure consistency with the material in the batch(es) used in the comparative bioavailability and biowaiver studies (e.g. limits for d10, d50 and d90). The criteria should be established statistically, based on the standard deviation of the test results from the previously mentioned studies. The following example is provided for illustrative purposes as possible acceptance criteria for particle size distribution limits:

- d10 not more than (NMT) 10% of total volume less than X µm;
- d50 XX µm–XXX µm;
- d90 not less than (NLT) 90% of total volume less than XXXX µm.

Other controls on particle size distribution can be considered acceptable, if scientifically justified.

Reference documents: ICH Q6A (6).

3.2.S.3.2 *Impurities (name, manufacturer)*

Information on impurities should be provided.

Details on the principles for the control of impurities (e.g. reporting, identification and qualification) are outlined in the ICH Q3A, Q3B and Q3C impurity guidelines (10–12). Additional information elaborating on some of the elements discussed in the ICH guidelines is outlined below.

Regardless of whether a pharmacopoeial standard is claimed, a discussion should be provided of the potential and actual impurities arising from the synthesis, manufacture or degradation of the API. This should cover starting materials, by-products, intermediates, chiral impurities and degradation products and should include the chemical names, structures and origins of the impurities. The discussion of pharmacopoeial APIs should not be limited to the impurities specified in the API monograph.

The tables in the QOS-PD template should be used to summarize the information on the API-related and process-related impurities. In the QOS- PD, the term “origin” refers to how and where the impurity was introduced (e.g. “Synthetic intermediate from Step 4 of the synthesis” or “Potential by-product due to rearrangement from Step 6 of the synthesis”). It should also be indicated if the impurity is a metabolite of the API.

The ICH thresholds for reporting, identification (used to set the limit for individual unknown impurities) and qualification are determined on the basis of potential exposure to the impurity, e.g. by the maximum daily dose (MDD) of the API. For APIs available in multiple dosage forms and strengths having different MDD values, it is imperative that the thresholds and corresponding controls for each of the

presentations be considered to ensure that the risks posed by impurities have been addressed. This is normally achieved by using the highest potential daily MDD, rather than the maintenance dose. For parenteral products the maximum hourly dose of the API should also be included.

It is acknowledged that APIs of semi-synthetic origin do not fall within the scope of the ICH impurity guidelines. However, depending on the nature of the API and the extent of the chemical modification steps, the principles regarding the control of impurities (e.g. reporting, identification and qualification) could be extended to apply to APIs of semi-synthetic origin. As an illustrative example, an API whose precursor molecule was derived from a fermentation process or a natural product of plant or animal origin, which has subsequently undergone several chemical modification reactions, would generally fall within the scope of the ICH impurity guidelines, whereas an API whose sole chemical step was the formation of a salt from a fermentation product generally would not. It is understood that there is some latitude for these types of APIs.

Identification of impurities

It is recognized by the pharmacopoeias that APIs can be obtained from various sources and thus can contain impurities not considered during the development of the monograph. Furthermore, a change in the production or source may give rise to additional impurities that are not adequately controlled by the official compendial monograph. As a result each PD is assessed independently to consider the potential impurities that may arise from the proposed route(s) of synthesis. For these reasons the ICH limits for unspecified impurities (e.g. NMT 0.10% or 1.0 mg per day intake (whichever is lower) for APIs having an MDD ≤ 2 g/day) are generally recommended, rather than the general limits for unspecified impurities that may appear in the official compendial monograph, which could potentially be higher than the applicable ICH limit.

Qualification of impurities

The ICH impurity guidelines should be consulted for options on the qualification of impurities. The limit specified for an identified impurity in an officially recognized pharmacopoeia is generally considered to be qualified. The following is an additional option for qualification of impurities in existing APIs:

The limit for an impurity present in an existing API can be accepted by comparing the results of tests for impurities found in the existing API with those observed in an innovator product using the same validated, stability- indicating analytical procedure (e.g. comparative (high-performance liquid chromatography (HPLC) studies). If samples of the innovator product are not available, the impurity profile may also be compared to a different prequalified FPP with the same route of administration and similar characteristics (e.g. tablet versus capsule). It is recommended that the studies be conducted on comparable samples (e.g. samples of a similar age) to obtain a meaningful comparison of the impurity profiles.

Levels of impurities generated from studies under accelerated or stressed storage conditions of the innovator or prequalified FPP are not considered acceptable/qualified.

A specified impurity present in the existing API is considered qualified if the amount of the impurity in the existing API reflects the levels observed in the innovator or prequalified FPP.

Basis for setting the acceptance criteria

The basis for setting the acceptance criteria for the impurities should be provided. This is established by considering the identification and qualification thresholds for API-related impurities (e.g. starting materials, by-products, intermediates, chiral impurities or degradation products) and the concentration limits for process-related impurities (e.g. residual solvents) according to the applicable ICH guidelines (e.g. Q3A (10), Q3C (12)).

The qualified level should be considered as the maximum allowable limit. However, limits which are considerably wider than the actual manufacturing process capability are generally discouraged. For this reason the acceptance criteria are also set taking into consideration the actual levels of impurities found in several batches of the API from each manufacturer, including the levels found in the batches used for the comparative bioavailability or biowaiver studies. When reporting the results of quantitative tests, the actual numerical results should be provided rather than vague statements such as “within limits” or “conforms”. In cases where a large number of batches have been tested it is acceptable to summarize the results of all the batches tested with a range of analytical results.

If there are identified impurities specified in an official compendial monograph that are not controlled by the proposed routine in-house analytical procedure, a justification for their exclusion from routine analyses should be provided (e.g. “Impurities D, E and F listed in *The International Pharmacopoeia* (Ph.Int.) monograph are not potential impurities from the proposed route of synthesis used by manufacturer X”). If acceptable justification cannot be provided it should be demonstrated that the routine in-house method is capable of separating and detecting the impurities specified in the official compendial monograph at an acceptable level (e.g. 0.10%). If such a demonstration cannot be performed, a one-time study should be conducted applying the pharmacopoeial method to several recent batches to demonstrate the absence of the impurities listed in the pharmacopoeia.

ICH class II solvent(s) used prior to the last step of the manufacturing process may be exempted from routine control in API specifications if suitable justification is provided. Submission of results demonstrating less than 10% of the ICH Q3C limit (option I) of the solvent(s) in three consecutive production-scale batches or six consecutive pilot-scale batches of the API or a suitable intermediate would be considered acceptable justification. The last step solvents used in the process should always be routinely controlled in the final API.

For guidance on acceptable residual solvent limits refer to ICH Q3C (12). The limit for residues of triethylamine (TEA) is either 320 ppm on the basis of ICH Q3C option I or 3.2 mg/day on the basis of permitted daily exposure (PDE).

The absence of known, established highly toxic impurities (genotoxic) used in the process or formed as a by-product should be discussed and suitable limits should be proposed. The limits should be justified by appropriate reference to available guidance (e.g. EMEA/CHMP/QWP/ 251344/2006 (13) or USFDA Guidance for Industry. *Genotoxic and carcinogenic impurities in drug substances and products, recommended approaches* (14)) or by providing experimental safety data or published data in peer-reviewed journals.

Residues of metal catalysts used in the manufacturing process and determined to be present in batches of API are to be controlled in specifications. This requirement does not apply to metals that are deliberate components of the pharmaceutical substance (such as a counter ion of a salt) or metals that are used as a pharmaceutical excipient in the FPP (e.g. an iron oxide pigment). The guideline on the specification limits for residues of metal catalysts or metal reagents (EMA/CHMP/SWP/4446/2000 (15)) or any equivalent approaches can be used to address this issue. The requirement normally does not apply to extraneous metal contaminants that are more appropriately addressed by GMP, good distribution practices (GDP) or any other relevant quality provision such as the heavy metal test in monographs of recognized pharmacopoeias that cover metal contamination originating from manufacturing equipment and the environment.

Reference documents: ICH Q6A, Q3A, Q3C (6, 10, 12).

3.2.S.4 Control of the API (name, manufacturer)

3.2.S.4.1 Specification (name, manufacturer)

The specification for the API should be provided.

As defined in ICH's Q6A guideline (6), a specification is:

“A list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which an API or FPP should conform to be considered acceptable for its intended use. ‘Conformance to specifications’ means that the API and/or FPP, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.”

Copies of the API specifications, dated and signed by authorized personnel (e.g. the person in charge of the quality control or quality assurance department) should be provided in the PD, including specifications from each API manufacturer as well as those of the FPP manufacturer.

The FPP manufacturer's API specification should be summarized according to the table in the QOS-PD template under the headings: tests, acceptance criteria and analytical procedures (including types, sources and versions for the methods).

- The *standard* declared by the applicant could be an officially recognized compendial standard (e.g. BP, JP, Ph.Eur., Ph.Int., USP) or an in-house (manufacturer's) standard.
- The specification reference number and version (e.g. revision number and/or date) should be provided for version control purposes.
- For the analytical procedures, the type should indicate the kind of analytical procedure used (e.g. visual, IR, UV, HPLC or laser diffraction), the source refers to the origin of the analytical procedure (e.g. BP, JP, Ph.Eur., Ph.Int., USP or in-house) and the version (e.g. code number/version/date) should be provided for version control purposes.

In cases where there is more than one API manufacturer, the FPP manufacturer's API specifications should be one single compiled set of specifications that is identical for each manufacturer. It is acceptable to lay down in the specification more than one acceptance criterion and/or analytical method for a single parameter with the statement "for API from manufacturer A" (e.g. in the case of residual solvents).

Any non-routine testing should be clearly identified as such and justified together with the proposal on the frequency of non-routine testing.

The ICH Q6A guideline (6) outlines recommendations for a number of universal and specific tests and criteria for APIs.

Reference documents: ICH Q6A, Q3A, Q3C (6, 10, 12) and officially recognized pharmacopoeias.

3.2.S.4.2 *Analytical procedures (name, manufacturer)*

The analytical procedures used for testing the API should be provided.

Copies of the in-house analytical procedures used to generate testing results provided in the PD, as well as those proposed for routine testing of the API by the FPP manufacturer, should be provided. Unless modified it is not necessary to provide copies of officially recognized compendial analytical procedures.

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay/impurity methods, gas chromatography (GC) methods) can be found in the 2.3.R Regional information section of the QOS-PD (i.e. 2.3.R.2). These tables should be used to summarize the in-house analytical procedures of the FPP manufacturer for determination of the residual solvents, assay and purity of the API, in section 2.3.S.4.2 of the QOS-PD. Other methods used to generate assay and purity data in the PD can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the QOS-PD. Officially recognized compendial methods need not be summarized unless modifications have been made.

Although HPLC is normally considered the method of choice for determining API-related impurities, other chromatographic methods such as GC and thin-layer chromatography (TLC) can also be used if appropriately validated. For determination of related substances, reference standards should normally be available for each of the identified impurities, particularly those known to be toxic and the concentration of the impurities should be quantified against their own reference standards. Impurity standards may be obtained from pharmacopoeias (individual impurities or resolution mixtures), from commercial sources or prepared in-house. It is considered acceptable to use the API as an external standard to estimate the levels of impurities, provided the response factors of those impurities are sufficiently close to that of the API, i.e. between 80 and 120%. In cases where the response factor is outside this range it may still be acceptable to use the API, provided a correction factor is applied. Data to support calculation of the correction factor should be provided for an in-house method. Unspecified impurities may be quantified using a solution of the API as the reference standard at a concentration corresponding to the limit established for individual unspecified impurities (e.g. 0.10%). The test for related substances in the Ph.Int. monograph for lamivudine serves as a typical example.

The system suitability tests (SSTs) represent an integral part of the method and are used to ensure the satisfactory performance of the chosen chromatographic system. As a minimum, HPLC and GC purity methods should include SSTs for resolution and repeatability. For HPLC methods to control API-related impurities, this is typically done using a solution of the API with a concentration corresponding to the limit for unspecified impurities. Resolution of the two closest eluting peaks is generally recommended. However, the choice of alternative peaks can be used if justified (e.g. choice of a toxic impurity). In accordance with the Ph.Int. section on Methods of analysis the repeatability test should include an acceptable number of replicate injections. HPLC assay methods should include SSTs for repeatability and in addition either peak asymmetry, theoretical plates or resolution. For TLC methods, the SSTs should verify the ability of the system to separate and detect the analyte(s) (e.g. by applying a spot corresponding to the API at a concentration corresponding to the limit of unspecified impurities).

Reference documents: ICH Q2 (16), *WHO Technical Report Series*, No. 943, Annex 3 (17).

3.2.S.4.3 Validation of analytical procedures (name, manufacturer)

Analytical validation information, including experimental data for the analytical procedures used for testing the API, should be provided.

Copies should be provided of the validation reports for the analytical procedures used to generate testing results provided in the PD, as well as those proposed for routine testing of the API by the FPP manufacturer.

Tables for summarizing a number of the different analytical procedures and the validation information (e.g. HPLC assay and impurity methods, GC methods) can be found

in the 2.3.R Regional information section of the QOS-PD (i.e. 2.3.R.2). These tables should be used to summarize the validation information of the analytical procedures of the FPP manufacturer for determination of residual solvents, assay and purity of the API, in section 2.3.S.4.3 of the QOS-PD. The validation data for other methods used to generate assay and purity data in the PD can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the QOS-PD.

As recognized by regulatory authorities and pharmacopoeias themselves, verification of compendial methods can be necessary. The compendial methods as published are typically validated based on an API or an FPP originating from a specific manufacturer. Different sources of the same API or FPP can contain impurities and/or degradation products that were not considered during the development of the monograph. Therefore, the monograph and compendial method should be demonstrated as suitable to control the impurity profile of the API from the intended source(s).

In general verification is not necessary for compendial API assay methods. However, specificity of a specific compendial assay method should be demonstrated if there are any potential impurities that are not specified in the compendial monograph. If an officially recognized compendial method is used to control API-related impurities that are not specified in the monograph, full validation of the method is expected with respect to those impurities.

If an officially recognized compendial standard is claimed and an in-house method is used in lieu of the compendial method (e.g. for assay or for specified impurities), equivalence of the in-house and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For impurity methods the sample analysed should be the API spiked with impurities at concentrations equivalent to their specification limits.

Reference documents: ICH Q2 (16).

3.2.S.4.4 Batch analyses (name, manufacturer)

Description of batches and results of batch analyses should be provided.

The information provided should include batch number, batch size, date and production site of relevant API batches used in comparative bioavailability or biowaiver studies, preclinical and clinical data (if relevant), stability, pilot, scale-up and, if available, production-scale batches. These data are used to establish the specifications and evaluate consistency in API quality.

Analytical results should be provided from at least two batches of at least pilot scale from each proposed manufacturing site of the API and should include the batch(es) used in the comparative bioavailability or biowaiver studies. A pilot-scale batch should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

Copies of the certificates of analysis, both from the API manufacturer(s) and the FPP manufacturer, should be provided for the profiled batches and any company

responsible for generating the test results should be identified. The FPP manufacturer's test results should be summarized in the QOS-PD.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "all tests meet specifications". For quantitative tests (e.g. individual and total impurity tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms".

A discussion and justification should be provided for any incomplete analyses (e.g. results not tested according to the proposed specification).

Reference documents: ICH Q6A, Q3A, Q3C (6, 10, 12).

3.2.S.4.5 Justification of specification (name, manufacturer)

Justification for the API specification should be provided.

A discussion should be provided on the inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, and differences from the officially recognized compendial standard(s). If the officially recognized compendial methods have been modified or replaced a discussion of the modifications or replacement method(s) should be included.

The justification for certain tests, analytical procedures and acceptance criteria may have been discussed in other sections of the PD (e.g. for impurities or particle size distribution) and does not need to be repeated here, although a cross-reference should be provided.

Reference documents: ICH Q6A, Q3A, Q3C (6, 10, 12), and officially recognized pharmacopoeias.

3.2.S.5 Reference standards or materials (name, manufacturer)

Information on the reference standards or reference materials used for testing of the API should be provided.

Information should be provided on the reference standard(s) used to generate data in the PD, as well as those to be used by the FPP manufacturer in routine API and FPP testing.

The source(s) of the reference standards or materials used in the testing of the API should be provided (e.g. those used for the identification, purity and assay tests). These could be classified as primary or secondary reference standards.

A suitable primary reference standard should be obtained from an officially recognized pharmacopoeial source (e.g. BP, JP, Ph.Eur., Ph.Int., USP) where one exists, and the lot number should be provided. Where a pharmacopoeial standard is claimed for the API and/or the FPP, the primary reference standard should be obtained from that pharmacopoeia when available. Primary reference standards from officially recognized pharmacopoeial sources do not need further structural elucidation.

Otherwise a primary standard may be a batch of the API that has been fully characterized (e.g. by IR, UV, NMR and mass spectrometry (MS) analyses). Further

purification techniques may be needed to render the material acceptable for use as a chemical reference standard. The purity requirements for a chemical reference substance depend upon its intended use. A chemical reference substance proposed for an identification test does not require meticulous purification since the presence of a small percentage of impurities in the substance often has no noticeable effect on the test. On the other hand, chemical reference substances that are to be used in assays should possess a high degree of purity (such as 99.5% on the dried or water/solvent free basis). Absolute content of the primary reference standard must be declared and should follow the scheme: 100% minus organic impurities (quantified by an assay procedure, e.g. HPLC or DSC) minus inorganic impurities minus volatile impurities by loss on drying (or water content minus residual solvents).

A secondary (or in-house) reference standard can be used by establishing it against a suitable primary reference standard, e.g. by providing legible copies of the IR of the primary and secondary reference standards run concomitantly and by providing its certificate of analysis, including assay determined against the primary reference standard. A secondary reference standard is often characterized and evaluated for its intended purpose with additional procedures other than those used in routine testing (e.g. if additional solvents are used during the additional purification process that are not used for routine purposes).

Reference standards should normally be established for specified impurities. Refer to 3.2.S.4.2 for additional guidance.

Reference documents: ICH Q6A (6), *WHO Technical Report Series*, No. 943, Annex 3 (17).

3.2.S.6 Container-closure system (name, manufacturer)

A description of the container-closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non- compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g. those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the API, including sorption to container and leaching, and/or safety of materials of construction.

The *WHO Guidelines on packaging for pharmaceutical products* (18) and the officially recognized pharmacopoeias should be consulted for recommendations on the packaging information for APIs.

Primary packaging components are those that are in direct contact with the API or FPP. The specifications for the primary packaging components should be provided and should include a specific test for identification (e.g. IR).

Copies of the labels applied on the secondary packaging of the API should be provided and should include the conditions of storage. In addition, the name and address of the manufacturer of the API should be stated on the container, regardless of whether relabelling is conducted at any stage during the API distribution process.

3.2.S.7 Stability (name, manufacturer)

3.2.S.7.1 Stability summary and conclusions (name, manufacturer)

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

The WHO guidelines *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (19) should be consulted for recommendations on the core stability data package required for the prequalification of APIs and FPPs.

As outlined in the WHO stability guidelines, the purpose of stability testing is to: “provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light.”

The tables in the QOS-PD template should be used to summarize the results from the stability studies and related information (e.g. conditions, testing parameters, conclusions and commitments).

Stress testing

As outlined in the ICH Q1A guidance document (20), stress testing of the API can help identify the likely degradation products which, in turn, can help to establish the degradation pathways and the intrinsic stability of the molecule and validate the stability-indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual API and the type of FPP involved.

Stress testing may be carried out on a single batch of the API. For examples of typical stress conditions refer to section 2.1.2 of *WHO Technical Report Series*, No. 953, Annex 2 (19), as well as, “A typical set of studies of the degradation paths of an active pharmaceutical ingredient”, in: *WHO Technical Report Series*, No. 929, Annex 5, Table A1 (21).

The objective of stress testing is not to completely degrade the API but to cause degradation to occur to a small extent, typically 10–30% loss of API by assay when compared with non-degraded API. This target is chosen so that some degradation occurs, but not enough to generate secondary products. For this reason the conditions and duration may need to be varied when the API is especially susceptible to a particular stress factor. In the total absence of degradation products after 10 days the API is considered stable under the particular stress condition.

The tables in the QOS-PD template should be used to summarize the results of the stress testing and should include the treatment conditions (e.g. temperatures, relative humidities, concentrations of solutions and durations) and the observations for the various test parameters (e.g. assay, degradation products). The discussion of results should highlight whether mass balance was observed.

Photostability testing should be an integral part of stress testing. The standard conditions are described in ICH Q1B (22). If “protect from light” is stated in one of the officially recognized pharmacopoeias for the API, it is sufficient to state “protect from light” on labelling, in lieu of photostability studies when the container-closure system is shown to be light protective.

When available it is acceptable to provide the relevant data published in the scientific literature (including, but not limited to, WHO Public Assessment Reports (WHOPARs), European Public Assessment Reports (EPARs)) to support the identified degradation products and pathways.

Accelerated and long-term testing

Available information on the stability of the API under accelerated and long-term storage conditions should be provided, including information in the public domain or obtained from scientific literature. The source of the information should be identified.

The required long-term storage conditions for APIs in the WHO Prequalification of Medicines Programme are either $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}/65\% \pm 5\% \text{ RH}$ or $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}/75\% \pm 5\% \text{ RH}$. Studies covering the proposed retest period under the above-mentioned long-term storage conditions will provide better assurance of the stability of APIs at the conditions of the supply chain corresponding to the WHO and its Prequalification of Medicines Programme environments. Alternative conditions should be supported with appropriate evidence, which may include literature references or in-house studies, demonstrating that storage at $30\text{ }^{\circ}\text{C}$ is inappropriate for the API. For APIs intended for storage in a refrigerator and those intended for storage in a freezer, refer to the WHO stability guidelines in the *WHO Technical Report Series*, No. 953, Annex 2 (19). APIs intended for storage below $-20\text{ }^{\circ}\text{C}$ should be treated on a case-by-case basis.

To establish the retest period, data should be provided on not less than three batches of at least pilot scale. The batches should be manufactured by the same synthesis route as production batches and using a method of manufacture and a procedure that simulates the final process to be used for production batches. The stability testing programme should be summarized and the results of stability testing should be summarized in the dossier and in the tables in the QOS-PD.

The information on the stability studies should include details such as storage conditions, batch number, batch size, container-closure system and completed (and proposed) test intervals. The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “all tests meet specifications”. Ranges of analytical results where relevant and any trends that were observed should be

included. For quantitative tests (e.g. individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms”. Where methods are different from those described in S.4.2, descriptions and validation of the methodology used in stability studies should be provided.

The minimum data required at the time of submitting the dossier (in the general case) are shown in Table 1.

Table 1
Minimum data required at the time of submitting the dossier

Storage temperature (°C)	Relative humidity (%)	Minimum time period (months)
Accelerated 40 ± 2	75 ± 5	6
Intermediate ^a	— ^a	— ^a
Long-term 30 ± 2	65 ± 5 or 75 ± 5	6

^a Where long-term conditions are 30 °C ± 2 °C/65% ± 5% RH or 30 °C ± 2 °C/75% ± 5% RH, there is no intermediate condition.

Refer to *WHO Technical Report Series*, No. 953, Annex 2 (19) for further information regarding the storage conditions, container-closure system, test specifications and testing frequency.

Proposed storage statement and retest period

A storage statement should be established for display on the label, based on the stability evaluation of the API. The WHO stability guidelines include a number of recommended storage statements that should be used when supported by the stability studies.

A retest period should be derived from the stability information and should be displayed on the container label.

After this retest period a batch of API destined for use in the manufacture of an FPP could be retested and then, if in compliance with the specification, could be used immediately (e.g. within 30 days). If retested and found compliant, the batch does not receive an additional period corresponding to the time established for the retest period. However, an API batch can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For APIs known to be labile (e.g. certain antibiotics) it is more appropriate to establish a shelf-life than a retest period (20).

Limited extrapolation of the real-time data from the long-term storage condition beyond the observed range to extend the retest period can be done at the time

of assessment of the PD, if justified. Applicants should consult the ICH Q1E guideline (23) for further details on the evaluation and extrapolation of results from stability data (e.g. if significant change was not observed within 6 months at accelerated conditions and the data show little or no variability, the proposed retest period could be up to twice the period covered by the long-term data, but should not exceed the long-term data by more than 12 months).

Reference documents: ICH Q1A (20), Q1B (22), Q1D (24), Q1E (23), *WHO Technical Report Series*, No. 953, Annex 2 (19).

3.2.S.7.2 Post-approval stability protocol and stability commitment (name, manufacturer)

The post-approval stability protocol and stability commitment should be provided.

Primary stability study commitment

When the available long-term stability data on primary batches do not cover the proposed retest period granted at the time of assessment of the PD, a commitment should be made to continue the stability studies in order to firmly establish the retest period. A written commitment (signed and dated) to continue long-term testing over the retest period should be included in the dossier when relevant.

Commitment stability studies

The long-term stability studies for the commitment batches should be conducted through the proposed retest period on at least three production batches. Where stability data were not provided for three production batches, a written commitment (signed and dated) should be included in the dossier.

The stability protocol for the commitment batches should be provided and should include, but not be limited to, the following parameters:

- number of batch(es) and different batch sizes, if applicable;
- relevant physical, chemical, microbiological and biological test methods;
- acceptance criteria;
- reference to test methods;
- description of the container-closure system(s);
- testing frequency;
- description of the conditions of storage (standardized conditions for long-term testing as described in these guidelines and consistent with the API labelling, should be used);
- other applicable parameters specific to the API.

Ongoing stability studies

The stability of the API should be monitored according to a continuous and appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of

degradation products). The purpose of the ongoing stability programme is to monitor the API and to determine that the API remains stable and can be expected to remain stable within the retest period in all future batches.

At least one production batch per year of API (unless none is produced during that year) should be added to the stability monitoring programme and tested at least annually to confirm the stability. In certain situations, additional batches should be included. A written commitment (signed and dated) to ongoing stability studies should be included in the dossier.

Refer to section 2.1.11 of *WHO Technical Report Series*, No. 953, Annex 2 (19), for further information on ongoing stability studies.

Any differences between the stability protocols used for the primary batches and those proposed for the commitment batches or ongoing batches should be scientifically justified.

Reference documents: ICH Q1A (20), Q1B (22), Q1D (24), Q1E (23), *WHO Technical Report Series*, No. 953, Annex 2 (19).

3.2.S.7.3 Stability data (name, manufacturer)

Results of the stability studies (e.g. forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

The actual stability results used to support the proposed retest period should be included in the dossier. For quantitative tests (e.g. individual and total degradation product tests and assay tests) it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms”.

Reference documents: ICH Q1A (20), Q1B (22), Q1D (24), Q1E (23), Q2 (16) *WHO Technical Report Series*, No. 953, Annex 2 (19).

3.2.P Drug product (or finished pharmaceutical product (FPP))

3.2.P.1 Description and composition of the FPP (name, dosage form)

A description of the FPP and its composition should be provided. The information provided should include, for example:

- **Description of the dosage form**

The description of the FPP should include the physical description, available strengths, release mechanism (e.g. immediate or modified (delayed or extended)), as well as any other distinguishable characteristics, e.g.

“The proposed XYZ 50-mg tablets are available as white, oval, film-coated tablets, debossed with ‘50’ on one side and a break-line on the other side.

The proposed XYZ 100-mg tablets are available as yellow, round, film-coated tablets, debossed with ‘100’ on one side and plain on the other side.”

- **Composition, i.e. list of all components of the dosage form, and their amount on a per unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g. compendial monographs or manufacturer's specifications).**

The tables in the QOS-PD template should be used to summarize the composition of the FPP and express the quantity of each component on a per unit basis (e.g. mg per tablet, mg per ml, mg per vial) and a percentage basis, including a statement of the total weight or measure of the dosage unit. The individual components for mixtures prepared in-house (e.g. coatings) should be included in the tables where applicable.

All components used in the manufacturing process should be listed, including those that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. solvents) and any others (e.g. nitrogen or silicon for stoppers). If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g. "1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride"). All overages should be clearly indicated (e.g. "contains 2% overage of the API to compensate for manufacturing losses").

The components should be declared by their proper or common names, quality standards (e.g. BP, JP, Ph.Eur., Ph.Int., USP, in-house) and, if applicable, their grades (e.g. "microcrystalline cellulose NF (PH 102)") and special technical characteristics (e.g. lyophilized, micronized, solubilized or emulsified).

The function of each component (e.g. diluent or filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent or antimicrobial preservative) should be stated. If an excipient performs multiple functions the predominant function should be indicated.

The qualitative composition, including solvents, should be provided for all proprietary components or blends (e.g. capsule shells, colouring blends or imprinting inks). This information (excluding the solvents) is to be listed in the product information (e.g. summary of product characteristics, labelling and package leaflet).

- **Description of accompanying reconstitution diluent(s)**

For FPPs supplied with reconstitution diluent(s) that are commercially available or that have been assessed and considered acceptable in connection with another PD with the WHO Prequalification of Medicines Programme, a brief description of the reconstitution diluents(s) should be provided.

For FPPs supplied with reconstitution diluent(s) that are not commercially available or have not been assessed and considered acceptable in connection with another PD with the WHO Prequalification of Medicines Programme,

information on the diluent(s) should be provided in a separate FPP portion (“3.2.P”), as appropriate.

- **Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable**

The container-closure used for the FPP (and accompanying reconstitution diluent, if applicable) should be briefly described, with further details provided under 3.2.P.7 Container-closure system, e.g.

“The product is available in HDPE bottles with polypropylene caps (in sizes of 100s, 500s and 1000s) and in PVC/aluminium foil unit dose blisters (in packages of 100s) (cards of 5 × 2, 10 cards per package).”

Reference documents: ICH Q6A (6).

3.2.P.2 Pharmaceutical development (name, dosage form)

The Pharmaceutical development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container-closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the product dossier. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and FPP quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the product dossier.

Pharmaceutical development information should include, at a minimum:

- the definition of the quality target product profile (QTPP) as it relates to quality, safety and efficacy, considering, for example, the route of administration, dosage form, bioavailability, strength and stability;
- identification of the potential critical quality attributes (CQAs) of the FPP so as to adequately control the product characteristics that could have an impact on quality;
- discussion of the potential CQAs of the API(s), excipients and container-closure system(s) including the selection of the type, grade and amount to deliver drug product of the desired quality;
- discussion of the selection criteria for the manufacturing process and the control strategy required to manufacture commercial lots meeting the QTPP in a consistent manner.

These features should be discussed as part of the product development using the principles of risk management over the entire life-cycle of the product (ICH Q8) (25).

For a discussion of additional pharmaceutical development issues specific to the development of FDCs reference should be made to section 6.3.2 of *WHO Technical Report Series*, No. 929, Annex 5 (21).

Reference documents: ICH Q6A (6), Q8 (25), Q9 (26), Q10 (27).

3.2.P.2.1 Components of the FPP (name, dosage form)

3.2.P.2.1.1 Active pharmaceutical ingredient (name, dosage form)

The compatibility of the API with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g. water content, solubility, particle size distribution, polymorphic or solid state form) of the API that can influence the performance of the FPP should be discussed. For FDCs, the compatibility of APIs with each other should be discussed.

Physicochemical characteristics of the API may influence both the manufacturing capability and the performance of the FPP.

Guidance on compatibility studies is provided in Appendix 3 of the *WHO Guidelines for registration of fixed-dose combination medicinal products* (*WHO Technical Report Series*, No. 929, Annex 5, 2005) (21). In addition to visual examination, chromatographic results (assay, purity) are required to demonstrate API-API and API-excipient compatibility. In general, API-excipient compatibility is not required to be established for specific excipients when evidence is provided (e.g. in the SmPC or product leaflet) that the excipients are present in the comparator product.

3.2.P.2.1.2 Excipients (name, dosage form)

The choice of excipients listed in 3.2.P.1, their concentration and their characteristics that can influence the FPP performance should be discussed relative to their respective functions.

When choosing excipients those with a compendial monograph are generally preferred and may be required in certain jurisdictions. Other resources are available for information on acceptable excipients and their concentrations, such as the US Food and Drug Administration (FDA) inactive ingredient guide (IIG) list (28) and the *Handbook of pharmaceutical excipients* (29). Use of excipients in concentrations outside established ranges is discouraged and generally requires justification (30). In addition, available guidelines should be referenced which discuss particular excipients to be avoided, for example azo-colourants as listed in the EMA Guideline CPMP/463/00 (31). Other guidance such as the *WHO Guidelines on development of paediatric medicines: points to consider in formulation* (32) may provide useful general guidance in this regard.

Ranges in concentrations or alternatives for excipients are normally not accepted unless supported by appropriate process validation data. Where relevant, compatibility study results (e.g. on compatibility of a primary or secondary amine API with lactose)

should be included to justify the choice of excipients. Specific details should be provided where necessary (e.g. on use of potato or corn starch).

Where antioxidants are included in the formulation, the effectiveness of the proposed concentration of the antioxidant should be justified and verified by appropriate studies.

Antimicrobial preservatives are discussed in 3.2.P.2.5.

3.2.P.2.2 Finished pharmaceutical product (name, dosage form)

3.2.P.2.2.1 Formulation development (name, dosage form)

A brief summary describing the development of the FPP should be provided, taking into consideration the proposed route of administration and usage. The differences between the comparative bioavailability or biowaiver formulations and the formulation (i.e. composition) described in 3.2.P.1 should be discussed. Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo studies (e.g. bioequivalence) should be discussed, when appropriate.

The WHO Prequalification of Medicines Programme defines an established multisource product as one that has been marketed by the applicant or manufacturer associated with the dossier for at least five years and for which at least 10 production batches were produced over the previous year or, if less than 10 batches were produced in the previous year, not less than 25 batches were produced in the previous three years. For products that meet the criteria of an established multisource product, all sections of P.2.2.1 of the dossier and QOS-PD should be completed with the exception of P.2.2.1 (a). In addition, a product quality review should be provided as outlined in Appendix 2.

The requirements for bioequivalence studies should be taken into consideration, for example, when formulating multiple strengths and/or when the product(s) may be eligible for a biowaiver. WHO reference documents (e.g. *WHO Technical Report Series*, No. 937, Annex 7) (33) should be consulted.

Product scoring may be recommended or required, for example, when scoring is indicated in the WHO Invitation for EOIs, or is specified for an invited FPP in the listing of recommended comparator products, or when division into fractional doses may be necessary according to approved posology.

If the proposed FPP is a functionally scored tablet a study should be undertaken to ensure the uniformity of dose in the tablet fragments. The data provided in the PD should include a description of the test method, individual values, mean and relative standard deviation (RSD) of the results. Uniformity testing (i.e. content uniformity for split portions containing less than 5 mg or less than 5% of the weight of the dosage unit portion, or mass uniformity for other situations) should be performed on each split portion from a minimum of 10 randomly selected whole tablets. As an illustrative example, the number of units (i.e. the splits) would be 10 halves for bisected tablets (one half of each tablet is retained for the test) or 10 quarters for quadrisectioned tablets (one quarter of each tablet is retained for the test). At least one batch of each strength

should be tested. Ideally the study should cover a range of the hardness values. The splitting of the tablets should be performed in a manner that would be representative of that used by the consumer (e.g. manually split by hand). The uniformity test on split portions can be demonstrated on a one-time basis and does not need to be added to the FPP specification(s). The tablet description in the FPP specification and in the product information (e.g. SmPC, labelling and package leaflet) should reflect the presence of a score.

If splitting of a tablet is intended for preparation of a paediatric dose a demonstration of content uniformity of tablet fragments may be required.

Where relevant, labelling should state that the score line is only to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses.

In vitro dissolution or drug release

A discussion should be included as to how the development of the formulation relates to development of the dissolution method(s) and the generation of the dissolution profile.

The results of studies justifying the choice of in vitro dissolution or drug release conditions (e.g. apparatus, rotation speed and medium) should be provided. Data should also be submitted to demonstrate whether the method is sensitive to changes in manufacturing processes and/or changes in grades and/or amounts of critical excipients and particle size where relevant. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters. Use of a single point test or a dissolution range should be justified based on the solubility and/ or biopharmaceutical classification of the API.

For slower dissolving immediate-release products (e.g. Q = 80% in 90 minutes), a second time point may be warranted (e.g. Q = 60% in 45 minutes).

Modified-release FPPs should have a meaningful in vitro release rate (dissolution) test that is used for routine quality control. Preferably this test should possess in vitro–in vivo correlation. Results demonstrating the effect of pH on the dissolution profile should be submitted if appropriate for the type of dosage form.

For extended-release FPPs, the testing conditions should be set to cover the entire time period of expected release (e.g. at least three test intervals chosen for a 12-hour release and additional test intervals for longer duration of release). One of the test points should be at the early stage of drug release (e.g. within the first hour) to demonstrate absence of dose dumping. At each test point, upper and lower limits should be set for individual units. Generally the acceptance range at each intermediate test point should not exceed 25% or $\pm 12.5\%$ of the targeted value. Dissolution results should be submitted for several lots, including those lots used for pharmacokinetic and bioavailability or biowaiver studies.

Recommendations for conducting and assessing comparative dissolution profiles can be found in Appendix 1.

3.2.P.2.2.2 Overages (name, dosage form)

Any overages in the formulation(s) described in 3.2.P.1 should be justified.

Justification of an overage to compensate for loss during manufacture should be provided, including information on the step(s) where the loss occurs, the reasons for the loss and batch analysis release data (assay results).

Overages for the sole purpose of extending the shelf-life of the FPP are generally not acceptable.

3.2.P.2.2.3 Physicochemical and biological properties (name, dosage form)

Parameters relevant to the performance of the FPP, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity, should be addressed.

3.2.P.2.3 Manufacturing process development (name, dosage form)

The selection and optimization of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.

Where relevant, justification for the selection of aseptic processing or other sterilization methods over terminal sterilization should be provided.

Differences between the manufacturing process(es) used to produce comparative bioavailability or biowaiver batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.

For products that meet the criteria of an established multisource product, in order to fulfil the requirements of section P.2.3, section P.2.3 (b) of the dossier and QOS-PD should be completed and a product quality review should be submitted as outlined in Appendix 2. The guidance that follows applies to all other products for which section P.2.3 should be completed in its entirety.

The rationale for choosing the particular pharmaceutical product (e.g. dosage form, delivery system) should be provided. The scientific rationale for the choice of the manufacturing, filling and packaging processes that can influence FPP quality and performance should be explained (e.g. wet granulation using high shear granulator). API stress study results may be included in the rationale. Any developmental work undertaken to protect the FPP from deterioration should also be included (e.g. protection from light or moisture).

The scientific rationale for the selection, optimization and scale-up of the manufacturing process described in 3.2.P.3.3 should be explained, in particular the critical aspects (e.g. rate of addition of granulating fluid, massing time and granulation end-point). A discussion of the critical process parameters (CPP), controls and robustness with respect to the QTPP and CQA of the product should be included (ICH Q8 (25)).

3.2.P.2.4 Container-closure system (name, dosage form)

The suitability of the container-closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the FPP should be discussed. This discussion should consider, e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the FPP).

Testing requirements to verify the suitability of the container-closure system contact material(s) depend on the dosage form and route of administration. The pharmacopoeias provide standards that are required for packaging materials, including, for example, the following:

- glass containers: (34, 35);
- plastic containers: (36, 37);
- rubber/elastomeric closures (38, 39).

Table 2 outlines the general recommendations for the various dosage forms for one-time studies to establish the suitability of the container-closure system contact materials.

Table 2

One-time studies to establish the suitability of the container-closure system contact materials

	Solid oral products	Oral liquid and topical products	Sterile products (including ophthalmics)
Description of any additional treatments ^a	×	×	× (sterilization and depyrogenation of the components)
Extraction studies	–	×	×
Interaction studies (migration/sorption)	–	×	×
Moisture permeability	× (uptake)	× (usually loss)	× (usually loss)
Light transmission	× ^b	×	×

× Information should be submitted.

– Information does not need to be submitted.

^a E.g. coating of tubes, siliconization of rubber stoppers, sulfur treatment of ampoules or vials.

^b Not required if product has been shown to be photostable.

For solid oral dosage forms and solid APIs, compliance with regulations on plastic materials coming into contact with food (for example (EU) No. 10/2011 (40)) can be considered acceptable.

The suitability of the container-closure system used for the storage, transportation (shipping) and use of any intermediate or in-process products (e.g. premixes or bulk FPP) should also be discussed.

A device is required to be included with the container-closure system for administration of oral liquids or solids (e.g. solutions, emulsions, suspensions and powders or granules), whenever the package provides for multiple doses.

In accordance with the Ph.Int. general chapter *Liquid preparations for oral use*:

“Each dose from a multidose container is administered by means of a device suitable for measuring the prescribed volume. The device is usually a spoon or a cup for volumes of 5 ml or multiples thereof, or an oral syringe for other volumes or, for oral drops, a suitable dropper.”

For a device accompanying a multidose container, the results of a study should be provided demonstrating the reproducibility of the device (e.g. consistent delivery of the intended volume), generally at the lowest intended dose.

A sample of the device should be provided with Module 1.

3.2.P.2.5 Microbiological attributes (name, dosage form)

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container-closure system to prevent microbial contamination should be addressed.

Where an antimicrobial preservative is included in the formulation, the amount used should be justified by submission of results of studies on the product formulated with different concentrations of the preservative(s) to demonstrate the least necessary but still effective concentration. The effectiveness of the agent should be justified and verified by appropriate studies (e.g. USP or Ph.Eur. general chapters on antimicrobial preservatives) using a batch of the FPP. If the lower limit for the proposed acceptance criterion for the assay of the preservative is less than 90.0%, the effectiveness of the agent should be established with a batch of the FPP containing a concentration of the antimicrobial preservative corresponding to the lower proposed acceptance criteria.

As outlined in the WHO stability guidelines (*WHO Technical Report Series*, No. 953, Annex 2, 2009 (19)), a single primary stability batch of the FPP should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf-life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

3.2.P.2.6 *Compatibility (name, dosage form)*

The compatibility of the FPP with reconstitution diluent(s) or dosage devices (e.g. precipitation of API in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labelling.

Where a device is required for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders or granules for such reconstitution) that are intended to be administered immediately after being added to the device, the compatibility studies mentioned in the following paragraphs are not required.

Where sterile, reconstituted products are to be further diluted, compatibility should be demonstrated with all diluents over the range of dilution proposed in the labelling. These studies should preferably be conducted on aged samples. Where the labelling does not specify the type of containers, compatibility (with respect to parameters such as appearance, pH, assay, levels of individual and total degradation products, subvisible particulate matter and extractables from the packaging components) should be demonstrated in glass, PVC and polyolefin containers. However, if one or more containers are identified in the labelling, compatibility of admixtures needs to be demonstrated only in the specified containers.

Studies should cover the duration of storage reported in the labelling (e.g. 24 hours under controlled room temperature and 72 hours under refrigeration). Where the labelling specifies coadministration with other FPPs, compatibility should be demonstrated with respect to the principal FPP as well as the coadministered FPP (i.e. in addition to other aforementioned parameters for the mixture, the assay and degradation levels of each coadministered FPP should be reported).

3.2.P.3 *Manufacture (name, dosage form)*

3.2.P.3.1 *Manufacturer(s) (name, dosage form)*

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

The facilities involved in the manufacturing, packaging, labelling and testing should be listed. If certain companies are responsible only for specific steps (e.g. manufacturing of an intermediate), this should be clearly indicated (*WHO good distribution practices for pharmaceutical products* (41)).

The list of manufacturers or companies should specify the actual addresses of production or manufacturing site(s) involved (including block(s) and unit(s)), rather than the administrative offices.

For a mixture of an API with an excipient, the blending of the API with the excipient is considered to be the first step in the manufacture of the final product and, therefore, the mixture does not fall under the definition of an API. The only exceptions are in the cases where the API cannot exist on its own. Similarly, for a mixture of APIs,

the blending of the APIs is considered to be the first step in the manufacture of the final product. Sites for such manufacturing steps should be listed in this section.

A valid manufacturing authorization for pharmaceutical production, as well as a marketing authorization, should be submitted to demonstrate that the product is registered or licensed in accordance with national requirements (Module 1, 1.2.2).

For each site where the major production step(s) are carried out, when applicable, attach a WHO-type certificate of GMP issued by the competent authority in terms of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce (Module 1, 1.2.2).

Justification for any differences to the product in the country or countries issuing the WHO-type certificate(s)

When there are differences between the product for which this application is submitted and that marketed in the country or countries which provided the WHO-type certificate(s), it is necessary to provide data to support the applicability of the certificate(s) despite the differences. Depending on the case, it may be necessary to provide validation data for example for differences in site of manufacture, specifications and formulation. Note that only minor differences are likely to be acceptable. Differences in container labelling need not normally be justified.

Regulatory situation in other countries

A listing should be provided of the countries in which this product has been granted a marketing authorization, this product has been withdrawn from the market and/or this application for marketing has been rejected, deferred or withdrawn (Module 1, 1.2.2).

Reference documents: WHO Technical Report Series, No. 961, Annex 3 (42) and No. 957, Annex 5 (41).

3.2.P.3.2 Batch formula (name, dosage form)

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

The tables in the QOS-PD template should be used to summarize the batch formula of the FPP for each proposed commercial batch size and to express the quantity of each component on a per batch basis, including a statement of the total weight or measure of the batch.

All components used in the manufacturing process should be included, including those that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. solvents) and any others (e.g. nitrogen or silicon for stoppers). If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g. “1 kg of active ingredient base = 1.075 kg active ingredient hydrochloride”). All overages should be clearly indicated (e.g. “Contains 5 kg (corresponding to 2%) overage of the API to compensate for manufacturing losses”).

The components should be declared by their proper or common names, quality standards (e.g. BP, JP, Ph.Eur., Ph.Int., USP, in-house) and, if applicable, their grades (e.g. “Microcrystalline cellulose NF (PH 102)”) and special technical characteristics (e.g. lyophilized, micronized, solubilized or emulsified).

3.2.P.3.3 Description of manufacturing process and process controls (name, dosage form)

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative description of the manufacturing process, including packaging, that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g. tumble blender, in-line homogenizer) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section 3.2.P.3.4. In certain cases, environmental conditions (e.g. low humidity for an effervescent product) should be stated.

The maximum holding time for bulk FPP prior to final packaging should be stated. The holding time should be supported by the submission of stability data if longer than 30 days. For an aseptically processed FPP, sterile filtration of the bulk and filling into final containers should preferably be continuous; any holding time should be justified.

Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section (3.2.P.3.3).

The information above should be summarized in the QOS-PD template and should reflect the production of the proposed commercial batches. See Glossary (section 2) for definitions of pilot-scale and production-scale batches.

For the manufacture of sterile products the class (e.g. A, B or C) of the areas should be stated for each activity (e.g. compounding, filling and sealing), as well as the sterilization parameters, including for equipment, container-closure system and terminal sterilization.

Reference documents: ICH Q8 (25), Q9 (26), Q10 (27).

3.2.P.3.4 Controls of critical steps and intermediates (name, dosage form)

Critical steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the manufacturing process, to ensure that the process is controlled.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Examples of applicable in-process controls include:

- granulations: moisture (limits expressed as a range), blend uniformity (e.g. low-dose tablets), bulk and tapped densities and particle size distribution;
- solid oral products: average weight, weight variation, hardness, thickness, friability, and disintegration checked periodically throughout compression, weight gain during coating;
- semi-solids: viscosity, homogeneity, pH;
- transdermal dosage forms: assay of API–adhesive mixture, weight per area of coated patch without backing;
- metered dose inhalers: fill weight or volume, leak testing, valve delivery;
- dry powder inhalers: assay of API–excipient blend, moisture, weight variation of individually contained doses such as capsules or blisters;
- liquids: pH, specific gravity, clarity of solutions;
- parenterals: appearance, clarity, fill volume or weight, pH, filter integrity tests, particulate matter, leak testing of ampoules, pre- filtration and/or pre-sterilization bioburden testing.

Reference documents: ICH Q2 (16), Q6A (6), Q8 (25), Q9 (26), Q10 (27), *WHO Technical Report Series*, No. 929, Annex 5 (21).

3.2.P.3.5 Process validation and/or evaluation (name, dosage form)

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g. validation of the sterilization process or aseptic processing or filling). Viral safety evaluation should be provided in 3.2A.2, if necessary.

For products that meet the criteria of an established multisource product, a product quality review as outlined in Appendix 2 may be submitted in lieu of the information below.

The following information should be provided for all other products:

1. a copy of the process validation protocol, specific to this FPP, described below;
2. a commitment that three consecutive, production-scale batch- es of this FPP will be subjected to prospective validation in ac- cordance with the above protocol. The applicant should submit a written commitment that information from these studies will be available for verification after prequalification by the WHO inspection team;
3. if the process validation studies have already been conducted (e.g. for sterile products), a copy of the process validation report should be provided in the PD in lieu of 1. and 2. above.

One of the most practical forms of process validation, mainly for non-sterile products, is the final testing of the product to an extent greater than that required in routine quality control. It may involve extensive sampling, far beyond that called for in routine quality control and testing to normal quality control specifications and often for certain parameters only. Thus, for instance, several hundred tablets per batch may be weighed to determine unit dose uniformity. The results are then analysed statistically to verify the “normality” of the distribution and to determine the standard deviation from the average weight. Confidence limits for individual results and for batch homogeneity are also estimated. Strong assurance is provided that samples taken at random will meet regulatory requirements if the confidence limits are well within compendial specifications.

Similarly, extensive sampling and testing may be performed with regard to any quality requirements. In addition, intermediate stages may be validated in the same way, e.g. dozens of samples may be assayed individually to validate mixing or granulation stages of low-dose tablet production by using the content uniformity test. Certain product characteristics may occasionally be skip-tested. Thus, subvisual particulate matter in parenteral preparations may be determined by means of electronic devices, or tablets or capsules tested for their dissolution profile if such tests are not performed on every batch.

Where ranges of batch sizes are proposed, it should be shown that variations in batch size would not adversely alter the characteristics of the finished product. It is envisaged that those parameters listed in the following validation scheme would need to be revalidated once further scale-up is proposed after prequalification.

The process validation protocol should include, but not be limited to, the following:

- a reference to the current master production document;
- a discussion of the critical equipment;
- the process parameters that can affect the quality of the FPP (critical process parameters (CPPs)) including challenge experiments and failure mode operation;
- details of the sampling: sampling points, stages of sampling, methods of sampling and the sampling plans (including schematics of blender or storage bins for uniformity testing of the final blend);
- the testing parameters and acceptance criteria including in- process and release specifications and comparative dissolution profiles of validation batches against the batch(es) used in the bioavailability or biowaiver studies;
- the analytical procedures or a reference to appropriate section(s) of the dossier;
- the methods for recording and evaluating results;
- the proposed timeframe for completion of the protocol.

The manufacture of sterile FPPs needs to take place in a well-controlled manufacturing area (e.g. a strictly controlled environment using highly reliable procedures and with appropriate in-process controls). A detailed description of these conditions, procedures and controls should be provided, together with actual copies of the standard operating procedures for the following:

- washing, treatment, sterilization and depyrogenation of containers, closures and equipment;
- filtration of solutions;
- lyophilization process;
- leaker test of filled and sealed ampoules;
- final inspection of the product;
- sterilization cycle.

The sterilization process used to destroy or remove microorganisms is probably the single most important process in the manufacture of parenteral FPPs. The process can make use of moist heat (e.g. steam), dry heat, filtration, gaseous sterilization (e.g. ethylene oxide) or radiation. It should be noted that terminal steam sterilization, when practical, is considered to be the method of choice to ensure sterility of the final FPP. Therefore, scientific justification for selecting any other method of sterilization should be provided.

The sterilization process should be described in detail and evidence should be provided to confirm that it will produce a sterile product with a high degree of reliability and that the physical and chemical properties as well as the safety of the FPP will not be affected. Details such as F_0 range, temperature range and peak dwell time for an FPP and the container-closure system should be provided. Although standard autoclaving cycles of 121 °C for 15 minutes or more would not need a detailed rationale, such justifications should be provided for reduced temperature cycles or elevated temperature cycles with shortened exposure times. If ethylene oxide is used, studies and acceptance criteria should control the levels of residual ethylene oxide and related compounds.

Any filters used should be validated with respect to pore size, compatibility with the product, absence of extractables and lack of adsorption of the API or any of the components.

For the validation of aseptic processing of parenteral products that cannot be terminally sterilized, simulation process trials should be conducted. This involves filling containers with culture media under normal conditions, followed by incubation. Refer to current WHO GMP guidelines for details.

Reference documents: ICH Q8 (25), Q9 (26), Q10 (27), *WHO Technical Report Series*, No. 961, Annex 3 (42).

3.2.P.4 Control of excipients (name, dosage form)

3.2.P.4.1 Specifications (name, dosage form)

The specifications for excipients should be provided.

The specifications from the applicant or the FPP manufacturer should be provided for all excipients, including those that may not be added to every batch (e.g. acid and alkali), those that do not appear in the final FPP (e.g. solvents) and any others used in the manufacturing process (e.g. nitrogen or silicon for stoppers).

If the standard claimed for an excipient is an officially recognized compendial standard, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the officially recognized compendial monograph.

If the standard claimed for an excipient is a non-compendial standard (e.g. in-house standard) or includes tests that are supplementary to those appearing in the officially recognized compendial monograph, a copy of the specification for the excipient should be provided.

For products submitted to the WHO Prequalification of Medicines Programme, only excipients with an officially recognized pharmacopoeial monograph should be used. Exceptions may be justified.

For excipients of natural origin, microbial limit testing should be included in the specifications. Skip-testing is acceptable if justified (submission of acceptable results of five production batches).

For oils of plant origin (e.g. soy bean oil or peanut oil) the absence of aflatoxins or biocides should be demonstrated.

The colours permitted for use are limited to those listed in the “Japanese pharmaceutical excipients”, the European Union (EU) “List of permitted food colours”, and the FDA “Inactive ingredient guide”. For proprietary mixtures, the supplier’s product sheet with the qualitative formulation should be submitted, in addition to the FPP manufacturer’s specifications for the product, including identification testing.

For flavours, the qualitative composition should be submitted, as well as a declaration that the excipients comply with foodstuff regulations (e.g. United States or EU regulations).

Information that is considered confidential may be submitted directly to the WHO Prequalification of Medicines Programme by the supplier who should make reference in the cover letter to the specific related product.

Other certifications of at-risk components may be required on a case-by-case basis.

If additional purification is undertaken on commercially available excipients, details of the process of purification and modified specifications should be submitted.

Reference documents: ICH Q6A (6).

3.2.P.4.2 Analytical procedures (name, dosage form)

The analytical procedures used for testing the excipients should be provided, where appropriate.

Copies of analytical procedures from officially recognized compendial monographs do not need to be submitted.

Reference document: ICH Q2 (16).

3.2.P.4.3 Validation of analytical procedures (name, dosage form)

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.

Copies of analytical validation information are generally not submitted for the testing of excipients, with the exception of the validation of in-house methods where appropriate.

Reference document: ICH Q2 (16).

3.2.P.4.4 Justification of specifications (name, dosage form)

Justification for the proposed excipient specifications should be provided, where appropriate.

A discussion of the tests that are supplementary to those appearing in the officially recognized compendial monograph should be provided.

3.2.P.4.5 Excipients of human or animal origin (name, dosage form)

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g. sources, specifications, description of the testing performed, viral safety data) (details in 3.2.A.2).

The following excipients should be addressed in this section: gelatin, phosphates, stearic acid, magnesium stearate and other stearates. If the excipients are of plant origin a declaration to this effect will suffice.

For excipients of animal origin, a letter of attestation should be provided confirming that the excipients used to manufacture the FPP are without risk of transmitting agents of animal spongiform encephalopathies.

Materials of animal origin should be avoided whenever possible.

When available a CEP demonstrating TSE-compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module 1.

Reference documents: ICH Q5A (43), Q5D (44), Q6B (45), WHO Technical Report Series, No. 908, Annex 1 (46).

3.2.P.4.6 Novel excipients (name, dosage form)

For excipient(s) used for the first time in an FPP or by a new route of administration, full details of manufacture, characterization, and controls, with cross-references to supporting safety data (non-clinical and/or clinical) should be provided according to the API and/or FPP format (details in 3.2.A.3).

Novel excipients are not accepted in the WHO Prequalification of Medicines Programme. For the purpose of these guidelines, a novel excipient is one that has not been used (at a similar level and by the same route of administration) in a product approved by an SRA or by WHO.

3.2.P.5 Control of FPP (name, dosage form)

3.2.P.5.1 Specification(s) (name, dosage form)

The specification(s) for the FPP should be provided.

As defined in ICH's Q6A guideline, a specification is:

“a list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which an API or FPP should conform to be considered acceptable for its intended use. “Conformance to specifications” means that the API and/or FPP, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.”

A copy of the FPP specification(s) from the applicant (as well as the company responsible for the batch release of the FPP, if different from the applicant), dated and signed by authorized personnel (i.e. the person in charge of the quality control or quality assurance department) should be provided in the PD. Two separate sets of specifications may be set out: after packaging of the FPP (release) and at the end of the shelf-life.

The specifications should be summarized according to the tables in the QOS-PD template including the tests, acceptance criteria and analytical procedures (listing types, sources and versions for the methods).

- The standard declared by the applicant could be an officially recognized compendial standard (e.g. BP, JP, Ph.Eur., Ph.Int., USP) or an in-house (manufacturer's) standard.
- The specification reference number and version (e.g. revision number and/or date) should be provided for version control purposes.
- For the analytical procedures, the type should indicate the kind of analytical procedure used (e.g. visual, IR, UV or HPLC); the source refers to the origin of the analytical procedure (e.g. BP, JP, Ph.Eur., Ph.Int., USP, in-house) and the version (e.g. code number/version/ date) should be provided for version control purposes.

ICH's Q6A guideline outlines recommendations for a number of *universal* and *specific tests* and criteria for FPPs. Specifications should include, at a minimum,

tests for appearance, identification, assay, purity, performance tests (e.g. dissolution), physical tests (e.g. loss on drying, hardness, friability and particle size), uniformity of dosage units, and, as applicable, identification and assay of antimicrobial or chemical preservatives (e.g. antioxidants) and microbial limit tests.

The following information provides guidance on specific tests that are not addressed by ICH's Q6A guideline:

- fixed-dose combination FPPs (FDC-FPPs):
 - analytical methods that can distinguish each API in the presence of the other API(s) should be developed and validated,
 - acceptance criteria for degradation products should be established with reference to the API they are derived from. If an impurity results from a chemical reaction between two or more APIs, its acceptance limits should in general be calculated with reference to the worst case (the API with the smaller area under the curve). Alternatively the content of such impurities could be calculated in relation to their reference standards,
 - a test and limit for content uniformity is required for each API present in the FPP at less than 5 mg or less than 5% of the weight of the dosage unit,
 - for the API(s) present at ≥ 5 mg and $\geq 5\%$ of the weight of the dosage unit, a test and limit for weight variation may be established in lieu of content uniformity testing;
- modified-release products: a meaningful API release method;
- inhalation and nasal products: consistency of delivered dose (throughout the use of the product), particle or droplet size distribution profiles (comparable to the product used in in vivo studies where applicable) and if applicable for the dosage form, moisture content, leak rate, microbial limits, preservative assay, sterility and weight loss;
- suppositories: uniformity of dosage units, melting point;
- transdermal dosage forms: peel or shear force, mean weight per unit area and dissolution.

Unless there is appropriate justification, the acceptable limit for the API content of the FPP in the release specifications is $\pm 5\%$ of the label claim (i.e. 95.0–105.0%).

For products such as tablets, capsules and suppositories where a test for uniformity of single-dose preparations is required, a test and limit for content uniformity is required when the API is present in the FPP at less than 5 mg or less than 5% of the weight of the dosage unit. Otherwise, the test for mass uniformity may be applied.

Skip-testing is acceptable for parameters such as identification of colouring materials and microbial limits, when justified by the submission of acceptable supportive results for five production batches. When justification for skip-testing has been accepted the specifications should include a footnote, stating, at a minimum, the following skip-testing requirements: at least every tenth batch and at least one batch annually is tested. In addition, for stability- indicating parameters such as microbial limits, testing will be performed at release and at the end of shelf-life during stability studies.

Any differences between release and shelf-life tests and acceptance criteria should be clearly indicated and justified. Note that such differences for parameters such as dissolution are normally not accepted.

Reference documents: ICH Q3B (11), Q3C (12), Q6A (6).

3.2.P.5.2 Analytical procedures (name, dosage form)

The analytical procedures used for testing the FPP should be provided.

Copies of the in-house analytical procedures used during pharmaceutical development (if used to generate testing results provided in the PD) as well as those proposed for routine testing should be provided. Unless modified it is not necessary to provide copies of analytical procedures described in officially recognized compendia.

Tables for summarizing a number of the different analytical procedures and the validation information (e.g. HPLC assay and impurity methods) can be found in the 2.3.R Regional information section of the QOS-PD (i.e. 2.3.R.2). These tables should be used to summarize the analytical procedures used for determination of the assay, related substances and dissolution of the FPP.

Refer to section 3.2.S.4.2 of these guidelines for additional guidance on analytical procedures.

Reference document: ICH Q2 (16).

3.2.P.5.3 Validation of analytical procedures (name, dosage form)

Analytical validation information, including experimental data, for the analytical procedures used for testing the FPP, should be provided.

Copies of the validation reports for the in-house analytical procedures used during pharmaceutical development (if used to support testing results provided in the PD) as well as those proposed for routine testing should be provided.

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay and impurity methods, and GC methods) can be found in the 2.3.R Regional information section of the QOS- PD (i.e. 2.3.R.2). These tables should be used to summarize the validation information of the analytical procedures used for determination of the assay, related substances and dissolution of the FPP.

As recognized by regulatory authorities and pharmacopoeias themselves, verification of compendial methods can be necessary. The compendial methods as

published are typically validated based on an API or an FPP originating from a specific manufacturer. The same API or FPP obtained from different sources can contain impurities and/or degradation products or excipients that were not considered during the development of the monograph. Therefore, the monograph and compendial method(s) should be demonstrated suitable for the control of the proposed FPP.

For officially recognized compendial FPP assay methods, verification should include a demonstration of specificity, accuracy and repeatability (method precision). If an officially recognized compendial method is used to control related substances that are not specified in the monograph, full validation of the method is expected with respect to those related substances.

If an officially recognized compendial standard is claimed and an in-house method is used in lieu of the compendial method (e.g. for assay or for related compounds), equivalence of the in-house and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For methods for the determination of related compounds, the sample analysed should be the placebo spiked with related compounds at concentrations equivalent to their specification limits.

Reference document: ICH Q2 (16).

3.2.P.5.4 Batch analyses (name, dosage form)

A description of batches and results of batch analyses should be provided.

Information on relevant FPP batches used to establish the specifications and evaluate consistency in manufacturing should be provided and should include strength and batch number, batch size, date and site of production and use (e.g. used in comparative bioavailability or biowaiver studies, preclinical and clinical studies (if relevant), stability, pilot, scale-up and, if available, production-scale batches).

Analytical results generated by the company responsible for the batch release of the FPP (generally the applicant or the FPP manufacturer, if different from the applicant) should be provided for not less than two batches of at least pilot scale, or in the case of an uncomplicated² FPP (e.g. immediate-release solid FPPs (with noted exceptions), or non-sterile solutions), at least one batch of at least pilot scale and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules) of each proposed strength of the FPP. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

The results should include those of tests on the batch(es) used in the comparative bioavailability or biowaiver studies. Copies of the certificates of analysis for these batches

² The term “complicated FPP” includes sterile products, metered dose inhaler products, dry powder inhaler products and transdermal delivery systems. Other specific products under “complicated FPP” include ritonavir/lopinavir FDC tablets and FDCs containing rifampicin or an artemisinin. As the invitations for EOI change over time, the listing of individual “complicated FPPs” is not meaningful and applicants should contact the Head of Assessments, WHO Prequalification of Medicines Programme in case of doubt.

should be provided in the PD and the company responsible for generating the testing results should be identified.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “all tests meet specifications”. The discussion should include ranges of analytical results, where relevant. For quantitative tests (e.g. individual and total impurity tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms” (e.g. “levels of degradation product A ranged from 0.2 to 0.4%”). Dissolution results should be expressed, at a minimum, as both the average and the range of individual results. Recommendations for conducting and assessing comparative dissolution profiles can be found in Appendix 1.

A discussion and justification should be provided for any incomplete analyses (e.g. for any parameters not tested according to the proposed specification).

Reference documents: ICH Q3B (11), Q3C (12), Q6A (6).

3.2.P.5.5 Characterization of impurities (name, dosage form)

Information on the characterization of impurities should be provided, if not previously provided in “3.2.S.3.2 Impurities”.

A discussion should be provided of all impurities that are potential degradation products (including those among the impurities identified in 3.2.S.3.2 as well as potential degradation products resulting from interaction of the API with other APIs (FDCs), excipients or the container-closure system) and FPP process-related impurities (e.g. residual solvents in the manufacturing process for the FPP).

Reference documents: ICH Q3B (11), Q3C (12), Q6A (6).

3.2.P.5.6 Justification of specification(s) (name, dosage form)

Justification for the proposed FPP specification(s) should be provided.

A discussion should be provided on the omission or inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, and differences from the officially recognized compendial standard(s). If the officially recognized compendial methods have been modified or replaced, a discussion should be included.

The justification for certain tests, analytical procedures and acceptance criteria (e.g. degradation products or dissolution method development) may have been discussed in other sections of the PD and would not need to be repeated here, although a cross-reference should be provided.

ICH Q6A (6) should be consulted for the development of specifications for FPPs.

3.2.P.6 Reference standards or materials (name, dosage form)

Information on the reference standards or reference materials used for testing of the FPP should be provided, if not previously provided in “3.2.S.5 Reference standards or materials”.

See section 3.2.S.5 for information that should be provided on reference standards or materials. Information should be provided on reference materials of FPP degradation products, where not included in 3.2.S.5.

Reference documents: ICH Q6A (6), *WHO Technical Report Series*, No. 943, Annex 3 (17).

3.2.P.7 Container-closure system (name, dosage form)

A description of the container-closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g. those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located in 3.2.P.2.

The WHO *Guidelines on packaging for pharmaceutical products* (18) and the officially recognized pharmacopoeias should be consulted for recommendations on the packaging information for FPPs.

Descriptions, materials of construction and specifications (of the company responsible for packaging the FPP, generally the FPP manufacturer) should be provided for the packaging components that are:

- in direct contact with the dosage form (e.g. container, closure, liner, desiccant and filler);
- used for drug delivery (including the device(s) for multidose solutions, emulsions, suspensions and powders or granules for reconstitution into solution, emulsion or suspension;
- used as a protective barrier to help ensure stability or sterility;
- necessary to ensure FPP quality during storage and shipping.

Primary packaging components are those that are in direct contact with the API or FPP.

The specifications for the primary packaging components should include a specific test for identification (e.g. IR). Specifications for film and foil materials should include limits for thickness or area weight.

Information to establish the suitability (e.g. qualification) of the container-closure system should be discussed in section 3.2.P.2. Comparative studies may be warranted for certain changes in packaging components (e.g. a comparative delivery study (droplet size) for a change in manufacturer of dropper tips).

3.2.P.8 Stability (name, dosage form)

3.2.P.8.1 Stability summary and conclusions (name, dosage form)

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life.

The WHO stability guidelines *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (19) should be consulted for recommendations on the core stability data package required for the prequalification of APIs and FPPs.

As outlined in the WHO stability guidelines, the purpose of stability testing is to provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability programme also includes the study of product-related factors that influence the quality of the API or FPP, for example, interaction of API with excipients, container-closure systems and packaging materials.

Stress testing

As outlined in the WHO stability guidelines, photostability testing should be conducted on at least one primary batch of the FPP if appropriate. If “protect from light” is stated in one of the officially recognized pharmacopoeias for the API or FPP it is sufficient to state “protect from light” on labelling, in lieu of photostability studies, when the container-closure system is shown to be light protective. Additional stress testing of specific types of dosage forms may be appropriate (e.g. cyclic studies for semi-solid products or freeze–thaw studies for liquid products).

Accelerated, intermediate (if necessary) and long-term testing

Stability data must demonstrate stability of the medicinal product throughout its intended shelf-life under the climatic conditions prevalent in the target countries. Merely applying the same requirements applicable to other markets could potentially lead to substandard products if stability studies are conducted at the storage conditions for countries in Climatic Zone I/II when the products are supplied in countries in Climatic Zones III and IV. Refer to *WHO Technical Report Series*, No. 953, Annex 2, Appendix 1 (7) for information on climatic zones. Effective as of September 2011, the required long-term storage conditions for the WHO Prequalification of Medicines Programme are $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}/75\% \pm 5\% \text{ RH}$, and after this date the long-term data submitted in the PD (see Table 3) should be at these conditions. The use of alternative long-term conditions will need to be justified and should be supported with appropriate evidence.

Other storage conditions are outlined in the WHO stability guidelines for FPPs packaged in impermeable and semi-permeable containers and those intended for storage in a refrigerator and in a freezer. FPPs intended for storage below $-20\text{ }^{\circ}\text{C}$ should be treated on a case-by-case basis.

Table 3
Minimum data required at the time of submitting the dossier (in the general case)

Storage temperature (°C)	Relative humidity (%)	Minimum time period (months)
Accelerated 40 ± 2	75 ± 5	6
Intermediate ^a	N/A	N/A
Long-term 30 ± 2	75 ± 5	6

^a Where long-term conditions are $30\text{ °C} \pm 2\text{ °C}/75\% \pm 5\% \text{ RH}$, there is no intermediate condition.

Refer to *WHO Technical Report Series*, No. 953, Annex 2 (19) for further information regarding the storage conditions. Reference should also be made to the WHO Prequalification of Medicines Programme web site for any exceptions to the stated requirements.

To establish the shelf-life, data should be provided on not less than two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g. immediate-release solid FPPs (with noted exceptions) or non-sterile solutions), at least one batch of at least pilot scale and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules) of each proposed strength of the FPP. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

The stability testing programme should be summarized and the results of stability testing should be reported in the dossier and summarized in the tables in the QOS-PD. Bracketing and matrixing of proportional strengths can be applied if scientifically justified.

For sterile products, sterility should be reported at the beginning and end of shelf-life. For parenteral products, subvisible particulate matter should be reported frequently, but not necessarily at every test interval. Bacterial endotoxins need only be reported at the initial test point. Weight loss from plastic containers should be reported over the shelf-life.

Any in-use period and associated storage conditions should be justified with experimental data, for example, after opening, reconstitution and/or dilution of any sterile and/or multidose products or after first opening of FPPs packed in bulk multidose containers (e.g. bottles of 1000s). If applicable, the in-use period and storage conditions should be stated in the product information.

The information on the stability studies should include details such as

- storage conditions;
- strength;
- batch number, including the API batch number(s) and manufacturer(s);

- batch size;
- container-closure system including orientation (e.g. erect, inverted, on-side) where applicable;
- completed (and proposed) test intervals.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “all tests meet specifications”. The discussion should include ranges of analytical results and any trends that were observed. For quantitative tests (e.g. individual and total degradation product tests and assay tests) actual numerical results should be provided rather than vague statements such as “within limits” or “conforms”. Dissolution results should be expressed, at a minimum, as both the average and range of individual results.

Applicants should consult ICH's Q1E guideline (23) for details on the evaluation and extrapolation of results from stability data (e.g. if significant change was not observed within 6 months at accelerated condition and the data show little or no variability, the proposed shelf-life could be up to twice the period covered by the long-term data, but should not exceed the long-term data by more than 12 months).

Proposed storage statement and shelf-life

The proposed storage statement and shelf-life (and in-use storage conditions and in-use period, if applicable) for the FPP should be provided.

The recommended labelling statements for use based on the stability studies, are provided in the WHO stability guidelines (19).

Reference documents: *WHO Technical Report Series*, No. 953, Annex 2 (19), ICH Q1A (20), Q1B (22), Q1C (47), Q1D (24), Q1E (23), Q3B (11), Q6A (6).

3.2.P.8.2 Post-approval stability protocol and stability commitment (name, dosage form)

The post-approval stability protocol and stability commitment should be provided.

Primary stability study commitment

When the available data on long-term stability of primary batches do not cover the proposed shelf-life granted at the time of assessment of the PD, a commitment should be made to continue the stability studies in order to firmly establish the shelf-life. A written commitment (signed and dated) to continue long-term testing over the shelf-life period should be included in the dossier.

Commitment stability studies

The long-term stability studies for the commitment batches should be conducted throughout the proposed shelf-life on at least three production batches of each strength in each container-closure system. Where stability data were not provided for three production batches of each strength, a written commitment (signed and dated) should be included in the dossier.

Ongoing stability studies

As described in the WHO stability guidelines (19), an ongoing stability programme is established to monitor the product over its shelf-life and to determine that the product remains and can be expected to remain within specifications under the storage conditions on the label. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every container-closure system, if relevant, should be included in the stability programme (unless none is produced during that year). Bracketing and matrixing may be applicable. A written commitment (signed and dated) to this effect should be included in the dossier.

Any differences between the stability protocols used for the primary batches and those proposed for the commitment batches or ongoing batches should be scientifically justified.

Reference document: ICH Q1A (20).

3.2.P.8.3 Stability data (name, dosage form)

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Information on characterization of impurities is located in 3.2.P.5.5.

The actual stability results and reports used to support the proposed shelf-life should be provided in the PD. For quantitative tests (e.g. individual and total degradation product tests and assay tests), actual numerical results should be provided rather than vague statements such as “within limits” or “conforms”.

Dissolution results should be expressed, at a minimum, as both the average and range of individual results.

Reference documents: ICH Q1A (20), Q1B (22), Q1C (47), Q1D (24), Q1E (23), Q2 (16).

3.2.A Appendices

3.2.A.1 Facilities and equipment

Not applicable (i.e. not a biotech product).

3.2.A.2 Adventitious agents safety evaluation

3.2.A.3 Novel excipients

Novel excipients are not accepted in the WHO Prequalification of Medicines Programme.

3.2.R Regional information

3.2.R.1 Production documentation

3.2.R.1.1 Executed production documents

A minimum of two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g. immediate-release solid FPPs (with noted exceptions) or non-sterile solutions), at least one batch of at least pilot scale (the batch used in comparative bioavailability or biowaiver studies) and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules), should be manufactured for each strength. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

For solid oral dosage forms, pilot scale is generally, at a minimum, one-tenth that of full production scale or 100 000 tablets or capsules, whichever is the larger.

Copies of the executed production documents should be provided for the batches used in the comparative bioavailability or biowaiver studies. Any notations made by operators on the executed production documents should be clearly legible.

If not included in the executed batch records through sufficient in- process testing, data should be provided for the batch used in comparative bioavailability or biowaiver studies that demonstrate the uniformity of this batch. The data to establish the uniformity of the biobatch should involve testing to an extent greater than that required in routine quality control.

English translations of executed records should be provided where relevant.

3.2.R.1.2 Master production documents

Copies of the FPP master production documents should be provided for each proposed strength, commercial batch size and manufacturing site.

The details in the master production documents should include, but not be limited to, the following:

- master formula;
- dispensing, processing and packaging sections with relevant material and operational details;
- relevant calculations (e.g. if the amount of API is adjusted based on the assay results or on the anhydrous basis);
- identification of all equipment by, at a minimum, type and working capacity (including make, model and equipment number, where possible);
- process parameters (e.g. mixing time, mixing speed, milling screen size, processing temperature range, granulation end-point and tablet machine speed (expressed as target and range));
- list of in-process tests (e.g. appearance, pH, assay, blend uniformity, viscosity, particle size distribution, loss on drying, weight variation,

hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity and filter integrity checks) and specifications;

- sampling plan with regard to the:
 - steps at which sampling should be done (e.g. drying, lubrication and compression),
 - number of samples that should be tested (e.g. for blend uniformity testing of low-dose FPPs, blend drawn using a sampling thief from x positions in the blender),
 - frequency of testing (e.g. weight variation every x minutes during compression or capsule filling);
- precautions necessary to ensure product quality (e.g. temperature and humidity control and maximum holding times);
- for sterile products, reference to standard operating procedures (SOPs) in appropriate sections and a list of all relevant SOPs at the end of the document;
- theoretical and actual yield;
- compliance with the GMP requirements.

Reference document: WHO Technical Report Series, No. 961 (48).

3.2.R.2 Analytical procedures and validation information

The tables presented in section 2.3.R.2 in the QOS-PD template should be used to summarize the analytical procedures and validation information from sections 3.2.S.4.2, 3.2.S.4.3, 2.3.S.4.4 (c), 2.3.S.7.3 (b), 3.2.P.5.2 and 3.2.P.5.3 where relevant.

4.3 Literature references

References to the scientific literature relating to both the API and FPP should be included in this section of the PD when appropriate.

References

1. Procedure for prequalification of pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2011, Annex 10 (WHO Technical Report Series, No. 961; https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1).
2. *ICH harmonised tripartite guideline: the common technical document for the registration of pharmaceuticals for human use: quality – M4Q*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2002.

3. Guidelines on submission of documentation for a multisource (generic) finished product: general format: preparation of product dossiers in common technical document format. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth report*. Geneva, World Health Organization, 2011, Annex 5 (WHO Technical Report Series, No. 961; https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1).
4. Guidelines on active pharmaceutical ingredient master file procedure. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-second report*. Geneva, World Health Organization, 2008, Annex 4 (WHO Technical Report Series, No. 948; https://iris.who.int/bitstream/handle/10665/43852/WHO_TRS_948_eng.pdf?sequence=1&isAllowed=y).
5. *Common technical document for the registration of pharmaceuticals for human use – quality questions & answers/location issues*. European Medicines Agency, 2009.
6. *ICH harmonised tripartite guideline: specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances – Q6A*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1999.
7. *ICH harmonised tripartite guideline: Good manufacturing practice guide for active pharmaceutical ingredients – Q7*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2000.
8. WHO good manufacturing practices for active pharmaceutical ingredients. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report*. Geneva, World Health Organization, 2010, Annex 2 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y).
9. Guidance on variations to a prequalified product dossier. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report*. Geneva, World Health Organization, 2007, Annex 6 (WHO Technical Report Series, No. 943; https://iris.who.int/bitstream/handle/10665/43632/WHO_TRS_943_eng.pdf?sequence=1&isAllowed=y).
10. *ICH harmonised tripartite guideline: impurities in new drug substances – Q3A*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2006.
11. *ICH harmonised tripartite guideline: impurities in new drug products – Q3B*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2006.
12. *ICH harmonised tripartite guideline impurities: guideline for residual solvents – Q3C*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2011.
13. Committee for Medicinal Products for Human Use (CHMP). *Guideline on the limits of genotoxic impurities*. European Medicines Agency, 2006 (CPMP/SWP/5199/02 EMEA/CHMP/QWP/251344/2006).
14. *US FDA Guidance for industry: Genotoxic and carcinogenic impurities in drug substances and products: recommended approaches*. US Food and Drug Administration, 2008.
15. Committee for Medicinal Products for Human Use (CHMP). *Guideline on the specification limits for residues of metal catalysts or metal reagents*. London, European Medicines Agency, 2008 (EMA/CHMP/SWP/4446/2000).
16. *ICH Harmonised tripartite guideline: validation of analytical procedures: text and methodology – Q2*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1994.

17. General guidelines for the establishment, maintenance and distribution of chemical reference substances. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report*. Geneva, World Health Organization, 2007, Annex 3 (WHO Technical Report Series, No. 943; https://iris.who.int/bitstream/handle/10665/43632/WHO_TRS_943_eng.pdf?sequence=1&isAllowed=y).
18. Guidelines on packaging for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002, Annex 9 (WHO Technical Report Series, No. 902; https://iris.who.int/bitstream/handle/10665/42424/WHO_TRS_902.pdf?sequence=1&isAllowed=y).
19. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2009, Annex 2 (WHO Technical Report Series, No. 953; https://iris.who.int/bitstream/handle/10665/44553/WHO_TRS_953_eng.pdf?sequence=1&isAllowed=y).
20. *ICH harmonised tripartite guideline: stability testing of new drug substances and products – Q1A*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2003.
21. Guidelines for registration of fixed-dose combination medicinal products. Appendix 3: Pharmaceutical development (or preformulation) studies. Table A1: Typical stress conditions in preformulation stability studies. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report*. Geneva, World Health Organization, 2005, Annex 5 (WHO Technical Report Series, No. 929; https://iris.who.int/bitstream/handle/10665/43157/WHO_TRS_929_eng.pdf?sequence=1&isAllowed=y).
22. *ICH harmonised tripartite guideline: Stability testing: Photostability testing of new drug substances and products – Q1B*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1996.
23. *ICH harmonised tripartite guideline: evaluation for stability data – Q1E*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2003.
24. *ICH harmonised tripartite guideline: bracketing and matrixing designs for stability testing of new drug substances and products – Q1D*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2002.
25. *ICH Harmonised tripartite guideline: pharmaceutical development – Q8*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2009.
26. *ICH Harmonised tripartite guideline: quality risk management – Q9*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2005.
27. *ICH harmonised tripartite guideline: pharmaceutical quality system – Q10*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2008.
28. *Inactive ingredient guide*. US Food and Drug Administration, <http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>
29. Rowe RC, Sheskey PJ, Quinn ME, eds. *Handbook of pharmaceutical excipients*, 6th ed. London, Pharmaceutical Press, 2009.
30. *Excipients in the labelling and package leaflet of medicinal products for human use*, 2018 (SANTE-2017-11668) https://health.ec.europa.eu/system/files/2018-03/guidelines_excipients_march2018_en_0.pdf

31. WHO Guidelines on development of paediatric medicines: points to consider in formulation. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-sixth report*. Geneva, World Health Organization, 2012, Annex 5 (WHO Technical Report Series, No. 970; https://iris.who.int/bitstream/handle/10665/75168/WHO_TRS_970.pdf?sequence=1&isAllowed=y).
32. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization, 2006, Annex 7 (WHO Technical Report Series, No. 937; https://apps.who.int/iris/bitstream/handle/10665/43443/WHO_TRS_937_eng.pdf?sequence=1).
33. Containers – glass. In: *United States Pharmacopeia*, 2nd suppl. Rockville, MD, 2007.
34. Glass containers for pharmaceutical use. In: *European Pharmacopoeia*. Strasbourg, European Directorate for the Quality of Medicines, 2010: 303–307.
35. Plastic containers and closures for pharmaceutical use. In: *European Pharmacopoeia*. Strasbourg, European Directorate for the Quality of Medicines, 2010: 308–309.
36. Containers – plastic. In: *United States Pharmacopeia*, 2nd suppl. Rockville, MD, 2007.
37. Elastomeric closures for injections, In: *United States Pharmacopeia*, 2nd suppl. Rockville, MD, 2007: 144–145.
38. Rubber closures for containers. In: *European Pharmacopoeia*. Strasbourg, European Directorate for the Quality of Medicines, 2010: 316–317.
39. Commission regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food.
40. WHO good distribution practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report*. Geneva, World Health Organization, 2010, Annex 5 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y).
41. Good manufacturing practices for pharmaceutical products: main principles. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2011, Annex 3 (WHO Technical Report Series, No. 961; https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1).
42. *ICH Harmonised tripartite guideline: viral safety evaluation of biotechnology products derived from cell lines of human or animal origin – Q5A*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2009.
43. *ICH Harmonised tripartite guideline: derivation and characterisation of cell substrates used for production of biotechnological/biological products – Q5D*. Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1997.
44. *ICH Harmonised tripartite guideline: specifications: test procedures and acceptance criteria for biotechnological/biological products – Q6B*. Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1999.
45. Recommendations on risk of transmitting animal spongiform encephalopathy agents via medicinal products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003, Annex 1 (WHO Technical Report Series, No. 908; https://iris.who.int/bitstream/handle/10665/42613/WHO_TRS_908.pdf?sequence=1&isAllowed=y).

46. *ICH harmonised tripartite guideline: stability testing for new dosage forms: Annex to the ICH harmonised tripartite guideline on stability testing for new drugs and products – Q1C*. Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1996.
47. Good manufacturing practices for sterile pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2011, Annex 6 (WHO Technical Report Series, No. 961; https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1).

Appendix 1

Recommendations for conducting and assessing comparative dissolution profiles

The dissolution measurements of the two FPPs (e.g. test and reference (comparator) or two different strengths) should be made under the same test conditions. A minimum of three time-points (zero excluded) should be included, the time-points for both reference (comparator) and test product being the same. The sampling intervals should be short for a scientifically sound comparison of the profiles (e.g. 5, 10, 15, 20, 30, 45 (60, 90, 120) minutes). The 15-minute time-point is critical to determine whether a product is very rapidly dissolving and to determine whether f_2 must be calculated. For extended-release FPPs, the time-points should be set to cover the entire duration of expected release, e.g. 1, 2, 3, 5 and 8 hours for a 12-hour release and additional test intervals for longer duration of release.

Studies should be performed in at least three media covering the physiological range, including pH 1.2 hydrochloric acid, pH 4.5 buffer and pH 6.8 buffer. *International Pharmacopoeia* buffers are recommended; other pharmacopoeial buffers with the same pH and buffer capacity are also accepted. Water may be considered as an additional medium, especially when the API is unstable in the buffered media to the extent that the data are unusable.

If both the test and reference (comparator) products show more than 85% dissolution in 15 minutes, the profiles are considered similar (no calculations required). Otherwise:

- Similarity of the resulting comparative dissolution profiles should be calculated using the following equation that defines a similarity factor (f_2):

$$f_2 = 50 \text{ LOG } \{ [1 + 1/n \sum_{t=1}^n (R_t - T_t)^2]^{-0.5} \times 100 \}$$

where R_t and T_t are the mean per cent API dissolved in reference (comparator) and test product, respectively, at each time-point. An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar.

- A maximum of one time-point should be considered after 85% dissolution of the reference (comparator) product has been reached. In the case where 85% dissolution cannot be reached due to poor solubility of the API, the dissolution should be conducted until an asymptote (plateau) has been reached.
- At least 12 units should be used for determination of each profile. Mean dissolution values can be used to estimate the similarity factor, f_2 . To use

mean data, the percentage coefficient of variation at the first time-point should be not more than 20% and at other time-points should be not more than 10%.

- When delayed-release products (e.g. enteric coated) are being compared, the recommended conditions are acid medium (pH 1.2) for 2 hours and buffer pH 6.8 medium.
- When comparing extended-release beaded capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the API, one condition (normally the release condition) will suffice.
- Surfactants should be avoided in comparative dissolution testing. A statement that the API is not soluble in any of the media is not sufficient and profiles in the absence of surfactant should be provided. The rationale for the choice and concentration of surfactant should be provided. The concentration of the surfactant should be such that the discriminatory power of the test will not be compromised.

Appendix 2

Product quality review requirements for *established multisource products*

For an established multisource product, a product quality review may satisfy the requirements of sections 3.2.P.2.2.1 (a), 3.2.P.2.3 (a) and 3.2.P.3.5 of the PD and QOS-PD.

A product quality review should be submitted with the objective of verifying the consistency of the quality of the FPP and its manufacturing process.

Rejected batches should not be included in the analysis but must be reported separately together with the reports of failure investigations, as indicated below.

Reviews should be conducted with no fewer than 10 consecutive batches manufactured over the period of the past 12 months or, where 10 batches were not manufactured in the past 12 months, no fewer than 25 consecutive batches manufactured over the period of the past 36 months and should include at least:

- a review of starting and primary packaging materials used in the FPP, especially those from new sources;
- a tabulated review and statistical analysis of quality control and in-process control results;
- a review of all batches that failed to meet established specification(s);
- a review of all critical deviations or non-conformances and related investigations;
- a review of all changes carried out to the processes or analytical methods;
- a review of the results of the stability-monitoring programme;
- a review of all quality-related returns, complaints and recalls, including export-only medicinal products;
- a review of the adequacy of previous corrective actions;
- a list of validated analytical and manufacturing procedures and their revalidation dates.

Notes

- Reviews must include data from all batches manufactured during the review period.
- Data should be presented in tabular or graphical form, when applicable.
- The above listing of requirements is specific to the dossier assessment process requirements and does not relieve the applicant of related GMP requirements.

6.6 Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities

Annex 5, WHO Technical Report Series, 986, 2014

Scope

The revision of the WHO *Guidelines on submission of documentation for prequalification of innovator finished pharmaceutical products approved by stringent regulatory authorities*¹ is extended to include not only innovator products, but also multisource products. The title is accordingly changed to *Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities*. These guidelines apply to both innovator² and multisource (generic) finished pharmaceutical products (FPPs) approved by SRAs.

Introduction

The World Health Organization (WHO) recognizes the scientific evaluation of finished pharmaceutical products (FPPs) by SRAs,¹ which apply similarly stringent standards for quality, safety and efficacy to those recommended by WHO. Where an applicant shares with WHO information on an FPP that has been approved by a stringent SRA (hereinafter called the reference SRA) and that is invited for prequalification, WHO will consider such FPPs for inclusion in the list of WHO-prequalified products, as and when information about such a product becomes available to WHO and when the applicant in question expresses interest in the product being prequalified by WHO.

¹ Stringent regulatory authority (SRA): a regulatory authority which is: (a) a member of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (as specified on www.ich.org); or (b) an ICH observer, being the European Free Trade Association (EFTA), as represented by Swissmedic and Health Canada (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

² Generally the innovator pharmaceutical product is that which was first authorized for marketing, on the basis of documentation of quality, safety and efficacy (WHO Technical Report Series, No. 937, 2006, Annex 7).

Guidelines on submission of documentation

The following should be submitted:

1. A covering letter, which should include:
 - a statement indicating that the information submitted is true and correct;
 - a statement confirming that for WHO prequalification, the FPP – including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, product information – will, at the time of submission and after prequalification, in all respects be the same as the product registered with the reference SRA;
 - a statement indicating that the product is actually on the market of the reference SRA's country or region.
2. A copy of the marketing authorization, or the equivalent thereof, issued by the reference SRA to demonstrate that the product is registered or licensed in accordance with the reference SRA requirements. If applicable, a copy of the latest renewal of the marketing authorization should also be provided.
3. A copy of the current WHO-type certificate of a pharmaceutical product issued and fully completed, including answers to each question, by the reference SRA.
4. The latest SRA-approved product information (summary of product characteristics (SmPC), or an equivalent thereof, the patient information leaflet (PIL), or equivalent thereof, and the labelling). Provide a web link to the SRA-approved product information, preferably on the website of the SRA itself, if available.
5. A list of the SRA-approved manufacturer(s) of the FPP, including manufacturers of intermediates, primary packaging sites and release-testing sites, with the physical address of the manufacturing site(s) (and unit if applicable).
6. A list of the SRA-approved manufacturer(s) of the active pharmaceutical ingredient(s) (API(s)) used in the manufacture of the FPP, with the physical address of the manufacturing site(s) (and unit if applicable).
7. If available, a public assessment report, such as the Scientific Discussion of the European Public Assessment Report (EPAR), issued by the reference SRA. Assessment report(s) issued by the reference SRA that are not publicly available may be requested.
8. A tabular listing of the batches manufactured for the market of the reference SRA's region or country since approval or during the past five years, whichever is shorter. The table should include at least the batch

number, batch size (number of units), date of manufacture and pack type/size. Also provide a copy of the most recent product quality review, prepared according to the requirements of the reference SRA.

9. A sample(s) of the product in market packaging(s). This should be provided with the submission to enable visual inspection thereof. Attach the respective certificate of analysis.
10. A copy of the currently approved FPP specifications (release and shelf-life), dated and signed or certified by authorized personnel, with the analytical test procedures.
11. The quality information summary (QIS-SRA). The QIS-SRA template, available on the WHO Prequalification Programme website (<http://apps.who.int/prequal/>), should be fully completed and submitted with the application. The QIS-SRA provides a condensed summary of key information on the FPP as approved by the reference SRA at the time of application for prequalification of the FPP.

Please note that the submission must be in English, and must include certified English translations of product information and other documents, if applicable. These documents should be made available electronically. The English language version of the product information, in the case of English translations, should also be submitted as Word files.

WHO may request additional data, when considered necessary for the use of the product in populations, settings or regions relevant for prequalified products. If necessary, this additional information, relevant for use of the product within the scope of the Prequalification Programme, will be included in the WHO public assessment report (WHOPAR) as a separate piece of information. Such information could be communicated to the reference SRA where appropriate. The SRA-approved product information will not be changed. WHO would normally not inspect the manufacturing site(s) of an SRA-approved product; however, there may be circumstances necessitating an inspection to be conducted in collaboration with the reference SRA, upon application or after prequalification of the FPP.

Variations to and renewal of the marketing authorization of an FPP that has been prequalified by WHO based on the approval by an SRA, remain the responsibility of the reference SRA.

Once the product has been prequalified, WHO should be provided with a copy of the regulatory approval letter of any changes to the key information on the FPP (as captured in the QIS-SRA), the product information, the revised QIS-SRA, the FPP specification and test procedures, where appropriate, immediately after the variation has been approved by the reference SRA.

Changes to the QIS-SRA, the product information, the specification and test procedures should be shown in track-change mode in Word files. The clean version

(in English language) of the updated product information should also be submitted. Other supporting information may be requested once the variation notification has been submitted.

WHO should be informed immediately in case of discontinuation of the product with the relevant SRA and of any critical safety or quality-related issues reported for batches on the market.

The preferred storage condition for WHO-prequalified products is “do not store above 30 °C”, based on demonstrated stability at long-term storage conditions of 30 °C/75% relative humidity (RH) and at accelerated storage conditions (40 °C/75% RH). If this storage condition is not indicated on the SmPC, PIL and labels of the product, applicants are encouraged to apply for a variation in this respect with the relevant SRA. This could also be done after prequalification of the product.

Products that received United States Food and Drug Administration (US-FDA) tentative approval or positive opinions under Article 58 of European Union Regulation (EC) No. 726/2004 or the Canada S.C. 2004, c. 23 (Bill C-9) procedure, are not within the scope of these guidelines. Such products can be co-listed on the WHO list of prequalified products in accordance with mutual agreements between WHO and these regulatory authorities.

6.7 WHO guidelines on variations to a prequalified product

Annex 3, WHO Technical Report Series, 981, 2013

Introduction	828
1. Background	829
1.1 Objectives	829
1.2 Scope and application	830
2. Guidance for implementation	831
2.1 Reporting types	831
2.1.1 Notifications	832
2.1.2 Minor variation (Vmin)	832
2.1.3 Major variation (Vmaj)	833
2.1.4 New applications and extension applications	833
2.1.5 Labelling information	833
2.2 Conditions to be fulfilled	833
2.3 Documentation required	833
3. Glossary	834
4. Administrative changes	836
2. Change in the name and/or corporate address of the supplier of the FPP	836
3. Change in the name or address of a manufacturer of an API that is not a supplier of a prequalified API or that is not supported by a CEP	836
4. Change in the name and/or address of a manufacturer of the FPP	837
5. Deletion of a manufacturing site or manufacturer	837
5. Changes to a CEP or to a confirmation of API-prequalification document	838
5. Submission of a new or updated CEP for an API or starting material or intermediate used in the manufacturing process of the API	838
6. Submission of a new or updated confirmation of API-prequalification document	839
7. Submission of a new or updated transmissible spongiform encephalopathy (TSE) CEP for an excipient or API (addition or replacement)	840
6. Quality changes	840
3.2. S Drug substance (or API)	840
3.2. S.2 Manufacture	840
8. Replacement or addition of a new manufacturing site or manufacturer of an API	840

9. Change or addition of a manufacturing block or unit at a currently accepted site of API manufacture	843
10. Change in the manufacturing process of the API	844
11. Change in the in-process tests or limits applied during the manufacture of the API	846
12. Change in batch size of the API or intermediate	847
13. Change to the specifications or analytical procedures applied to materials used in the manufacture of the API (e.g. raw materials, starting materials, reaction intermediates, solvents, reagents, catalysts)	848
3.2. S.4 Control of the API by the API manufacturer	850
14. Changes to the test parameters, acceptance criteria, or analytical procedures of the API manufacturer that do not require a change to the FPP manufacturer's API specifications	850
3.2. S.4 Control of the API by the FPP manufacturer	851
15. Change to the test parameters or acceptance criteria of the API specifications of the FPP manufacturer	851
16. Change to the analytical procedures used to control the API by the FPP manufacturer	853
3.2. S.6 Container-closure system	855
17. Change in the immediate packaging (primary and functional secondary components) for the storage and shipment of the API	855
18. Change in the specifications of the immediate packaging for the storage and shipment of the API	856
19. Change to an analytical procedure on the immediate packaging of the API	856
3.2. S.7 Stability	858
20. Change in the retest period or shelf-life of the API	858
21. Change in the labelled storage conditions of the API	858
3.2. P Drug product (or FPP)	859
3.2. P.1 Description and composition of the FPP	859
22. Change in the composition of a solution dosage form	859
23. Change in the colouring system or the flavouring system currently used in the FPP	860
24. Change in weight of tablet coatings or capsule shells	862
25. Change in the composition of an immediate-release solid oral dosage form	862
26. Change or addition of imprints, embossing or other markings, including replacement or addition of inks used for product markings and change in scoring configuration	864
27. Change in dimensions without change in qualitative or quantitative composition and mean mass	865
3.2. P.3 Manufacture	866
28. Addition or replacement of a manufacturing site for part or all of the manufacturing process for an FPP	866
29. Replacement or addition of a site involving batch control testing	868
30. Change in the batch size of the FPP	868
31. Change in the manufacturing process of the FPP	870
32. Change to in-process tests or limits applied during the manufacture of the FPP or intermediate	871

3.2. P.4	Control of excipients	872
33.	Change in source of an excipient from a TSE risk to a material of vegetable or synthetic origin	872
34.	Change in the specifications or analytical procedures for an excipient	872
35.	Change in specifications of an excipient to comply with an officially recognized pharmacopoeia	873
3.2. P.5	Control of FPP	874
36.	Change in the standard claimed for the FPP from an in-house to an officially recognized pharmacopoeial standard	874
37.	Change in the specifications of the FPP involving test parameters and acceptance criteria	874
38.	Change in the analytical procedures for the FPP	876
3.2. P.7	Container-closure system	877
39.	Replacement or addition of a primary packaging type	877
40.	Change in the package size	878
41.	Change in the shape or dimensions of the container or closure	878
42.	Change in qualitative and/or quantitative composition of the immediate packaging material	879
43.	Change in the specifications of the immediate packaging	880
44.	Change to an analytical procedure on the immediate packaging	880
45.	Change in any part of the (primary) packaging material not in contact with the FPP formulation (e.g. colour of flip-off caps, colour code rings on ampoules, or change of needle shield)	881
46.	Change to an administration or measuring device that is not an integral part of the primary packaging (excluding spacer devices for metered dose inhalers)	882
3.2. P.8	Stability	882
47.	Change in the shelf-life of the FPP (as packaged for sale)	882
48.	Change in the in-use period of the FPP (after first opening or after reconstitution or dilution)	883
49.	Change in the labelled storage conditions of the finished pharmaceutical product (as packaged for sale), the product during the in-use period or the product after reconstitution or dilution	884
Appendix 1	Examples of changes that make a new application or extension application necessary	885
Appendix 2	Changes to excipients	886

Introduction

The variation guidelines have been completely updated and expanded, bringing them into line with the principles of the new generic quality guidelines, WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.

The guidelines¹ retain the basic structure and function of the previous variation guidelines, and have been expanded to include the classification of additional post-approval/post-prequalification changes and to establish the level of risk inherent to each change.² Although the general requirements have not significantly changed, the additional details help the reader to classify changes that may occur related to all the major sections of a quality dossier, to understand the considerations necessary to assess the risk of each change, and to determine the documentation required to support the change.

In some cases, changes that previously were considered major changes by default are now classified minor variations or notifications, and some minor variations have been reclassified as notifications. In addition, for some categories that previously required acceptance of the change prior to implementation, the applicant can now implement the change immediately upon notification.

The change categories are organized according to the structure of the common technical document (CTD). The specific CTD sections associated with individual data requirements have been identified in order to assist in the filing of documentation (reproduced with corresponding numbers in bold). Presentation corresponds to section 1.4 in Annex 4 of WHO Technical Report Series, No. 970.³

Changes are classified as major only in those instances where the level of risk is considered to be high and it is deemed necessary to provide the WHO Prequalification of Medicines Programme (WHO/PQP) with adequate time for an assessment of the supporting documentation. Particular circumstances are identified where lower reporting requirements (annual notification (AN), immediate notification (IN) or minor variation (Vmin)) are possible. In all cases where notification to WHO/PQP or acceptance by WHO/PQP is required prior to implementation, assessment timelines will be published in order to provide predictable and reasonable timeframes.

¹ Guidance on variations to a prequalified product dossier. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report*. Geneva, World Health Organization, 2007 (WHO Technical Report Series, 943), Annex 6.

² WHO Guidelines on quality risk management. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh report*. Geneva, World Health Organization, 2013 (WHO Technical Report Series, 981), Annex 2.

³ Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-sixth report*. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 4.

In addition, the guidelines assist in understanding the possible consequences of the listed changes, and may be useful as a risk management tool to promote or enhance best practices within organizations.

A companion Question and Answer document is in preparation to assist in interpretation of the guidelines. This document will address many of the questions raised during the guidelines circulation process.

1. Background

This guidance document is technically and structurally inspired by the European Union Institutions and Bodies Commission's Guideline on the details of the various categories of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products. It is intended to provide supportive information on how to present an application to implement a change to a product.

This guidance supersedes the guidance published in 2007.⁴

An applicant is responsible for the safety, efficacy and quality of a product throughout its life-cycle. Therefore, the applicant is required to make changes to the details of the product in order to accommodate technical and scientific progress, or to improve or introduce additional safeguards for the prequalified product. Such changes, whether administrative or substantive, are referred to as variations and may be subject to acceptance by WHO/PQP prior to implementation.

Technical requirements for the different types of variations are set out in these guidelines in order to facilitate the submission of appropriate documentation by applicants and their assessment by WHO/PQP and to ensure that variations to the medicinal product do not result in health concerns.

The procedure for submitting variations is not within the scope of these guidelines. Advice on the procedure for submitting a variation and current review timelines are set out on the WHO/PQP web site which may be updated from time to time. Applicants are advised to consult information on the web site whenever they are considering the submission of a variation application.

1.1 Objectives

These guidelines are intended to:

- assist applicants with the classification of changes made to the quality part of a prequalified finished pharmaceutical product (FPP);
- provide guidance on the technical and other general data requirements to support changes to the quality attributes of the active pharmaceutical ingredient (API) or FPP.

⁴ See footnote 1.

1.2 Scope and application

These guidelines apply to applicants intending to make changes to the quality sections of product dossiers for an API or an FPP. This guidance should be read in conjunction with the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*⁵ as well as other related WHO guidelines.

This guidance document is applicable only to APIs and excipients manufactured by chemical synthesis or semi-synthetic processes and FPPs containing such APIs and excipients. APIs produced by fermentation and APIs of biological, biotechnological or herbal origin are treated as special cases. The applicant is requested to contact WHO/PQP regarding planned variations to such products.

The notification requirements for API-related changes differ depending on the manner in which information on the API was submitted in the FPP application, namely, use of a prequalified API, use of a European Pharmacopoeia Certificate of Suitability (CEP), use of the API master file (APIMF) procedure, or as provided in full within the dossier.

The conditions and documentation stipulated in this guidance for API-related variations focus primarily on those FPPs that relied upon the provision of full API information within the FPP dossier. In general FPPs that rely upon the APIMF procedure have reduced reporting requirements because the API manufacturers themselves have notified the relevant API-related change directly to WHO/PQP. Similarly, when an FPP relies upon a CEP or a prequalified API, FPP applicants are required to notify WHO/PQP only when the associated CEP or Confirmation of API Prequalification document has been revised.

Guidance for API manufacturers on the technical and procedural requirements for changes to prequalified APIs and to APIs supported by the APIMF procedure is available on the Prequalification web site. Regardless of whether the API-related change is notified primarily by the API manufacturer (API prequalification (API-PQ) procedure, APIMF procedure or CEP), or the FPP manufacturer (full API information in dossier) the technical requirements are in principle the same as those stipulated in these guidelines.

Whenever FPPs have been prequalified on the basis of approval by a stringent regulatory authority (SRA) (innovator products or generic products), subsequent applications for variations should be approved by the same SRA and WHO/PQP should be notified of the approval of the changes. Applicants are advised to refer to the Letter of Prequalification.

When a variation leads to a revision of the summary of product characteristics (SmPC), the patient information leaflet (PIL), labelling and packaging leaflet and updated product information should be submitted as part of the application.

⁵ See footnote 3.

For variations that require generation of stability data on the API or FPP, the stability studies required, including commitment batches, should always be continued to cover the currently accepted retest or shelf-life period. WHO/PQP should be informed immediately if any problems with the stability of APIs or FPPs occur during storage, e.g. if found to be outside specifications or potentially outside specifications.

Applicants should be aware that some variations may require the submission of additional consequential variations, including where the variation states, “no variation is required, such changes are handled as amendments to the APIMF by the APIMF holder”. Therefore, for any given change the applicant should consider whether one or more variations may be required to be submitted.

If changes to the dossier only concern editorial changes, such changes need not be submitted as a separate variation, but can be included as a notification together with a subsequent variation concerning that part of the dossier. In such a case, a declaration should be provided that the contents of the associated sections of the dossier have not been changed by the editorial changes beyond the substance of the variation submitted.

2. Guidance for implementation

2.1 Reporting types

The definitions outlined in the following reporting types are intended to provide guidance with respect to the classification of quality-related changes. Specific examples of changes are provided in these guidelines. However, it should be noted that a change not covered by these guidelines, should be considered as a major change by default. Whenever the applicant is unclear about the classification of a particular change, WHO/PQP should be contacted. It remains the responsibility of the applicant to submit relevant documentation to justify that the change will not have a negative impact on the quality of the product.

Individual changes normally require the submission of separate variations. Grouping of variations is acceptable only under the following circumstances:

- when variations are consequential to each other, e.g. introduction of a new impurity specification that requires a new analytical procedure;
- when the same change affects multiple FPPs, e.g. addition of a new API manufacturing site for multiple FPPs;
- when all the changes are annual notification.

For the purposes of classification, an application involving two or more types of variations will be considered as the highest risk type, e.g. a variation grouping both a minor change and a major change will be classified as a major change.

Applicants are also advised to exercise caution whenever several changes to the same FPP are envisaged. Although each of the individual changes may be classified as a

particular reporting type, classification within a higher risk category may be warranted as a result of the composite effect of these changes. In all such cases, applicants are advised to contact WHO/PQP prior to submission of the variation application to obtain guidance on classifying such changes.

2.1.1 Notifications

Notifications are changes that could have minimal or no adverse effects on the overall safety, efficacy and quality of the FPP. Such notifications do not require prior acceptance, but must be notified to WHO/PQP immediately after implementation (immediate notification (IN)), or within 12 months following implementation (annual notification (AN)) of the change.

It should be highlighted that an IN or AN may be rejected in specific circumstances with the consequence that the applicant must cease to apply the already implemented variation.

Annual notification (AN)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change. The change should be summarized as part of the notification but the indicated documentation is not required to be submitted. The documentation indicated for ANs should be available on request or at the time of inspection. ANs should be submitted to WHO/PQP within 12 months of implementation of the changes. For convenience applicants may group several AN changes as a single submission.

Immediate notification (IN)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the notification application. Such changes can be implemented immediately at the time of submission and they can be considered accepted if an objection is not issued by WHO/PQP within 30 calendar days of the date of acknowledgement of receipt of the application.

2.1.2 Minor variation (Vmin)

Minor variations are changes that may have minor effects on the overall safety, efficacy and quality of the FPP. Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the variation application.

Such variations can be implemented if no objection letter has been issued within a time period indicated on the WHO/PQP web site. Should questions arise during the specified period, the change can only be implemented on receipt of a letter of acceptance from WHO/PQP.

2.1.3 Major variation (Vmaj)

Major variations are changes that could have major effects on the overall safety, efficacy and quality of the FPP. The documentation required for the changes included in this reporting type should be submitted. Prior acceptance by WHO/PQP is required before the changes can be implemented. A letter of acceptance will be issued for all major variations if and when the variation is considered acceptable.

2.1.4 New applications and extension applications

Certain changes are so fundamental that they alter the terms of the accepted dossier and consequently cannot be considered as changes. In these cases a new dossier must be submitted. Examples of such changes are listed in Appendix 1.

2.1.5 Labelling information

For any change to labelling information (SmPC, PIL, labels) not covered by the variation categories described in this document, WHO/PQP must be notified and submission of the revised labelling information is expected as per the guidance on the WHO/PQP web site.

2.2 Conditions to be fulfilled

For each variation, attempts have been made to identify particular circumstances where lower reporting requirements (IN, AN or Vmin) are possible. A change that does not meet all of the conditions stipulated for these specific circumstances is considered to be a Vmaj.

In some circumstances Vmaj categories have been specifically stated for a given variation. This has been done to indicate to applicants what documents should be provided. This is for informational purposes only. The list of documentation is not intended to be comprehensive and further documentation may be required. For all changes it remains the responsibility of the applicant to provide all necessary documents to demonstrate that the change does not have a negative effect on the safety, efficacy or quality of the FPP.

2.3 Documentation required

Examples of variations are organized according to the structure of the CTD. For each variation, certain documents have been identified as supporting data and are organized according to CTD structure. Regardless of the documents specified, applicants should ensure that they have provided all relevant information to support the variation.

Where applicable, the following should be included in the application:

- a variation application form (a template can be downloaded from the web site). All sections of this form should be completed and the document signed. Electronic versions of the application form, both as a Word document and a scanned signed PDF, should be provided in addition to the printed version;

- an updated quality information summary (QIS) (if applicable);
- replacement of the relevant sections of the dossier as per CTD format;
- copies of SmPC, PIL and labels, if relevant.

It should be noted that WHO/PQP reserves the right to request further information not explicitly described in these guidelines.

The QIS provides a summary of the key quality information from the product dossier. For FPPs that have an agreed-upon QIS, the QIS should be revised and submitted (in Word format only) with every variation application. Any revised sections within the QIS should be highlighted. If there is no change to the QIS as a result of the variation, a statement should be made in the covering letter to this effect.

Alternative approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. It is also important to note that WHO/PQP may request information or material, or define conditions not specifically described in this guidance, in order to adequately assess the safety, efficacy and quality of an FPP.

3. Glossary

The definitions provided below apply to the terms used in this guidance. They may have different meanings in other contexts and documents.

active pharmaceutical ingredient (API)

A substance used in the FPP, intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings.

active pharmaceutical ingredient (API) starting material

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house.

applicant

For the purposes of this document, the term applicant refers to any person or entity who has participated in the procedure for prequalification of FPPs by submission of the required documentation on a product that has been listed after evaluation as prequalified.

biobatch

The batch used to establish bioequivalence or similarity to the comparator product as determined in bioequivalence or biowaiver studies, respectively.

final intermediate

The last reaction intermediate in the synthetic pathway that undergoes synthetic transformation to the API or the crude API. Purification is not considered to be a synthetic transformation.

finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product which has undergone all stages of manufacture including packaging in its final container and labelling.

in-process control

Check performed during manufacture to monitor or to adjust the process in order to ensure that the final product conforms to its specifications.

manufacturer

A company that carries out operations such as production, packaging, repackaging, labelling and re-labelling of pharmaceuticals.

officially recognized pharmacopoeia (or compendium)

Those pharmacopoeias recognized in the WHO/PQP (i.e. *The International Pharmacopoeia* (Ph. Int.), the *European Pharmacopoeia* (Ph. Eur.), the *British Pharmacopoeia* (BP), the *Japanese Pharmacopoeia* (JP) and the *United States Pharmacopoeia* (USP)).

pilot-scale batch

A batch of an API or FPP manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger, unless otherwise adequately justified.⁶

production batch

A batch of an API or FPP manufactured at production scale by using production equipment in a production facility as specified in the application.

Stringent regulatory authority (SRA)

A stringent regulatory authority is:

- the medicines regulatory authority in a country which is: (a) a member of the International Conference on Harmonisation (ICH) (European Union (EU), Japan and the United States); or (b) an ICH Observer, being the

⁶ Procedure for prequalification of pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2009 (WHO Technical Report Series, 953), Annex 3.

European Free Trade Association (EFTA) as represented by SwissMedic and Health Canada (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time);

- only in relation to good manufacturing practices (GMP) inspections: a medicines regulatory authority that is a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) as specified at <http://www.picscheme.org>

4. Administrative changes

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
1 Change in the name and/or corporate address of the supplier of the FPP.	1	1	IN

Conditions to be fulfilled

1. Confirmation that the supplier of the product remains the same legal entity.

Documentation required

1. A formal document from a relevant official body (e.g. the national medicines regulatory authority (NMRA)) in which the new name and/or address is mentioned.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
2 Change in the name or address of a manufacturer of an API that is not a supplier of a prequalified API or that is not supported by a CEP.	1	1–2	IN

Conditions to be fulfilled

1. No change in the location of the manufacturing site and in the manufacturing operations.

Documentation required

1. A formal document from a relevant official body (e.g. NMRA) in which the new name and/or address is mentioned.
2. An updated Letter of Access in case of change in the name of the holder of the APIMF.

continues

Table *continued*

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
3 Change in the name and/or address of a manufacturer of the FPP.	1	1	IN
Conditions to be fulfilled			
1. No change in the location of the manufacturing site and in the manufacturing operations.			
Documentation required			
1. Copy of the modified manufacturing authorization or a formal document from a relevant official body (e.g. NMRA) in which the new name and/or address is mentioned.			
Description of change	Conditions to be fulfilled	Documentation required	Reporting type
4 Deletion of a manufacturing site or manufacturer involving:			
4a production of the API starting material	1	1	AN
4b production or testing of the API intermediate or API	1–2	1	IN
4c production, packaging or testing of the intermediate or FPP	1–2	1	IN
Conditions to be fulfilled			
1. At least one other site continues to perform the same function(s) as the site(s) intended to be deleted.			
2. The deletion of the site is not a result of critical deficiencies in manufacturing.			
Documentation required			
1. Clear identification of the manufacturing, packaging and/or testing site to be deleted, in the letter accompanying the application.			

5. Changes to a CEP or to a confirmation of API-prequalification document

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
5	Submission of a new or updated CEP for an API or starting material or intermediate used in the manufacturing process of the API:			
5a.1	from a currently accepted manufacturer	1–5	1–5	AN
5a.2		1–4	1–6	IN
5a.3		1, 3–4	1–6	Vmin
5b.1	from a new manufacturer	1–4	1–6	IN
5b.2		1, 3–4	1–6	Vmin

Conditions to be fulfilled

1. No change in the FPP release and shelf-life specifications.
2. Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for any impurities including organic, inorganic and genotoxic impurities and residual solvents, with the exception of residual solvents when the limits stipulated comply with ICH requirements.
3. The manufacturing process of the API, starting material or intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.
4. For low solubility APIs the polymorph is the same, and whenever particle size is critical (including low solubility APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the biobatch.
5. No revision of the FPP manufacturer's API specifications is required.

Documentation required

1. Copy of the current (updated) CEP, including any annexes and a declaration of access for the CEP to be duly filled out by the CEP holder on behalf of the FPP manufacturer or applicant to the WHO/PQP who refers to the CEP.
2. A written commitment that the applicant will inform WHO/PQP in the event that the CEP is withdrawn and an acknowledgement that withdrawal of the CEP will require additional consideration of the API data requirements to support the product dossier.
3. Replacement of the relevant pages of the dossier with the revised information for the CEP submission option stipulated under section 3.2.5 of the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.
4. (S.2.5) For sterile APIs, data on the sterilization process of the API, including validation data.

continues

Table continued

Documentation required

5. (P.8.2) In the case of the submission of a CEP for an API, if the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one batch of the FPP of at least pilot-scale, and to continue the study throughout the currently accepted shelf-life and to immediately report any out-of-specification results to WHO/PQP.
6. (S.4.1) Copy of FPP manufacturer's revised API specifications.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
6	Submission of a new or updated confirmation of API-prequalification document			
6a.1	from a currently accepted manufacturer	1–3	1–3, 5	AN
6a.2		1–2	1–5	Vmin
6b.1	from a new manufacturer	1–3	1–3, 5	IN
6b.2		1–2	1–5	Vmin

Conditions to be fulfilled

1. No change in the FPP release and shelf-life specifications.
2. For low solubility APIs the API polymorph is the same, and whenever particle size is critical (including low solubility APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the biobatch.
3. There is no difference in impurity profile of the proposed API to be supplied, including organic, inorganic, genotoxic impurities and residual solvents, compared to that of the API currently supplied. The proposed API manufacturer's specifications do not require the revision of the FPP manufacturer's API specifications.

Documentation required

1. Copy of the current (updated) confirmation of API-PQ document. The API manufacturer should duly fill out the authorization box with the name of the applicant or FPP manufacturer seeking to use the document.
2. Replacement of the relevant pages of the dossier with the revised information for the API-PQ procedure submission option (*Option 1: confirmation of API Prequalification document*) stipulated under section 3.2.S. of the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.
3. (S.2.5) For sterile APIs, data on the sterilization process of the API, including validation.
4. (S.4.1) Copy of FPP manufacturer's revised API specifications.

continues

Table *continued***Documentation required**

5. (P.8.2) If the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one batch of at least pilot-scale of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out-of-specification results to WHO/PQP.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
7 Submission of a new or updated transmissible spongiform encephalopathy (TSE) CEP for an excipient or API (addition or replacement)	None	1	AN

Conditions to be fulfilled

None

Documentation required

1. Copy of the current (updated) TSE CEP.

6. Quality changes

3.2. S Drug substance (or API)

3.2. S.2 Manufacture

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
8 Replacement or addition of a new manufacturing site or manufacturer of an API involving:			
8a.1 API testing only	1, 2, 4	1, 3–4	IN
8a.2	2, 4	1, 3–4	Vmin
8b.1 production of API starting material	3–4	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder.	
8b.2	1–2	1–5	Vmin
8b.3	None	1, 2, 5, 7–8, 12, 13	Vmaj

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
8c.1	production of API intermediate	3–4	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder.	
8c.2		4, 6	1–2, 12	IN
8c.3		None	1, 2, 5, 7–8, 12, 13	Vmaj
8d.1	production of API (APIMF procedure)	3, 7–9	1, 2, 6, 8	IN
8d.2		3, 7, 9	1, 2, 6–8	Vmin
8e.1	production of API (full dossier)	1, 9–11	1–2, 4, 8–9	IN
8e.2		None	1, 2, 4, 5, 7–8, 10–11, 13	Vmaj

Conditions to be fulfilled

1. The API is non-sterile.
2. The transfer of analytical methods has been successfully undertaken.
3. The new site is supported by an APIMF that is currently accepted through the APIMF procedure and the FPP manufacturer holds a valid Letter of Access.
4. No change in the FPP manufacturer's API specifications.
5. The impurity profile of the API starting material is essentially the same as other accepted sources. The introduction of the new supplier does not require the revision of the API manufacturer's API starting material specifications. The route of synthesis is verified as identical to that already accepted.
6. Specifications (including in-process, methods of analysis of all materials), method of manufacture and detailed route of synthesis are verified as identical to those already accepted. The introduction of the new supplier does not require the revision of the API manufacturer's API intermediate specifications.
7. No change in the FPP release and end-of-shelf-life specifications.
8. No difference in impurity profile of the proposed API to be supplied, including organic, inorganic and genotoxic impurities and residual solvents. The proposed API manufacturer's specifications do not require the revision of the FPP manufacturer's API specifications.
9. For low-solubility APIs the API polymorph is the same, and whenever particle size is critical (including low-solubility APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the biobatch.

continues

Table *continued***Conditions to be fulfilled**

10. Specifications (including in-process controls, methods of analysis of all materials), method of manufacture (including batch size) and detailed route of synthesis are verified as identical to those already accepted (such situations are generally limited to additional sites by the same manufacturer or a new contract manufacturing site with evidence of an acceptable and similar quality system to that of the main manufacturer).
11. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current *WHO Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products* (<https://iris.who.int/handle/10665/68932>) or EMA's *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* ([https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52011XC0305\(04\)](https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52011XC0305(04))) or equivalent guidelines of the ICH region and associated countries.

Documentation required

1. (S.2.1) Name, address, and responsibility of the proposed site or facility involved in manufacture or testing (including block(s) and unit(s)). A valid testing authorization or a certificate of GMP compliance, if applicable.
2. (S.2.2) A side-by-side comparison of the manufacturing flowcharts for production of the API, intermediate, or API starting material (as applicable) at the parent and proposed sites and a tabulated summary of the differences.
3. (S.4.3) Copies or summaries of validation reports or method transfer reports, which demonstrate equivalence of analytical procedures to be used at the proposed testing site.
4. (S.4.4) Description of the batches, copies of certificates of analysis and batch analysis data (in a comparative tabular format) for at least two (minimum pilot-scale) batches of the API from the currently accepted and proposed manufacturers and/or sites.
5. Relevant sections of (S) documentation in fulfilment of requirements for full information provided in the dossier under section 3.2.S of the *WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.⁷
6. The open part of the new APIMF (with a Letter of Access provided in Module 1) and documentation in fulfilment of requirements for the APIMF option under section 3.2.S of the *WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.⁸
7. (P.8.2) If the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one production-scale batch of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to WHO/PQP.

*continues*⁷ See footnote 3.⁸ See footnote 3.

Table *continued***Conditions to be fulfilled**

5. No change in the route of synthesis, quality control procedures and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable). Minor changes in the equipment are acceptable.

Documentation required

1. (S.2) A declaration from the supplier of the FPP that the route of synthesis, quality control procedures and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable) are the same as those already accepted.
2. (S.2.1) Name, address, and responsibility of the proposed production site or facility involved in manufacturing and/or testing (including block(s) and unit(s)). A valid manufacturing and/or testing authorization and a certificate of GMP compliance, if available.
3. (S.4.4) Description of the batches, copies of certificates of analysis and batch analysis data (in a comparative tabular format) for at least two (minimum pilot-scale) batches of the API from the currently accepted and proposed units or blocks.
4. (S.2.2) A summary of differences between manufacture and control of the API at the currently accepted and proposed units or blocks, if applicable.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
10a	change in the manufacturing process	1–3, 9	1–2, 8	AN
10b.1		1–2, 4, 6–9	3–4, 11–12	IN
10b.2	change in the manufacturing process of the API	1–2, 4, 6–8, 10	3–4, 11–12	Vmin
10c		1–2, 4–7	3–4, 11–12	Vmin
10d		None	2–14	Vmaj

Conditions to be fulfilled

1. No change in the physical state (e.g. crystalline, amorphous) of the API.
2. For low solubility APIs, there is no change in the polymorphic form and whenever particle size is critical (including low solubility APIs) there is no significant change in the particle size distribution compared to that of the API lot used in the preparation of the biobatch.
3. The API manufacturing site is currently accepted through the APIMF procedure.
4. Where materials of human or animal origin are used in the process, the manufacturer does not use any new process for which assessment of viral safety data or TSE risk assessment is required.
5. No change in the route of synthesis (i.e. intermediates remain the same) and there are no new reagents, catalysts or solvents used in the process.

continues

Table *continued***Conditions to be fulfilled**

6. No change in qualitative and quantitative impurity profile or in physicochemical properties of the API.
7. The change does not affect the sterilization procedures of a sterile API.
8. The change involves only steps before the final intermediate.
9. The change does not require revision of the starting material, intermediate or API specifications.
10. The change does not require revision of the API specifications.

Documentation required

1. A copy of the APIMF amendment acceptance letter.
2. (P.8.2) If the quality characteristics of the API are changed in a way that may impact the stability of the FPP, a commitment to put under stability one production-scale batch of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to WHO/PQP.
3. (S.2.2) A side-by-side comparison of the current process and the new process.
4. (S.2.2) A flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es).
5. (S.2.3) Information on the quality and controls of the materials (e.g. raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed API, where applicable.
6. (S.2.3) Either a TSE CEP for any new source of material or, where applicable, documented evidence that the specific source of the material that carries a risk of TSE has previously been assessed by the competent authority and shown to comply with the current *WHO guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products* (<https://iris.who.int/handle/10665/68932>) or EMA's *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* ([https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52011XC0305\(04\)](https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52011XC0305(04))) or equivalent guidelines of the ICH region and associated countries.
7. (S.2.4) Information on controls of critical steps and intermediates, where applicable.
8. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization, if applicable.
9. (S.3.1) Evidence for elucidation of structure, where applicable.
10. (S.3.2) Information on impurities.
11. (S.4.1) A copy of currently accepted specifications of API (and starting material and intermediate, if applicable).
12. (S.4.4) Description of the batches, certificates of analysis or batch analysis report, and summary of results, in a comparative tabular format, for at least two batches (minimum pilot-scale) manufactured according to the current and proposed processes.

continues

Table *continued***Documentation required**

13. (S.7.1) Results of two batches of at least pilot-scale with a minimum of three months of accelerated (and intermediate as appropriate) and three months of long-term testing of the proposed API.
14. For low-solubility APIs where the polymorphic form has changed or whenever particle size is critical (including low-solubility APIs) where there is dissimilar particle size distribution compared to the lot used in the biobatch, evidence that the differences do not impact the quality and bioavailability of the FPP.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
11	Change in the in-process tests or limits applied during the manufacture of the API:			
11a	any change in the manufacturing process controls	1	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder	
11b	tightening of in-process limits	2–4	1	AN
11c	addition of a new in-process test and limit	2, 5	1–5	AN
11d	addition or replacement of an in-process test as a result of a safety or quality issue	None	1–5, 7, 8–10	Vmin
11e.1	deletion of an in-process test	2, 6–7	1–3, 6	AN
11e.2		None	1–3, 7–10	Vmaj
11f	relaxation of the in-process test limits	None	1–3, 5, 7–10	Vmaj

Conditions to be fulfilled

1. API manufacturing site is currently accepted through the APIMF procedure.
2. The change is not necessitated by unexpected events arising during manufacture e.g. a new unqualified impurity or a change in total impurity limits.
3. The change is within the range of currently accepted limits.
4. The analytical procedure remains the same, or changes to the analytical procedure are minor.
5. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.

continues

Table continued

Conditions to be fulfilled				
6. The affected parameter is non-significant.				
7. The change does not affect the sterilization procedures of a sterile API.				
Documentation required				
1. A comparison of the currently accepted and the proposed in-process tests.				
2. (S.2.2) Flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es).				
3. (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed API.				
4. Details of any new non-pharmacopoeial analytical method and validation data where relevant.				
5. Justification for the new in-process test and/or limits.				
6. Justification and/or risk-assessment showing that the parameter is non-significant.				
7. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization, where applicable.				
8. (S.3.2) Information on impurities, if applicable.				
9. (S.4.1) Copy of currently accepted specifications of API (and intermediates, if applicable).				
10. (S.4.4) Description of the batches, certificates of analysis or batch analysis report and summary of results, in a comparative tabular format, for at least two batches (minimum pilot-scale) for all specification parameters.				
Description of change		Conditions to be fulfilled	Documentation required	Reporting type
12	Change in batch size of the API or intermediate involving:			
12a	up to 10-fold compared to the currently accepted batch size	1–2, 4, 6	1, 3–4	AN
12b.1	downscaling	1–4	1, 3–4	AN
12b.2		1–3	1–4	IN
12c	any change in scale (APIMF procedure)	5	1–2, 4–5	AN
12d	more than 10-fold increase compared to the currently accepted batch size	1–2, 4, 6	1, 3–4	Vmin

continues

Table *continued***Conditions to be fulfilled**

1. No changes to the manufacturing process other than those necessitated by changes in scale (e.g. use of a different size of equipment).
2. The change does not affect the reproducibility of the process.
3. The change is not necessitated by unexpected events arising during manufacture or due to stability concerns.
4. The change does not concern a sterile API.
5. The API manufacturing site and batch size is currently accepted through the APIMF procedure.
6. The proposed batch size increase is relative to either the originally accepted batch size, or the batch size accepted through a subsequent major or minor variation.

Documentation required

1. (S2.2) A brief narrative description of the manufacturing process.
2. (S2.5) Where applicable, evidence of process validation and/or evaluation studies for sterilization.
3. (S4.1) Copy of the currently accepted specifications of the API (and of the intermediate, if applicable).
4. (S4.4) Batch analysis data (in tabular format) issued by the FPP manufacturer for a minimum of two batches each of the currently accepted batch size and the proposed batch size.
5. A copy of the APIMF amendment acceptance letter.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
13	Change to the specifications or analytical procedures applied to materials used in the manufacture of the API (e.g. raw materials, starting materials, reaction intermediates, solvents, reagents, catalysts) involving:			
13a	any change	1	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder	
13b	tightening of the specification limits	2–4	1–3	AN
13c	minor change to an analytical procedure	5–7	2–3	AN
13d	addition of a new specification parameter and a corresponding analytical procedure where necessary	2, 7–9	1–3	AN

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
13e	deletion of a specification parameter or deletion of an analytical procedure	2, 10	1–4	AN
13f	addition or replacement of a specification parameter as a result of a safety or quality issue	None	1–3, 5	Vmin
13g	relaxation of the currently accepted specification limits for solvents, reagents, catalysts and raw materials	4, 7, 9–10	1, 3–4	IN
13h	relaxation of the currently accepted specification limits for API starting materials and intermediates	None	1–3, 5	Vmaj

Conditions to be fulfilled

1. API manufacturing site is currently accepted through the APIMF procedure.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any change is within the range of currently accepted limits.
4. The analytical procedure remains the same.
5. The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments, to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method).
6. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated analytical procedure is at least equivalent to the former analytical procedure.
7. No change to the total impurity limits; no new impurities are detected.
8. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
9. The change does not concern a genotoxic impurity.
10. The affected parameter is non-significant or the alternative analytical procedure has been previously accepted.

continues

Table *continued***Documentation required**

1. Comparative table of currently accepted and proposed specifications.
2. (S.2.3) Information on the quality and controls of the materials (e.g. raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed API, where applicable.
3. (S.2.4) Information on intermediates, where applicable.
4. Justification and/or risk assessment showing that the parameter is non-significant.
5. (S.3.2) Information on impurities, where applicable.

3.2. S.4 Control of the API by the API manufacturer

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
14 Changes to the test parameters, acceptance criteria, or analytical procedures of the API manufacturer that do not require a change to the FPP manufacturer's API specifications involving:			
14a a. API supported through the APIMF procedure.	1–2	No variation is required; such changes are handled as amendments to the associated APIMF	
14b b. API not supported through the APIMF procedure.	2	1–4	IN

Conditions to be fulfilled

1. The revised test parameters, acceptance criteria, or analytical procedures have been submitted as amendments to the associated APIMF and accepted.
2. The API manufacturer has provided the relevant documentation to the FPP manufacturer. The FPP manufacturer has considered the API manufacturer's revisions and determined that no consequential revisions to the FPP manufacturer's API test parameters, acceptance criteria, or analytical procedures are required to ensure that adequate control of the API is maintained.

Documentation required

1. (S.4.1) Copy of the current and proposed API specifications dated and signed by the API manufacturer.
2. (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (S.4.3) Copies or summaries of validation reports for new or revised analytical procedures, if applicable.
4. Justification as to why the change does not affect the FPP manufacturer's specifications.

3.2. S.4 Control of the API by the FPP manufacturer

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
15	Change to the test parameters or acceptance criteria of the API specifications of the FPP manufacturer involving:			
15a	updating a test parameter or acceptance criterion controlled in compliance with an officially recognized pharmacopoeial monograph as a result of an update to this monograph to which the API is controlled.	11	1–5	AN
15b.1	deletion of a test parameter	1–2	1, 6	AN
15b.2		10	1, 6, 8	IN
15b.3		None	1, 6	Vmaj
15c.1	addition of a test parameter	1, 4–8	1–6	AN
15c.2		1, 5–6, 10	1–6, 8	IN
15c.3		1, 5–6	1–6	Vmin
15c.4		None	1–7	Vmaj
15d.1	replacement of a test parameter	1, 5–8	1–6	IN
15d.2		5, 7, 10	1–6, 8	Vmin
15d.3		None	1–7	Vmaj
15e.1	tightening of an acceptance criterion	1, 3, 9	1, 6	AN
15f.1	relaxation of an acceptance criterion	1, 5–9	1, 6	IN
15f.2		5, 7, 10	1, 6, 8	Vmin
15f.3		None	1, 6–7	Vmaj

Conditions to be fulfilled

1. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
2. The deleted test has been demonstrated to be redundant with respect to the remaining tests.
3. The change is within the range of currently accepted acceptance criteria.

continues

Table continued

Conditions to be fulfilled

4. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
 5. For insoluble APIs there is no change in the polymorphic form and whenever particle size is critical (including low-solubility APIs) there is no change in particle size distribution acceptance criteria.
 6. No additional impurity found over the ICH identification threshold.
 7. The change does not concern sterility testing.
 8. The change does not involve the control of a genotoxic impurity.
 9. The associated analytical procedure remains the same.
 10. The change has resulted from a revision of the API manufacturer's specifications and is accepted as part of an APIMF amendment.
 11. No change is required in FPP release and shelf-life specifications.
-

Documentation required

1. (S.4.1) A copy of the proposed API specifications (of the FPP manufacturer) dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications. In addition, if the change has resulted from a revision to the API manufacturer's specifications, a copy of the API specifications (of the API manufacturer) dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
 2. (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
 3. (S.4.3) Copies or summaries of validation or verification reports issued by the FPP manufacturer, if new analytical procedures are used.
 4. (S.4.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.
 5. (S.4.4) Description of the batches, certificates of analysis or batch analysis report, and summary of results in tabular format, for at least one batch if new tests and/or analytical methods are implemented.
 6. (S.4.5) Justification of the proposed API specifications (e.g. test parameters, acceptance criteria, or analytical procedures).
-

continues

Table continued

Documentation required				
7. (P.2) Where changes have occurred to the particle size criteria of an insoluble API or wherever particle size is critical, evidence is provided that the changes do not affect the in vitro release properties and bioavailability of the FPP. In general, it is sufficient to provide multipoint comparative dissolution profiles (in three media covering the physiological range (pH 1.2 or (0.1N HCl), 4.5 and 6.8) without surfactant) for one batch of FPP manufactured using API that meets the proposed criteria; one batch of FPP manufactured using API that meets the currently accepted criteria; and data on the FPP batch used in the registration bioequivalence study. However, if the routine dissolution medium contains a surfactant, the applicant should contact WHO/PQP for advice. For changes to the polymorph of an insoluble API the applicant should contact WHO/PQP for advice before embarking upon any investigation.				
8. Copy of the APIMF amendment acceptance letter.				
Description of change		Conditions to be fulfilled	Documentation required	Reporting type
16	Change to the analytical procedures used to control the API by the FPP manufacturer involving:			
16a	change in an analytical procedure as a result of a revision to the officially recognized pharmacopoeial monograph to which the API is controlled.	None	1–3	AN
16b	change from a currently accepted in-house analytical procedure to an analytical procedure in an officially recognized pharmacopoeia or from the analytical procedure in one officially recognized pharmacopoeia to an analytical procedure in another official recognized pharmacopoeia	None	1–4	IN

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
16c.1	addition of an analytical procedure	1–3	1–3	AN
16c.2		3, 8	1–3, 5	AN
16c.3		8	1–3, 5	Vmin
16c.4		None	1–3	Vmaj
16d.1	modification or replacement of an analytical procedure	1–6	1–4	AN
16d.2		2–3, 5–6, 8	1–5	AN
16d.3		1–3, 5–6	1–4	Vmin
16d.4		5–6, 8	1–5	Vmin
16d.5		None	1–4	Vmaj
16e.1	deletion of an analytical procedure	6–7	1, 6	AN
16e.2		6, 8	1, 5, 6	IN
16e.3		None	1, 6	Vmaj

Conditions to be fulfilled

1. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. No new impurities have been detected as a result of the use of the new analytical method.
4. The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method), and no new impurities are detected.
5. Comparative studies are available demonstrating that the proposed analytical procedure is at least equivalent to the currently accepted analytical procedure.
6. The change does not concern sterility testing.
7. The deleted analytical procedure is an alternative method and is equivalent to a currently accepted method.
8. The new or modified analytical method is identical to that used by the API manufacturer and has been accepted as part of an amendment to the associated APIMF.

Documentation required

1. (S.4.1) Copy of the proposed API specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.

continues

Table continued

Documentation required				
2.	(S.4.2)	Copies or summaries of analytical procedures if new or significantly modified analytical procedures are used.		
3.	(S.4.3)	Copies or summaries of validation or verification reports issued by the FPP manufacturer if new or significantly modified analytical procedures are used.		
4.	(S.4.4)	Comparative analytical results demonstrating that the proposed analytical procedures are at least equivalent to the accepted analytical procedures.		
5.		A copy of the APIMF acceptance letter.		
6.	(S.4.5)	Justification for the deletion of the analytical procedure, with supporting data.		

3.2. S.6 Container-closure system

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
17a	Change in the immediate packaging (primary and functional secondary	3, 4	1–2, 4	AN
17b	components) for the storage and shipment of the API	1–2, 4	2–3	IN
17c		4	1–3	Vmin

Conditions to be fulfilled				
1.	Results demonstrate that the proposed primary packaging type is at least equivalent to the currently accepted primary packaging type with respect to its relevant properties (e.g. including results of transportation or interaction studies, and moisture permeability among others).			
2.	The change does not concern a sterile API.			
3.	The change has previously been accepted through the APIMF procedure.			
4.	The change is not the result of stability issues.			

Documentation required				
1.	(S.2.5)	Evidence of process validation and/or evaluation studies for sterilization if different from the current process.		
2.	(S.6)	Information on the proposed primary packaging (e.g. description and specifications) and data in fulfillment of condition 1.		
3.	(S.7.1)	Results of (or a commitment to study in the case of demonstrated equivalent or more protective packaging) a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing of the API in the proposed primary packaging type.		
4.		A copy of the APIMF amendment acceptance letter.		

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
18	Change in the specifications of the immediate packaging for the storage and shipment of the API involving:			
18a	tightening of specification limits	1–2	1	AN
18b	addition of a test parameter	2–3	1–3	AN
18c	deletion of a non-critical parameter	2	1, 4	AN
18d	any change (APIMF procedure)	4	No variation is required; such changes are handled as amendments to the associated APIMF	

Conditions to be fulfilled

1. The change is within the range of currently accepted limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. The change has previously been accepted through the APIMF procedure.

Documentation required

1. (S.4.5) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications.
2. (S.4.2) Details of method and summary of validation of new analytical procedure.
3. (S.6) Certificate of analysis for one batch.
4. Justification to demonstrate that the parameter is not critical.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
19	Change to an analytical procedure on the immediate packaging of the API involving:			
19a	minor change to an analytical procedure	1–3	1	AN

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
19b	other changes to an analytical procedure including addition or replacement of an analytical procedure	2–4	1	AN
19c	deletion of an analytical procedure	5	2	AN
19d	any change (APIMF procedure)	6	No variation is required; such changes are handled as amendments to the associated APIMF	

Conditions to be fulfilled

1. The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method).
2. Appropriate (re)validation studies have been performed in accordance with the relevant guidelines.
3. Comparative studies indicate the new analytical procedure to be at least equivalent to the currently accepted procedure.
4. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5. The deleted analytical procedure is an alternative method and is equivalent to a currently accepted method.
6. The change has previously been accepted through the APIMF procedure.

Documentation required

1. (S.6) Comparative validation results demonstrating that the currently accepted and proposed procedures are at least equivalent.
2. Justification for deletion of the analytical procedure.

3.2. S.7 Stability

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
20	Change in the retest period or shelf-life of the API involving:			
20a	any change (APIMF procedure)	4	4	IN
20b	reduction	3	1–2	IN
20c	extension	1–2	1–3	Vmin

Conditions to be fulfilled

1. No change to the primary packaging in direct contact with the API or to the recommended condition of storage.
2. Stability data were generated in accordance with the currently accepted stability protocol.
3. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
4. The revised retest period has previously been accepted through the APIMF procedure.

Documentation required

1. (S.7.1) Proposed retest period or shelf-life, summary of stability testing according to currently accepted protocol and test results.
2. (S.7.2) Updated post-acceptance stability protocol and stability commitment and justification of change, when applicable.
3. (S.7.3) Stability data to support the change.
4. A copy of the APIMF acceptance letter.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
21	Change in the labelled storage conditions of the API involving:			
21a	any change in storage conditions (APIMF procedure)	1	1	IN
21b	any change in storage conditions	2	2	Vmin

Conditions to be fulfilled

1. The revised storage conditions have previously been accepted through the APIMF procedure.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.

continues

Table continued

Documentation required				
1. A copy of the APIMF acceptance letter.				
2. (S.7.1) Stability and/or compatibility test results to support the change to the storage conditions.				

3.2. P Drug product (or FPP)

3.2. P.1 Description and composition of the FPP

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
22a	Change in the composition of a solution dosage form	1–6	2, 4, 7, 9–10	IN
22b		None	1–10	Vmaj

Conditions to be fulfilled				
1. The affected excipient(s) does/do not function to affect the solubility and/or the absorption of the API.				
2. The affected excipient(s) does/do not function as a preservative or preservative enhancer.				
3. No change in the specifications of the affected excipient(s) or the FPP.				
4. No change in the physical characteristics of the FPP (e.g. viscosity, osmolality, pH).				
5. The change does not concern a sterile FPP.				
6. The excipients are qualitatively the same. The change in the amount (or concentration) of each excipient is within $\pm 10\%$ of the amount (or concentration) of each excipient in the originally prequalified product.				

Documentation required				
1. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence.				
2. (P.1) Description and composition of the FPP.				
3. (P.2) Discussion on the components of the proposed product (e.g. choice of excipients, compatibility of API and excipients, suitability studies on the packaging system for the changed product).				
4. (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.				
5. (P.4) Control of excipients, if new excipients are proposed.				

continues

Table *continued***Documentation required**

6. (P.4.5) If applicable, either a CEP for any new component of animal origin susceptible to TSE risk or, where applicable, documented evidence that the specific source of the TSE risk material has been previously assessed by an NMRA in the ICH region or associated countries and shown to comply with the scope of the current guidelines in the countries of the ICH region or associated countries. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals, and use of the material.
7. (P.5) Copies of FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot- or production-scale batches. If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.
8. (P.8.1) Results of stability testing generated on at least two pilot- or production-scale batches with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
9. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of each strength of the proposed product into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
10. (R.1) Copies of relevant pages of blank master production documents with changes highlighted, as well as relevant pages of the executed production document for one batch and confirmation that there are no changes to the production documents other than those highlighted.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
23	Change in the colouring system or the flavouring system currently used in the FPP involving:			
23a	reduction or increase of one or more components of the colouring or the flavouring system	1–3, 6	1, 4, 6–7	AN
23b	deletion, addition or replacement of one or more components of the colouring or the flavouring system	1–6	1–7	IN

Conditions to be fulfilled

1. No change in the functional characteristics of the pharmaceutical form e.g. disintegration time or dissolution profile.
2. Any minor adjustment to the formulation to maintain the total weight is made using an excipient which currently makes up a major part of the FPP formulation.

continues

Table continued

Conditions to be fulfilled

3. Specifications for the FPP are updated only with respect to appearance, odour and/or taste or if relevant, deletion or addition of a test for identification.
4. Any new component must comply with section 3.2.P.4 of the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.⁹
5. Any new component does not include the use of materials of human or animal origin for which assessment of viral safety data is required, or is in compliance with the current WHO *Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products* (<https://iris.who.int/handle/10665/68932>) or EMA's *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* ([https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52011XC0305\(04\)](https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52011XC0305(04))) or an equivalent guide from the ICH region and associated countries.
6. Where applicable, the change does not affect the differentiation between strengths and for paediatric formulations it does not require submission of results of taste acceptability studies.

Documentation required

1. Sample of the FPP.
2. (P.2) Discussion on the components of the FPP (e.g. compatibility of API and qualitative composition of the colouring or flavouring system if purchased as a mixture, with specifications, if relevant).
3. (P.4.5) Either a CEP for any new component of animal origin susceptible to TSE risk or, where applicable, documented evidence that the specific source of the TSE risk material has been previously assessed by an NMRA in the ICH region or associated countries and shown to comply with the scope of the current guidelines in the countries of the ICH region or associated countries. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals, and use of the material.
4. (P.5) Copies of revised FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot- or production-scale batches.
5. (P.5.3) If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.
6. (P.8.1) Results of stability testing generated on at least two pilot- or production-scale batches with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
7. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch and confirmation that there are no changes to the production documents other than those highlighted.

continues

⁹ See footnote 3.

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
24	Change in weight of tablet coatings or capsule shells involving:			
24a	immediate-release oral FPPs	1–3	2–5	AN
24b	gastro-resistant, modified or prolonged release FPPs	None	1–5	Vmaj

Conditions to be fulfilled

1. Multipoint in vitro dissolution profiles of the proposed version of the product (determined in the routine release medium on at least two batches of pilot- or production-scale), are similar to the dissolution profiles of the biobatch.
2. Coating is not a critical factor for the release mechanism.
3. Specifications for the FPP are updated only with respect to weight and dimensions, if applicable.

Documentation required

1. Justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence (*Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms*, WHO Technical Report Series, No. 937, 2006, Annex 8).
2. (P.2) Comparative multipoint in vitro dissolution profiles in the routine release medium (or media), on at least two batches of pilot- or production-scale of the proposed product versus the biobatch.
3. (P.5) Copies of revised FPP release and shelf-life specifications and certificates of analysis for a minimum of one pilot- or production-scale batch.
4. (P.8.1) Results of stability testing generated on at least one pilot- or production-scale batch with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
5. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch and confirmation that there are no changes to the production documents other than those highlighted.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
25	Change in the composition of an immediate-release solid oral dosage form including:			
25a.1	replacement of a single excipient with a comparable	1–5	1–10	Vmin
25a.2	excipient at a similar concentration	None	1–10	Vmaj

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
25b.1	quantitative changes in excipients	1–4	1–4, 7–10	Vmin
25b.2		None	1–4, 7–10	Vmaj

Conditions to be fulfilled

1. No change in functional characteristics of the pharmaceutical form.
2. Only minor adjustments (see Appendix 2) are made to the quantitative composition of the FPP; any minor adjustment to the formulation to maintain the total weight is made using an excipient which currently makes up a major part of the FPP formulation.
3. Stability studies have been started under conditions according to WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*¹⁰ (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot- or production-scale batches, satisfactory stability data covering at least 3 months are at the disposal of the applicant, and the stability profile is similar to that of the currently accepted product.
4. The dissolution profile of the proposed product determined on a minimum of two pilot-scale batches is similar to the dissolution profile of the biobatch.
5. The change is not the result of stability issues and/or does not result in potential safety concerns, i.e. differentiation between strengths.

Documentation required

1. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence.
2. (P.1) Description and composition of the FPP.
3. (P.2) Discussion on the components of the proposed product (e.g. choice of excipients, compatibility of API and excipients), comparative multipoint in vitro dissolution profiles obtained on at least two batches of pilot- or production-scale of the proposed product and the biobatch (depending on the solubility and permeability of the drug, dissolution in the routine release medium or in multiple media covering the physiological pH range).
4. (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
5. (P.4) Control of excipients, if new excipients are proposed.

*continues*¹⁰ See footnote 3.

Table *continued***Documentation required**

6. (P.4.5) If applicable, either a CEP for any new component of animal origin susceptible to TSE risk or, where applicable, documented evidence that the specific source of the TSE risk material has been previously assessed by an NMRA in the ICH region or associated countries and shown to comply with the scope of the current guidelines in the countries of the ICH region or associated countries. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals and its use.
7. (P.5) Copies of FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot- or production-scale batches. If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.
8. (P.8.1) Results of stability testing generated on at least two pilot- or production-scale batches with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
9. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of each strength of the proposed product into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
10. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch, and confirmation that there are no changes to the production documents other than those highlighted.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
26	Change or addition of imprints, embossing or other markings, including replacement or addition of inks used for product markings and change in scoring configuration involving:			
26a	changes in imprints, embossing or other markings	1–3	1–2, 5–6	IN
26b	deletion of a scoreline	2–5	1, 5–6	IN
26c.1	addition of a scoreline	2–4	1, 3, 5–6	Vmin
26c.2		None	1, 3–6	Vmaj

continues

Table continued

Conditions to be fulfilled

1. Any ink complies with section 3.2.P.4 of the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.¹¹
2. The change does not affect the stability or performance characteristics (e.g. release rate) of the FPP.
3. Changes to the FPP specifications are those necessitated only by the change to the appearance or to the scoring.
4. Addition or deletion of a score line from a generic product is consistent with a similar change in the comparator product or was requested by WHO/PQP.
5. The scoring is not intended to divide the FPP into equal doses.

Documentation required

1. Sample of the FPP.
2. (P.1.) Qualitative composition of the ink, if purchased as a mixture.
3. (P.2) Demonstration of the uniformity of the dosage units of the tablet portions, where the scoring is intended to divide the FPP into equal doses.
4. (P.2) Demonstration of the similarity of the release rate of the tablet portions for gastro-resistant, modified or prolonged release products.
5. (P.5) Copies of revised FPP release and shelf-life specifications.
6. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documentation for one batch and confirmation that there are no changes to the production documents other than those highlighted.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
27	Change in dimensions without change in qualitative or quantitative composition and mean mass of:		
27a	tablets, capsules, suppositories and pessaries other than those stated in change no. 27b	1–2	2–6 IN
27b	gastro-resistant, modified or prolonged-release FPPs and scored tablets	1–2	1–6 Vmin

continues

¹¹ See footnote 3.

Table *continued***Conditions to be fulfilled**

1. Specifications for the FPP are updated only with respect to dimensions of the FPP.
2. Multipoint in vitro dissolution profiles of the current and proposed versions of the product (determined in the routine release medium, on at least one batch of pilot- or production-scale), are comparable.

Documentation required

1. For gastro-resistant, modified or prolonged release FPPs, justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence. For scored tablets where the scoring is intended to divide the FPP into equal doses, demonstration of the uniformity of the tablet portions.
2. Sample of the FPP.
3. (P.2) Discussion on the differences in manufacturing process(es) between the currently accepted and proposed products and the potential impact on product performance.
4. (P.2) Comparative multipoint in vitro dissolution profiles in the routine release medium, on at least one batch of pilot- or production-scale of the current and proposed products.
5. (P.5) Copies of revised FPP release and shelf-life specifications.
6. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of executed production documentation for one batch and confirmation that there are no changes to the production documents other than those highlighted.

3.2. P.3 Manufacture

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
28	Addition or replacement of a manufacturing site for part or all of the manufacturing process for an FPP involving:			
28a	secondary packaging of all types of FPPs	2–3	1	IN
28b	primary packaging site of:	2–5	1, 5–6	IN
28b.1	solid FPPs (e.g. tablets, capsules), semi-solid FPPs (e.g. ointments, creams) and solution liquid FPPs	2–4	1, 8	IN
28b.2	other liquid FPPs (suspensions, emulsions)	2–5	1, 5, 8	IN

continues

Table *continued*

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
28c	all other manufacturing operations except batch control and/or release testing	1–3, 5	1–9	Vmin

Conditions to be fulfilled

1. No change in the batch formula, description of manufacturing process and process controls, equipment class and process controls, controls of critical steps and intermediates, or FPP specifications.
2. Satisfactory inspection in the last three years either by WHO or an SRA.
3. Site appropriately authorized by an NMRA (to manufacture the pharmaceutical form and the product concerned).
4. The change does not concern a sterile FPP.
5. Validation protocol is available or validation of the manufacturing process at the new site has been successfully carried out on at least three production-scale batches in accordance with the current protocol.

Documentation required

1. Evidence that the proposed site has been appropriately authorized in the last three years, for the pharmaceutical form and the product concerned:
 - a copy of the current manufacturing authorization, a GMP certificate or equivalent document issued by the NMRA;
 - a GMP statement or equivalent issued by WHO or an SRA;
 - date of the last satisfactory inspection concerning the packaging facilities by WHO or an SRA in the last three years.
2. Date and scope (with indication as to whether scope was e.g. product-specific or related to a specific pharmaceutical form) of the last satisfactory inspection.
3. (P.2) Where applicable, for semisolid and liquid formulations in which the API is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology.
4. (P.2) For solid dosage forms, data on comparative dissolution tests in the routine release medium, with demonstration of similarity of dissolution profiles with those of the biobatch, performed on one production-scale batch each from current and proposed manufacturing sites and comparison with the biobatch results, with commitment to generate dissolution profiles on two more production-scale batches.
5. (P.3.5) Process validation reports or validation protocol (scheme) for three batches of the proposed batch size, which includes comparative dissolution against the biobatch results with f₂ calculation as necessary.
6. (P.5.1) Copies of release and shelf-life specifications.

continues

Table *continued***Documentation required**

7. (P.5.4) Batch analysis data on one production-scale batch from the proposed site and comparative data on the last three batches from the previous site.
8. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the FPP produced at the new site into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
9. (R.1) Executed production documents for one batch of the FPP manufactured at the new site.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
29	Replacement or addition of a site involving batch control testing	1–2	1–3	AN

Conditions to be fulfilled

1. Site is appropriately authorized by the NMRA and satisfactorily inspected either by WHO or an SRA.
2. Transfer of methods from the current testing site to the proposed testing site has been successfully completed.

Documentation required

1. Clear identification of the currently accepted and proposed quality control sites on the letter accompanying the application.
2. Documented evidence that the site is appropriately authorized by the NMRA and satisfactorily inspected either by WHO or an SRA.
3. (P.5.3) Documented evidence of successful transfer of analytical procedures from the current to the proposed site.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
30	Change in the batch size of the FPP involving:			
30a	up to and including a factor of 10 compared to the biobatch	1–7	2, 5–6	IN
30b	downscaling	1–5	2, 6	AN
30c	other situations	1–7	1–7	Vmin

continues

Table *continued***Conditions to be fulfilled**

1. The change does not affect the reproducibility and/or consistency of the product.
2. The change pertains only to immediate-release oral pharmaceutical forms and to non-sterile liquid forms.
3. Changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change in batch size, e.g. use of different-sized equipment.
4. A validation protocol is available or validation of the manufacture of three production-scale batches has been successfully undertaken in accordance with the current validation protocol.
5. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
6. The change does not require supporting in vivo data.
7. The biobatch size was at least 100 000 units in the case of solid oral dosage forms.

Documentation required

1. (P.2) For solid dosage forms: dissolution profile data, in the routine release medium, on a minimum of one representative production-scale batch and comparison of the data with the biobatch results and one production-scale batch of the previous batch size. Data on the next two full production-scale batches should be available on request and should be reported if they do not meet dissolution profile similarity (f2) requirements. For semi-solid dosage forms (e.g. lotions, gels, creams and ointments), containing the API in the dissolved or non-dissolved form, comparative in vitro data on membrane diffusion (membrane release testing) should be submitted or be available on request.
2. (P.3.5) Process validation reports for three batches of the proposed batch size or validation protocol (scheme).
3. (P.5.1) Copies of release and shelf-life specifications.
4. (P.5.4) Batch analysis data (in a comparative tabular format) on a minimum of one production-scale batch manufactured to both the currently accepted and the proposed batch sizes. Batch data on the next two full production-scale batches should be available on request and should be reported immediately by the supplier of the product, if outside specifications (with proposed remedial action).
5. (P.8.2) Updated post-acceptance stability protocol (approved by authorized personnel) and stability commitment to place the first production-scale batch of each strength at the proposed scale into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
6. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documentation for one batch (if manufactured as required by documentation 4) (above) and confirmation that there are no changes to the production documents other than those highlighted.
7. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence.

continues

Table *continued*

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
31a	Change in the manufacturing process of the FPP	1–9	1–4, 6–7	AN
31b		1–3, 5–9	1–7	Vmin

Conditions to be fulfilled

1. The change does not require supporting in vivo data.
2. No change in qualitative and quantitative impurity profile or in physicochemical properties; dissolution profiles are similar to those of the biobatch.
3. The manufacturing processes for the currently accepted and proposed products use the same principles (e.g. a change from wet to dry granulation, from direct compression to wet or dry granulation or vice versa would be considered a change in manufacturing principle), the same processing intermediates and there are no changes to any manufacturing solvent used in the process.
4. The same classes of equipment, operating procedures, in-process controls (with no widening or deleting of limits) are used for the currently accepted and proposed products; no change in critical process parameters.
5. No change in the specifications of the intermediates or the FPP.
6. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
7. The change does not involve packaging or labelling where the primary packaging provides a metering and/or delivery function.
8. The change does not concern a gastro-resistant, modified or prolonged-release FPP.
9. The change does not affect the sterilization parameters of a sterile FPP.

Documentation required

1. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence.
2. (P.2) Discussion on the development of the manufacturing process; where applicable:
 - comparative in vitro testing, e.g. multipoint dissolution profiles in the routine release medium for solid dosage units (one production batch and comparative data on one batch from the previous process and the biobatch results; data on the next two production batches should be available on request or reported if outside specification);
 - comparative in vitro membrane diffusion (membrane release testing) for non-sterile semisolid dosage forms containing the API in the dissolved or non-dissolved form (one production batch and comparative data on one batch from the previous process and the biobatch results; data on the next two production batches should be submitted or be available on request);
 - microscopic imaging of particles to check for visible changes in morphology and comparative size distribution data for liquid products in which the API is present in non-dissolved form.

continues

Table continued

Documentation required				
3. (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.				
4. (P.5) Specification(s) and certificate of analysis for one production-scale batch manufactured according to the currently accepted process and for a batch manufactured according to the proposed process.				
5. (P.8.1) Results of stability testing generated on at least two pilot batches (for uncomplicated products, one pilot batch; the other one can be smaller) with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.				
6. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the proposed product into the long-term stability programme.				
7. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as executed production documentation for one batch and confirmation that there are no changes to the currently accepted production documents other than those highlighted.				
Description of change		Conditions to be fulfilled	Documentation required	Reporting type
32	Change to in-process tests or limits applied during the manufacture of the FPP or intermediate involving:			
32a	tightening of in-process limits	1–2, 5	1	AN
32b	deletion of a test	2, 4	1, 6	AN
32c	addition of new tests and limits	2–3	1–6	AN
32d	revision or replacement of a test	2–3	1–6	IN
Conditions to be fulfilled				
1. The change is within the range of acceptance limits.				
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.				
3. Any new test does not concern a novel, non-standard technique or a standard technique used in a novel way.				
4. The deleted test has been demonstrated to be redundant with respect to the remaining analytical procedures (e.g. colour) and does not affect the critical quality attributes of the product (e.g. blend uniformity, weight variation).				
5. No change in the analytical procedure.				

continues

Table *continued***Documentation required**

1. (P.5.1) Copy of the proposed in-process specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
4. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.
5. (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using current and proposed methods, if new analytical procedures are implemented.
6. (P.5.6) Justification for the addition or deletion of the tests and limits.

3.2. P.4 Control of excipients

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
33	Change in source of an excipient from a TSE risk to a material of vegetable or synthetic origin.	1	1	AN

Conditions to be fulfilled

1. No change in the excipient and FPP release and shelf-life specifications.

Documentation required

1. Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthetic origin.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
34	Change in the specifications or analytical procedures for an excipient involving:			
34a	deletion of a non-significant in-house parameter	2	1–3	AN
34b	addition of a new test parameter or analytical procedure	2–3	1–2	AN

continues

Table continued

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
34c	tightening of specification limits	1–2, 4	1–2	AN
34d	change or replacement of an analytical procedure	2–3	1–2	Vmin

Conditions to be fulfilled

1. The change is within the range of currently accepted limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. No change in the analytical procedure.

Documentation required

1. Justification for the change.
2. (P.5) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications and details of procedure and summary of validation of any new analytical procedure (if applicable).
3. Justification to demonstrate that the parameter is not critical.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
35	Change in specifications of an excipient to comply with an officially recognized pharmacopoeia	1	1	AN

Conditions to be fulfilled

1. No change to the specifications other than those required to comply with the pharmacopoeia (e.g. no change in particle size distribution).

Documentation required

1. Comparative table of currently accepted and proposed specifications for the excipient.

3.2. P.5 Control of FPP

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
36a	Change in the standard claimed for the FPP from an in-house to an officially recognized pharmacopoeial standard	1–3	1–5	AN
36b	Update to the specifications to comply with an officially recognized pharmacopoeial monograph as a result of an update to this monograph to which the FPP is controlled	None	1, 3, 5	AN

Conditions to be fulfilled

1. The change is made exclusively to comply with the officially recognized pharmacopoeia.
2. No change to the specifications that results in a potential impact on the performance of the FPP (e.g. dissolution test).
3. No deletion of or relaxation of any of the tests, analytical procedures or acceptance criteria of the specifications. Any deletion or relaxation of the tests should meet the conditions of 37a or 37d and should follow the corresponding reporting types.

Documentation required

1. (P.5.1) Copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.
3. (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using current and proposed procedures, if new analytical procedures are implemented.
4. (P.5.6) Justification for the proposed FPP specifications.
5. (P.5.3) Demonstration of the suitability of the monograph to control the FPP.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
37	Change in the specifications of the FPP involving test parameters and acceptance criteria:			
37a	deletion of a test parameter	5	1, 6	AN

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
37b	addition of a test parameter	2–4, 7	1–6	AN
37c	tightening of an acceptance criterion	1–2	1, 6	AN
37d	relaxation of an acceptance criterion	2, 4, 6–7	1, 5–6	IN
37e	replacement of a test parameter	2–4, 6–7	1–6	IN

Conditions to be fulfilled

1. The change is within the range of currently accepted limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. No additional impurity found over the ICH identification threshold.
5. The deleted test has been demonstrated to be redundant with respect to the remaining tests.
6. The change to the specifications does not affect the stability and the performance of the product.
7. The change does not concern sterility testing.

Documentation required

1. (P.5.1) Copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
4. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.
5. (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using currently accepted and proposed procedures, if new analytical procedures are implemented.
6. (P.5.6) Justification for the proposed FPP specifications.

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
38	Change in the analytical procedures for the FPP involving:			
38a	deletion of an analytical procedure	5	1, 6	AN
38b	addition of an analytical proceduref	3–4, 6–7	1–5	AN
38c.1	modification or replacement of an analytical procedure	1–4, 6–7	1–5	AN
38c.2		2–4, 6–7	1–5	Vmin
38d	updating the analytical procedure with an officially recognized pharmacopoeial monograph as a result of an update to that monograph	None	1–5	AN
38e	change from an in-house analytical procedure to an analytical procedure in an officially recognized pharmacopoeial monograph or from the analytical procedure in one officially recognized pharmacopoeial monograph to an analytical procedure in another officially recognized pharmacopoeial monograph	2, 7	1–3, 5	IN

Conditions to be fulfilled

1. The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method), and no new impurities are detected.
2. Comparative studies demonstrate that the proposed analytical procedure is at least equivalent to the currently accepted analytical procedure.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. The change does not concern sterility testing.
5. The deleted analytical procedure is an alternative method and is equivalent to a currently accepted analytical procedure.

continues

Table *continued***Conditions to be fulfilled**

6. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
7. No new impurities have been detected.

Documentation required

1. (P.5.1) A copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (P.5.3) Copies or summaries of validation reports, including verification data for assay or purity methods, if new analytical procedures are used.
4. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.
5. (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using currently accepted and proposed analytical procedures.
6. Justification for the deletion of the analytical procedure, with supporting data.

3.2. P.7 Container-closure system

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
39a	Replacement or addition of a primary packaging type	1	1–2, 4–6	Vmin
39b		None	1–6	Vmaj

Conditions to be fulfilled

1. The change does not concern a sterile FPP.

Documentation required

1. Samples of the product as packaged in the new container-closure system.
2. (P.2) Data on the suitability of the container-closure system (e.g. extractable/leachable testing, permeation testing, light transmission) demonstrating equivalent or superior protection compared to the current packaging system. For changes to functional packaging, data to demonstrate the functioning of the new packaging.
3. (P.3.5) For sterile FPPs, process validation and/or evaluation studies.

continues

Table *continued***Documentation required**

4. (P.7) Information on the proposed primary packaging type (e.g. description, materials of construction of primary packaging components, specifications, and results of transportation studies, if appropriate).
5. (P.8.1) Stability summary and conclusions, results for a minimum of two batches of pilot- or production-scale, of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and where applicable, results of photostability studies.
6. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the proposed product into the long-term stability programme, unless data were provided in documentation 5.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
40	Change in the package size involving:			
40a	change in the number of units (e.g. tablets, ampoules, etc.) in a package	1–2	1–2	IN
40b.1	change in the fill weight or fill volume of non-parenteral multidose products	1–3	1–2	IN
40b.2		1–2	1–2	Vmin

Conditions to be fulfilled

1. The change is consistent with the posology and treatment duration accepted in the SmPC.
2. No change in the primary packaging material.
3. No increase in the headspace or surface/volume ratio.

Documentation required

1. Justification for the new pack-size, indicating that the new size is consistent with the dosage regimen and duration of use as accepted in the SmPC.
2. (P.8.2) A written commitment that stability studies will be conducted in accordance with the WHO guidelines for products where stability parameters could be affected.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
41	Change in the shape or dimensions of the container or closure for:			
41a	non-sterile FPPs	1–2	1–3	AN
41b	sterile FPPs	1–2	1–4	Vmin

continues

Table *continued*

Conditions to be fulfilled				
1. No change in the qualitative or quantitative composition of the container and/or closure. 2. The change does not concern a fundamental part of the packaging material, which could affect the delivery, use, safety or stability of the FPP.				
Documentation required				
1. Samples of the product packaged in the new container-closure system. 2. (P.7) Information on the proposed container-closure system (e.g. description, materials of construction, and specifications). 3. (P.8.1) In the case of changes to the thickness of a packaging component or for sterile FPPs: stability summary and conclusions, results for a minimum of two batches of pilot- or production-scale, of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and, where applicable, results of photostability studies. In the case of a change in the headspace or a change in the surface/volume ratio for non-sterile FPPs, a commitment for the above studies. 4. (P.3.5) Evidence of revalidation studies in the case of terminally sterilized products. The batch numbers of the batches used in the revalidation studies should be indicated, where applicable.				
Description of change		Conditions to be fulfilled	Documentation required	Reporting type
42	Change in qualitative and/or quantitative composition of the immediate packaging material for:			
42a	solid FPPs	1–3	1–3	IN
42b	semisolid and liquid FPPs	1–3	1–3	Vmin
Conditions to be fulfilled				
1. The change does not concern a sterile FPP. 2. No change in the packaging type and material (an example of an allowable change is blister to blister). 3. The relevant properties of the proposed packaging are at least equivalent to those of the currently accepted material.				
Documentation required				
1. (P.2) Data demonstrating the suitability of the proposed packaging material (e.g. extractable/leachable testing, light transmission, permeation testing for oxygen, carbon dioxide, and moisture). 2. (P.7) Information on the proposed packaging material (e.g. description, materials of construction, and specifications).				

continues

Table *continued***Documentation required**

3. (P.8.1) Stability summary and conclusions, results of (or a commitment to study in the case of demonstrated equivalent or more protective packaging) a minimum of two batches of pilot- or production-scale, of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and, where applicable, results of photostability studies.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
43	Change in the specifications of the immediate packaging involving:			
43a	tightening of specification limits	1–2	1	AN
43b	addition of a test parameter	2–3	1–2	AN
43c	deletion of a non-critical parameter	2	1, 3	AN

Conditions to be fulfilled

1. The change is within the range of currently accepted limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.

Documentation required

1. (P.7) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications.
2. (P.7) Description of the analytical procedure and summary of validation of the new analytical procedure.
3. Documentation to demonstrate that the parameter is not critical.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
44	Change to an analytical procedure on the immediate packaging involving:			
44a	minor change to an analytical procedure	1–3	1	AN

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
44b	other changes to an analytical procedure including addition or replacement of an analytical procedure	2–4	1	AN
44c	deletion of an analytical procedure	5	2	AN

Conditions to be fulfilled

1. The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method).
2. Appropriate (re)validation studies have been performed in accordance with the relevant guidelines.
3. Comparative studies indicate the new analytical procedure to be at least equivalent to the former procedure.
4. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5. The deleted analytical procedure is an alternative method and is equivalent to a currently accepted method.

Documentation required

1. (P.7) Description of the method and comparative validation results demonstrating that the currently accepted and proposed methods are at least equivalent.
2. Documentation to demonstrate the equivalence of the deleted method and a currently accepted method.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
45	Change in any part of the (primary) packaging material not in contact with the FPP formulation (e.g. colour of flip-off caps, colour code rings on ampoules, or change of needle shield).	1	1–2	IN

continues

Table *continued***Conditions to be fulfilled**

1. The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the FPP.

Documentation required

1. (P.7) Information on the proposed packaging material (e.g. description, materials of construction, and specifications).
2. Sample of the FPP.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
46	Change to an administration or measuring device that is not an integral part of the primary packaging (excluding spacer devices for metered dose inhalers) involving:			
46a	addition or replacement	1, 2	1–2	IN
46b	deletion	3	3	IN

Conditions to be fulfilled

1. The proposed measuring device is designed to accurately deliver the required dose for the product concerned in line with the posology, and results of such studies are available.
2. The proposed device is compatible with the FPP.
3. The FPP can be accurately delivered in the absence of the device.

Documentation required

1. (P.2) Data to demonstrate accuracy, precision and compatibility of the device.
2. Sample of the device.
3. Justification for the deletion of the device.

3.2. P.8 Stability

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
47	Change in the shelf-life of the FPP (as packaged for sale) involving:			
47a	reduction	3	1–3	IN
47b	extension	1–2	1–3	Vmin

continues

Table *continued*

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
49	Change in the labelled storage conditions of the FPP (as packaged for sale), the product during the in-use period or the product after reconstitution or dilution	1	1–2	Vmin
Conditions to be fulfilled				
1. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.				
Documentation required				
1. (P.8.1) If applicable, stability and/or compatibility test results to support the change to the storage conditions.				
2. (P.8.2) Updated post-acceptance stability protocol and stability commitment and justification of change.				

Appendix 1

Examples of changes that make a new application or extension application necessary

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
1. Change of the API to a different API 2. Inclusion of an additional API in a multicomponent product 3. Removal of one API from a multicomponent product 4. Change in the dose and/or strength of one or more APIs 5. Change from an immediate-release product to an extended or delayed-release dosage form or vice versa 6. Change from a liquid to a powder for reconstitution or vice versa 7. Changes in the route of administration	None	1	New application/extension application
Conditions to be fulfilled			
None			
Documentation required			
1. Documents in fulfilment of the requirements outlined in the WHO <i>Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part</i>.¹²			

¹² See footnote 3.

Appendix 2

Changes to excipients

Excipient	Percentage excipient (w/w) out of total target dosage form core weight
Filler	± 5.0
Disintegrant	
• starch	± 3.0
• other	± 1.0
Binder	± 0.5
Lubricant	
• Ca or Mg Stearate	± 0.25
• other	± 1.0
Glidant	
• talc	± 1.0
• other	± 0.1

- These percentages are based on the assumption that the active pharmaceutical ingredient (API) in the finished pharmaceutical product (FPP) is formulated to 100.0% of label/potency declaration. The total additive effect of all changes to excipients should be not more than 5.0% relative to the target dosage form weight (e.g. in a product consisting of API, lactose, microcrystalline cellulose and magnesium stearate, the lactose increases by 2.5% and microcrystalline cellulose decreases by 2.5%).
- If an excipient serves multiple functions (e.g. microcrystalline cellulose as a filler and as a disintegrant), then the most conservative recommended range should be applied (e.g. $\pm 1.0\%$ for microcrystalline cellulose should be applied in this example). If a wider range is proposed, scientific justification and supporting data should be provided to demonstrate that the wider range will not affect the other function of the excipient.

6.8 Guidelines on the requalification of prequalified dossiers
Annex 6, WHO Technical Report Series, 957,
2010

1. Introduction	888
2. Requalification of prequalified dossiers	889
Appendix 1 Summary of key product information	890
Appendix 2 Variations to the product	892

1. Introduction

In accordance with the provisions set out in section 12 (Maintenance of prequalification status) of the *Procedure for prequalification of pharmaceutical products*¹, holders of WHO-prequalified products should submit a quality review 5 years from the date of prequalification of the product, or when requested to do so by WHO Prequalification (whichever date is earlier).

Section 12 of the above-mentioned guidelines states that:

WHO will furthermore arrange for the products and manufacturing sites included in the list to be re-evaluated at regular intervals. If, as a result of this re-evaluation, it is found that a product and/or specified manufacturing site no longer complies with the WHO-recommended standards, such products and manufacturing sites will be removed from the list. Failure of a manufacturer or applicant to participate in the re-evaluation procedure will also lead to removal from the list.

Re-evaluation, including re-inspections of manufacturing sites and contract research organizations (CROs), will be done at regular intervals, based on risk assessment, but at least once every 5 years.

Re-evaluation, including re-inspections, shall also be performed:

- if any fraud or omissions by the applicant, manufacturer(s) of a finished pharmaceutical product (FPP) or active pharmaceutical ingredient (API), or CROs in the initial assessment procedure or during the follow-up activities, becomes evident; and
- if WHO or any United Nations agency considers that a batch or batches of supplied prequalified pharmaceutical products are not in compliance with the specifications which were found to be applicable upon prequalification.

Requalification will be applicable to multisource FPPs (generics) where the full dossiers have been submitted, assessed and prequalified by WHO. Renewal of marketing authorization for products that have been listed by WHO based on approval by a stringent regulatory agency² (SRA) remains the responsibility of the relevant SRA.

¹ Procedure for prequalification of pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2009, Annex 4 (WHO Technical Report Series, No. 953) (https://iris.who.int/bitstream/handle/10665/44553/WHO_TRS_953_eng.pdf?sequence=1&isAllowed=y).

² Stringent regulatory authority (SRA): a regulatory authority which is:
a member of the International Conference on Harmonisation (ICH) (as specified on www.ich.org); or
an ICH observer, being the European Free Trade Association (EFTA), as represented by Swiss Medic, Health Canada and World Health Organization (WHO) (as may be updated from time to time); or
a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

2. Requalification of prequalified dossiers

The objective of this quality review submission is to enable WHO to requalify the product based on an assessment of the data and information submitted by the holder of a prequalified product, which includes verification of the acceptability of the product and its conformity to current norms and standards, and assessment of consistency of the quality of the prequalified FPPs, and its manufacturing process(es) over the identified period.

The holder of a prequalified product should submit the following documents electronically (in pdf format and in also in WinWord where indicated):

- A covering letter, which should contain a clear statement by the responsible person submitting the quality review, indicating that the information submitted is true and correct.
- Summary of key product information (as per Appendix 1).
- Variations to the product (as per Appendix 2).
- A pharmaceutical quality information form (PQIF)³, completed in WinWord format. It should reflect the requirements of current prequalification guidelines and should also take into account technical and scientific progress. The API and FPP specifications should be provided in tabulated format, comparing the specifications at prequalification and at the time of the requalification submission.
- Copies of the current API and FPP specifications, duly signed and dated, including the test methods. The specifications should indicate the reference number, version number, effective date and change history if any.

A product quality review may be submitted as supportive documentation. It may also be requested by WHO.

³ Presentation of pharmaceutical quality information. In: *Guidance for submission of documentation for prequalification of multi-source (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis*. Annex 8 (http://apps.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc).

Appendix 1

Summary of key product information

This section compares key information on the FPP at the time of prequalification and at the time of the submission for requalification. Table A1.1 should be completed by the holder of the prequalified product. Include remarks as a footnote to Table A1.1, where deemed necessary, to clarify the information provided.

Table A1.1
Summary of key product information

Item	Prequalified dossier	Current data ^a
Product number (e.g. HA001)		
INN, strength and pharmaceutical form		
Applicant (name, physical address and contact numbers)		
Manufacturing site(s) of FPP, with physical address (including unit and block numbers) and contact numbers (list separately if different steps are performed by different sites, e.g. packaging, quality control)		
Batch size(s) of FPP		
Product description (visual appearance)		
Primary and secondary packaging material(s) and pack size(s)		
Storage conditions of FPP		
Shelf-life of FPP		
FPP specification(s) reference number and/or version ^b		
Manufacturer(s) of API(s), with physical address (including unit and block numbers) and contact numbers (list each API separately)		
Number/version of each APIMF associated with the FPP		
Storage conditions of API		
Retest period of API(s)		
API specification(s) reference number and/or version (for each API) ^b		
All commitments and their outcomes		

Table A1.1 *continued*

INN, international nonproprietary name; FPP, finished pharmaceutical product; API, active pharmaceutical ingredient; APIME, active pharmaceutical ingredient master file.

^a If there has been no update of the dossier then indicate “N/A” (not applicable).

^b According to the latest editions of *The International Pharmacopoeia* (Ph.Int.), the *European Pharmacopoeia* (Ph.Eur), the *British Pharmacopoeia* (BP) and/or the *United States Pharmacopeia* (USP). Where in-house specifications have been approved and there is now a monograph in any of the internationally-recognized pharmacopoeias (Ph.Int., Ph.Eur, BP, or USP), the specifications should be updated to comply with the new monograph or demonstrated to be at least equivalent. In the case that no compendial monograph exists, the applicant should ensure that the approved in- house specifications are updated, through the variation process, to reflect the requirements of current prequalification guidelines and to take into account technical and scientific progress (e.g. current ICH guidelines, general chapters of the Ph.Int.). Each new version of the documents should allow traceability to the prequalified dossier and approved variations.

Appendix 2

Variations to the product

The holder of the prequalified product should submit a review, in tabular format, of any minor and/or major changes (including those pending) to the initially prequalified product or to the terms of the initially prequalified dossier. Table A2.1 should be completed by the holder of the prequalified product.

Table A2.1

Information on variations to the prequalified product

Reference no.	Date of submission	Date of approval/ rejection and reference number of the letter	Date of implementation
Major changes			
Description of the change, e.g. change in the primary packaging site of a sterile product			
Minor changes			
Description of the change according to the PQ variation guide			

Add as many rows as necessary.

Note. Requests for variations should have been submitted in accordance with WHO's Guidance on variations to a prequalified product dossier⁴.

⁴ WHO Guidance on variations to a prequalified product dossier. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report*. Geneva, World Health Organization, 2007, Annex 6 (WHO Technical Report Series, No. 943) (https://iris.who.int/bitstream/handle/10665/43632/WHO_TRS_943_eng.pdf?sequence=1&isAllowed=y).

6.9 Prequalification of quality control laboratories: procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies

Annex 3, WHO Technical Report Series, 1003, 2017

Introduction	894
1. Steps of the procedure	895
1.1 Publication of invitation for Expressions of Interest	895
1.2 Submission of EOIs and laboratory information	896
1.3 Screening of submitted laboratory information	897
1.4 Evaluation of the laboratory information	897
1.5 Site inspection	897
1.6 Report and outcome of inspection	898
1.7 Results of assessment	899
1.8 Monitoring of prequalified QCLs	899
1.9 Monitoring of complaints	901
1.10 Cost recovery	901
1.11 Confidentiality undertaking	901
1.12 Conflict of interest	902
References	902

Introduction

This document provides an update of the procedure originally published as Annex 12 in World Health Organization (WHO) Technical Report Series, No. 961, 2011. WHO provides United Nations (UN) agencies, their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States, on request, with advice on the acceptability, in principle, of quality control laboratories (QCLs) that are found to meet WHO-recommended quality standards for such laboratories. These standards are set out in *Good practices for pharmaceutical quality control laboratories* (GPCL) (1), and include, where applicable, good practices for pharmaceutical microbiology laboratories (2) and the relevant parts of good manufacturing practices (GMP) (3). This is done through a standardized quality assessment procedure. The purpose of the quality assessment procedure is to evaluate whether the QCLs to be used for the quality control of pharmaceutical products meet the requirements recommended by WHO for such laboratories.

Participation in the prequalification procedure is voluntary and any pharmaceutical QCL (governmental or private) providing quality control services for pharmaceutical products to UN agencies, their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States is eligible.

Accreditation, such as ISO (in terms of ISO/IEC17025), is encouraged and will also be considered in the prequalification procedure. Laboratories are recommended to work towards obtaining accreditation.

The quality assessment procedure established by WHO is based on the following principles:

- evidence that the laboratory provides or is committed to offering quality control services for pharmaceutical products to UN agencies and their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States;
- a general understanding of the documented quality assurance management and quality control testing activities of the laboratory;
- evaluation of information submitted by the laboratory;
- assessment of compliance with WHO-recommended quality standards for QCLs, i.e. GPCL (1), including, where applicable, good practices for pharmaceutical microbiology laboratories (2) and the relevant parts of GMP (3);
- monitoring of performance of prequalified laboratories.

WHO invites the national medicines regulatory authority (NMRA), having regulatory oversight over a laboratory participating in the prequalification procedure,

to join as an observer in the inspection of the laboratory's compliance with WHO-recommended standards for QCLs. WHO recommends that laboratories expressing an interest in participating in the prequalification procedure inform the regulatory authority of the country in which they are established as well as relevant networks (e.g. the official medicines control laboratories network) of their submission for prequalification.

This procedure is to be followed for prequalification of QCLs for use by UN agencies and their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States.

1. Steps of the procedure

WHO requires information related to the activities of, and quality control of pharmaceutical products in, laboratories interested in being assessed under this procedure. Interested QCLs should submit the information about their activities as requested by WHO (see point 1.2 below). In addition to the evaluation of the information submitted, a site inspection (or inspections) may be performed.

If, due to insufficient resources and time constraints, WHO has to set priorities in the assessment of interested laboratories, then priority will be given to QCLs in areas where UN agencies, their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States identify the need for testing of the quality of pharmaceutical products.

Applications from laboratories that belong to or are affiliated with a manufacturer of pharmaceutical products, particularly those that have an interest in having one or more of their products prequalified by WHO or whose product(s) is/are already prequalified by WHO, may be given lower priority or may not be evaluated at all.

WHO reserves the right to terminate the quality assessment of a laboratory when the laboratory is not able to provide, or fails to provide, the required information, when the information supplied is inadequate to complete the quality assessment effectively, and when the laboratory fails to collaborate in inspections required by WHO and/or is unable to implement corrective actions that WHO may require within a specified time period.

1.1 Publication of invitation for Expressions of Interest

WHO will publish an invitation to QCLs to submit an Expression of Interest (EOI) to participate in the prequalification procedure. Such an invitation will specify the scope of quality control testing which is subject to prequalification and will be published widely, i.e. on the WHO website and possibly also through other media, such as the international press. The invitation will be open and transparent, inviting all interested QCLs to submit an EOI for prequalification.

1.2 Submission of EOIs and laboratory information

Each interested laboratory should provide the WHO focal point indicated in the invitation for EOIs with:

- a cover letter expressing interest in participating in the prequalification procedure;
- evidence that the laboratory provides, or is committed to offering, quality control services for pharmaceutical products to UN agencies, their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States; and
- the relevant laboratory information.

WHO will record the receipt of the EOI from each laboratory in a register. If the laboratory has documented its quality system as a quality manual, this can be submitted, provided that it is supplemented with the information required for the laboratory information file (LIF) (see below) that is not provided in the quality manual.

The information should be submitted as described in the document *Guidelines for preparing a laboratory information file (4)* and cover the areas listed below:

- general information on the laboratory, including activities proposed for prequalification;
- quality management system implemented, and inspections and external audits performed in the laboratory;
- participation in proficiency testing schemes and/or collaborative trials;
- internal audits;
- control of documentation and records;
- personnel;
- premises;
- equipment;
- reagents, reference substances and reference materials;
- subcontracting of testing (where applicable);
- handling of samples;
- validation and/or verification of analytical procedures;
- investigation of out-of-specification (OOS) results;
- stability testing (where applicable);
- microbiological testing (where applicable).

Guidelines for the submission of EOIs and for the preparation and submission of the relevant information are available on the WHO website at <http://apps.who.int/prequal/> and will be sent to interested laboratories upon request.

1.3 Screening of submitted laboratory information

The *Guidelines for preparing a laboratory information file* (4) will be used in an initial screening of the information supplied. The information will not be evaluated if it is not complete. In such cases the laboratory will be requested to provide additional information within a specified time. If the additional information is not received by the deadline, the application will be rejected.

1.4 Evaluation of the laboratory information

Laboratory information that complies with the requirements set out in section 1.2 will be evaluated in accordance with a standard operating procedure (SOP) established by WHO to ensure uniformity in evaluation of the information. The information will be evaluated against the WHO-recommended quality standards for QCLs, i.e. GPCL (1), including, where applicable, good practices for pharmaceutical microbiology laboratories (2) and the relevant parts of GMP (3), and the laboratory will be considered for a possible site inspection.

A laboratory may submit the report of the inspection or audit performed by a regulatory authority applying standards at least equivalent to WHO-recommended quality standards for QCLs, i.e. GPCL (1), including, where applicable, good practices for pharmaceutical microbiology laboratories (2) and the relevant parts of GMP (3), and the response of the laboratory to the observations made by the authority during inspection or audit.

Based on an SOP established by WHO for review of external inspections and audits, if the laboratory is considered to be operating at an acceptable level of compliance with WHO-recommended standards, WHO may decide that it is not necessary to conduct a site inspection.

1.5 Site inspection

Depending on the outcome of the evaluation of the laboratory information, WHO may plan and coordinate inspections of the laboratory to assess compliance with WHO-recommended quality standards for such laboratories, i.e. GPCL (1), including where applicable good practices for pharmaceutical microbiology laboratories (2) and the relevant parts of GMP (3).¹ The inspection will be performed by an inspector, or a team of inspectors, having the relevant qualifications and experience in the field of quality control of pharmaceutical products.

External inspectors will be appointed in accordance with an SOP established by WHO and will act as temporary advisers to WHO. The external inspectors must comply with the confidentiality and conflict of interest rules of WHO, as laid down in the relevant sections of this procedure. A WHO staff member will coordinate the team. The

¹ Training modules can be found on the WHO Prequalification website (<http://apps.who.int/prequal/>).

inspector or inspection team will perform the inspections and report on the findings in accordance with SOPs established by WHO to ensure a standard harmonized approach.

A representative or representatives of the NMRA having regulatory oversight over a laboratory participating in the prequalification procedure will be invited to accompany the team as an observer.

With a view to coordinating inspection activities, avoiding duplication and promoting information sharing without prejudice to the protection of any confidential and proprietary information of the laboratory in accordance with the terms of this procedure, WHO may disclose inspection-related information to regulatory authorities of WHO Member States, UN agencies and to the European Directorate for the Quality of Medicines & HealthCare.

1.6 Report and outcome of inspection

The inspector or inspection team will finalize a report describing the findings according to the established WHO SOP and format. The report will be communicated by WHO to the laboratory and a copy will be sent to the NMRA having regulatory oversight over the laboratory.

If any additional information is required, or if a corrective action has to be taken by the laboratory, WHO will postpone its decision on the acceptability of the laboratory concerned until the additional information has been evaluated, or the corrective action has been taken, and found satisfactory. If the decision cannot be made based on the information received, a follow-up inspection will be performed.

In the event of any disagreement between a laboratory and WHO, an SOP for the handling of such disagreements will be followed to discuss and resolve the issue.

As WHO is responsible for the quality assessment procedure, the ownership of the reports lies with WHO (without prejudice, however, to any confidential and proprietary information of the laboratory contained in this report). Thus, WHO shall be entitled to use and publish such reports subject always, however, to the protection of any confidential and proprietary information of the laboratory. “Confidential information” in this context means:

- confidential intellectual property, “know-how” and trade secrets (including, e.g. programmes, processes or methods, unpublished aspects of trademarks and patents);
- commercial confidences (e.g. structures and development plans).

Provisions of confidentiality will be contained in the letters exchanged between WHO and the laboratory, to be agreed upon before the evaluation of the information and site inspection.

Notwithstanding the foregoing, WHO reserves the right to share the full reports with the relevant authorities of any interested Member State of the Organization and interested UN agencies.

1.7 Results of assessment

Once WHO is satisfied that the quality assessment process for the laboratory is complete, and that the laboratory is acceptable in principle for use by UN agencies and their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States (i.e. it has been found to meet the WHO-recommended quality standards for QCLs), the laboratory at the specified site will be included in a list referred to as “List of prequalified quality control laboratories”.

Laboratories on the list will be considered to be able to test products in compliance with WHO-recommended quality standards for QCLs. Inclusion in the list does not, however, imply any approval by WHO of the laboratories (which is the sole prerogative of national authorities).

Before publication of its name on the list of prequalified laboratories, each laboratory will receive a letter from WHO informing it of the outcome of the quality assessment process for that particular laboratory.

A copy of this letter will be sent to the NMRA of the country where the laboratory is located. The list of prequalified laboratories will be published on the WHO website and will specify the areas of expertise assessed and considered prequalified. The list will be updated whenever new relevant information is obtained.

In accordance with World Health Assembly Resolution WHA57.14 of 22 May 2004, WHO will – subject to the protection of any confidential and proprietary information – publish WHO Public Inspection Reports on the laboratories considered to meet WHO-recommended quality standards for QCLs. These reports will be published on the WHO website.

1.8 Monitoring of prequalified QCLs

Once the laboratory is included in the list of prequalified QCLs, it should inform WHO without delay about the implementation of any changes that may have an impact on the prequalification of the laboratory (such as changes to facility, equipment or key personnel) and should submit an updated LIF.

Each prequalified QCL will be re-evaluated at regular intervals (annually) or earlier, when information indicating the necessity for re-evaluation is obtained by WHO.

To enable WHO to carry out re-evaluation, all prequalified laboratories are requested to submit a brief annual report on their activities. The report should cover all activities related to quality control of pharmaceutical products within the preceding three years and should be submitted by the end of March of the subsequent year. The following items should be included in the report:

- a summary of services provided to UN agencies and their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States;

- a summary of number of samples analysed, differentiating between compliant and noncompliant samples including any OOS/out-of-trend investigations;
- a list of analytical methods used;
- a summary of complaints received from customers concerning results of analyses performed by the laboratory;
- brief details of participation in proficiency testing schemes (organizing party, methods involved, outcomes and, if appropriate, corrective measures adopted);
- listing of inspections and audits performed by external parties, identifying the party and the scope of the inspection and audit;
- in the case that changes have been implemented, which have an impact on the content of the LIF, a summary of these changes should be included in the report and an updated LIF should be attached.

WHO will conduct re-inspections of prequalified laboratories in accordance with SOPs established by WHO. The frequency of such re-inspections depends on WHO's assessment of the quality risk management factors described below. Normally, however, such re-inspections will take place at least once every three years. The following factors will be taken into account when planning inspections:

- major changes, e.g. to premises, equipment or key personnel;
- the results of previous inspection(s)/audit(s) by WHO or another external party, and history of compliance of the laboratory with WHO-recommended quality standards;
- the outcomes of participation of the laboratory in proficiency testing schemes;
- number and significance of complaints made known to the QCL by customers;
- laboratory experience with testing of pharmaceutical products;
- WHO experience with testing services provided by the laboratory.

WHO reserves the right to proceed with the re-inspection of a prequalified laboratory at any time this is considered necessary based on information or complaints received by WHO. The NMRA that has regulatory oversight over the laboratory will be invited to participate in the re-inspection as an observer.

WHO may suspend or withdraw a prequalified QCL from the list of prequalified QCLs when there is evidence of noncompliance with the WHO-recommended quality standards for such laboratories and/or this procedure.

The re-evaluation of the prequalification status of a QCL may not be prioritized if the laboratory has not, for a continuous period of more than three years, provided

quality control services for pharmaceutical products to UN agencies, their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States. In such cases, WHO will request the QCL to provide evidence that such services had been offered to, or commitments made to continue to offer such services, to UN agencies, their partners, procurement agencies serving national authorities and/or national authorities.

1.9 Monitoring of complaints

Complaints concerning the results of analysis of pharmaceutical products performed by the prequalified laboratory or concerning the service provided by the prequalified laboratory, which are communicated to WHO, will be investigated in accordance with an SOP established by WHO. The NMRA that has regulatory oversight over the laboratory will be invited to participate in the investigation of the complaint.

After conducting its investigation, WHO will provide a written report of the problem, which may, where appropriate, include recommendations for action to the laboratory under investigation and to the NMRA having the regulatory oversight over the laboratory.

1.10 Cost recovery

WHO reserves the right to charge for the quality assessment procedure on a cost-recovery basis.

1.11 Confidentiality undertaking

WHO will require any external inspectors (acting as temporary advisers to WHO) to treat all information to which they gain access during the inspections of the laboratory, or otherwise in connection with the discharge of their responsibilities in regard to the prequalification procedure, as confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set out below.

Such inspectors will be required to take all reasonable measures to ensure that confidential information:

- is not used for any purpose other than the activities described in this document;
- is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

External inspectors will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

- was known to them prior to any disclosure by or on behalf of WHO (including by laboratories); or
- was in the public domain at the time of disclosure by or on behalf of WHO (including by laboratories); or
- has become part of the public domain through no fault of theirs; or
- has become available to them from a third party not in breach of any legal obligations of confidentiality.

1.12 Conflict of interest

Before undertaking the work, each external inspector will also (in addition to the above-mentioned confidentiality undertaking) be required to sign a declaration of interest. If, based on this declaration of interest, it is felt that there is no risk of a real or perceived conflict of interest (or it is felt that there is only an insignificant and/or irrelevant conflict of interest), and it is thus deemed appropriate for the inspector in question to undertake this work, he/she will discharge his/her functions exclusively as an adviser to WHO. In this connection, each inspector is required to confirm that the information disclosed by him/her in the declaration of interest is correct and complete, and that he/she will immediately notify WHO of any change in this information.

All external inspectors furthermore agree that, at the laboratory's request, WHO will advise the laboratory in advance of the identity of each inspector and the composition of the team performing the site inspection and provide curricula vitae of the external inspectors. The laboratory then has the opportunity to express possible concerns regarding any of the external inspectors to WHO prior to the visit. If such concerns cannot be resolved in consultation with WHO, the laboratory may object to an external inspector's participation in the site visit. Such an objection must be made known to WHO by the laboratory within 10 days of being notified of the proposed team composition. In the event of such an objection, WHO reserves the right to cancel its agreement with the inspector in question and the activities to be undertaken by that inspector, in whole or in part.

References

1. Good practices for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 1 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y).
2. WHO good practices for pharmaceutical microbiology laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 2 (WHO Technical Report Series, No. 961; https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1).

3. Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. WHO guidelines, good practices, related regulatory guidance and GXP training materials. Geneva: World Health Organization; 2016.
4. WHO guidelines for preparing a laboratory information file. Revision. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-eighth report. Geneva: World Health Organization; 2011: Annex 13 (WHO Technical Report Series, No. 961; https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1).

7. Regulatory standards: collaborative procedures and reliance

7.1 Good reliance practices in the regulation of medical products: high level principles and considerations

Annex 10, WHO Technical Report Series, 1033, 2021

Background

WHO supports reliance on the work of other regulators as a general principle in order to make the best use of available resources and expertise. This principle allows leveraging the output of others whenever possible while placing a greater focus at national level on value-added regulatory activities that cannot be undertaken by other authorities, such as, but not limited to: vigilance, market surveillance, and oversight of local manufacturing and distribution. Reliance facilitates timely access to safe, effective, quality-assured medical products (see section 3. Scope) and can support regulatory preparedness and response, particularly during public health emergencies.

Good reliance practices (GRlP) are anchored in overall good regulatory practices (GRP) (1), which provide a means for establishing sound, affordable, effective regulation of medical products as an important part of health system strengthening. If implemented effectively, GRP can result in consistent regulatory processes, sound regulatory decision-making, increased efficiency of regulatory systems and better public health outcomes. NRAs are encouraged to adopt GRP to ensure that they are using the most efficient regulatory processes possible.

WHO is establishing and implementing a framework for evaluating regulatory authorities and designating those that meet the requirements as “WHO-listed authorities” (WLA) (4). Using the WHO Global Benchmarking Tool (5) and performance evaluation, WHO will assess the maturity and performance of a regulatory authority to determine whether it meets the requirements of a WLA and thereby provide a globally recognized, evidence-based, transparent system that can be used by NRAs as a basis for selecting reference regulatory authorities to practise reliance. A list of reference regulatory authorities is available on the WHO website (6).

In September 2019, WHO held a consultation to solicit input on the nature, structure and overall content of a document outlining GRelP. The meeting concluded that the concept note and recommendations on regulatory reliance principles of the Pan American Health Organization (PAHO) and the Pan American Network for Drug Regulatory Harmonization (7) should be used as a basis for the WHO document on GRelP. The high-level document would be complemented by a repository of case studies, practice guides and examples of practical application of GRelP.

Abbreviations to Annex 10	907
1. Introduction	908
2. Purpose	909
3. Scope	909
4. Glossary	910
5. Key concepts	912
5.1 Reliance versus recognition	913
5.2 Unilateral versus mutual reliance or recognition	913
5.3 Life cycle approach	914
5.4 Risk-based approach	914
5.5 Regional reliance mechanisms	915
6. Principles of good reliance practices	915
6.1 Universality	916
6.2 Sovereignty of decision-making	916
6.3 Transparency	916
6.4 Respect of national and regional legal bases	916
6.5 Consistency	917
6.6 Competence	917
7. Considerations	917
7.1 General considerations	918
7.2 Potential barriers	921
7.3 Enablers	922
8. Conclusions	923
References	924
Appendix 1 Examples of use of reliance	926

Abbreviations to Annex 10

AMRH	African Medicines Regulatory Harmonisation
APEC	Asia-Pacific Economic Cooperation
API	active pharmaceutical ingredient
ASEAN	Association of Southeast Asian Nations
CRP	collaborative registration procedure
GRP	good regulatory practices
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMDRF	International Medical Device Regulators Forum
NRA	national regulatory authority; for the purpose of this document, the term also refers to regional regulatory authorities such as the European Medicines Agency
OECD	Organisation for Economic Co-operation and Development
PAHO	Pan American Health Organization
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co operation Scheme
ZAZIBONA	Zambia, Zimbabwe, Botswana and Namibia; initial participants in the Southern African Development Community collaborative procedure for joint assessment of medicines

1. Introduction

The United Nations Sustainable Development Goals and the drive for universal health coverage require that patients have access to quality-assured, effective and safe medical products. Strong regulatory systems for medical products remain a critical element of well-functioning health systems and important contributors to improving access and ultimately achieving universal health coverage.

Establishing and sustaining mature regulatory systems requires adequate resources, including skilled, capable human resources and a significant financial investment. The globalization of markets, the sophistication of health technologies, the rapid evolution of regulatory science and the increasing complexity of supply chains have shown regulators the importance of international cooperation in ensuring the safety, quality, efficacy or performance¹ of locally used products. In view of the extent and complexity of the regulatory oversight required to address these challenges, NRAs must consider enhanced, innovative, more effective forms of collaboration to make the best use of the available resources and expertise, avoid duplication and concentrate their regulatory efforts and resources where they are most needed.

Reliance represents a smarter, more efficient way of regulating medical products in the modern world. Countries are therefore encouraged to formulate and implement strategies to strengthen their regulatory systems consistent with GRP, including pursuing regulatory cooperation and convergence, as well as reliance. Reliance benefits patients and consumers, industry, national governments, the donor community and international development partners by facilitating and accelerating access to quality-assured, effective and safe medical products.

The use of reliance to enhance the efficiency of regulatory systems has a long history. The WHO Certification scheme on the quality of pharmaceutical products moving in international commerce (8), introduced in 1969, is a form of reliance, as it provides assurance to countries that participate in the Scheme of the quality of pharmaceutical products. The European Union introduced the “mutual recognition procedure” for marketing authorizations between its member states in 1995, and the outcomes of good manufacturing practices inspections have been shared for years in the context of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) (9) and mutual recognition agreements.

WHO investigated the use of reliance more recently in a survey conducted on behalf of the International Pharmaceutical Regulators Programme (10). The results showed that regulatory reliance is broadly accepted and widely practised with regard to medical products, especially among well resourced regulatory authorities. The responses also reflected an evolving situation, with varying experience and promise in

¹ “Efficacy” applies to medicines and vaccines and “performance” to medical devices, including in-vitro diagnostics.

the use of reliance-based approaches. While use of reliance may be an emerging trend in some regions, the commonly stated goals are to increase efficiency, help to strengthen regulatory systems and optimize the use of resources. The results and suggestions from the survey were taken into account in preparation of this document.

In view of the increasing prevalence and importance of reliance in the regulation of medical products, Member States have requested WHO to prepare practical guidance on the topic while ensuring that the approaches meet the intended objectives. This document and additional guidance that follow are intended to assist countries in implementing a sound, evidence-based, practical, effective approach to reliance.

2. Purpose

The purpose is to promote a more efficient approach to regulation, thereby improving access to quality-assured, effective and safe medical products. The document presents the overarching principles of regulatory reliance in the oversight of medical products and use of reliance to enhance the effectiveness and efficiency of regulatory oversight. It provides high-level guidance, definitions, key concepts and considerations to guide reliance mechanisms and activities, illustrative examples of reliance approaches and conclusions. It will be complemented by a “reliance toolbox”, consisting of practice guides, case studies and a more comprehensive repository of examples.

3. Scope

The document covers reliance activities in the field of regulation of medical products (i.e. medicines, vaccines, blood and blood products and medical devices including in-vitro diagnostics), addressing all the regulatory functions in the full life cycle of a medical product, as defined in the Global Benchmarking Tool (5): registration and marketing authorization, vigilance, market surveillance and control, licensing establishments, regulatory inspection, laboratory testing, clinical trials oversight and NRA lot release. The document is intended for all NRAs, irrespective of their level of maturity or resources, and also for policy-makers, governments, industry, other developers of medical products and other relevant stakeholders.

The concept of reliance covers all types of medical products and regulatory activities. Reliance approaches should be given consideration in particular for medical products for priority diseases for which there are unmet medical needs, medical products to be used in public health emergencies or during shortages and also for orphan and paediatric medical products.

4. Glossary

Definitions are essential to ensure a common understanding of concepts and clarity in interpreting guidance on reliance. In addition to the definitions provided below, reference is made to the WHO document on good regulatory practices (1), which includes definitions of harmonization, convergence and other relevant terms.

Abridged regulatory pathways. Regulatory procedures facilitated by reliance, whereby a regulatory decision is solely or partially based on application of reliance. This usually involves some work by the national regulatory authority (NRA) that is practising reliance (see section 5.4 Risk-based approach). It is expected that use of reliance in these pathways will save resources and time as compared with standard pathways, while ensuring that the standards of regulatory oversight are maintained.

Assessment. For the purpose of this document, this term covers any evaluation conducted for a regulatory function (e.g. evaluation of a clinical trial application or of an initial marketing authorization for a medical product or any subsequent post-authorization changes, evaluation of safety data, evaluation as part of an inspection).

Equivalence of regulatory systems. Implies strong similarity between two regulatory systems, as mutually established and documented through objective evidence. Equivalence can be established using criteria and approaches such as similarity of the regulatory framework and practices, adherence to the same international standards and guidelines, experience gained in use of assessments for regulatory decision making, joint activities and exchanges of staff. It is expected that equivalent regulatory systems will result in similar standards and levels of regulatory oversight or “control”.

International standards and guidelines. For the purpose of this document, the term includes relevant WHO standards and guidelines and any other relevant internationally recognized standards (e.g. International Organization for Standardization or pharmacopoeial standards) and guidelines (e.g. International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] or guidelines of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co operation Scheme [PIC/S]).

Mutual recognition agreement. According to a definition issued by the Organisation for Economic Co-operation and Development (OECD), a mutual recognition agreement is:

a principle of international law whereby states party to mutual recognition agreements recognize and uphold legal decisions taken by competent authorities in another member state. Mutual recognition is a process which allows conformity assessments (of qualifications, product...) carried out in one country to be recognized in another country (2).

Recognition. Acceptance of the regulatory decision of another regulator or trusted institution. Recognition should be based on evidence that the regulatory requirements of the reference regulatory authority are sufficient to meet the regulatory requirements of the relying authority. Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement.

Reference regulatory authority. For the purpose of this document, a national or regional authority or a trusted institution such as WHO prequalification (WHO PQ) whose regulatory decisions and/or regulatory work products are relied upon by another regulatory authority to inform its own regulatory decisions.

Regional regulatory system. A system composed of individual regulatory authorities, or a regional body composed of individual regulatory authorities, operating under a common regulatory framework but not necessarily under a common legal framework. The common framework must at least ensure equivalence among the members in terms of regulatory requirements, practices and quality assurance policies. The system or regional body may have enforcement powers to ensure compliance with the common regulatory framework.

Reliance. The act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision. The relying authority remains independent, responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others.

Sameness of product. For the purpose of this document, sameness of product means that two products have identical essential characteristics (i.e. the product being submitted to the relying authority and the product approved by the reference regulatory authority should be essentially the same). All relevant aspects of drugs, medical devices and in vitro diagnostics, including those related to the quality of the product and its components, should be considered to confirm that the product is the same or sufficiently similar (e.g. same qualitative and quantitative composition, same strength, same pharmaceutical form, same intended use, same manufacturing process, same suppliers of active pharmaceutical ingredients, same quality of all excipients). Additionally, the results of supporting studies of safety, efficacy and quality, indications and conditions of use should be the same. The impact of potential, justified differences should be assessed by the manufacturer (for the purpose of this document, manufacturer also means marketing authorization holder) and the relying national regulatory authority (NRA) in determining the possibility of using foreign regulatory assessments or decisions.

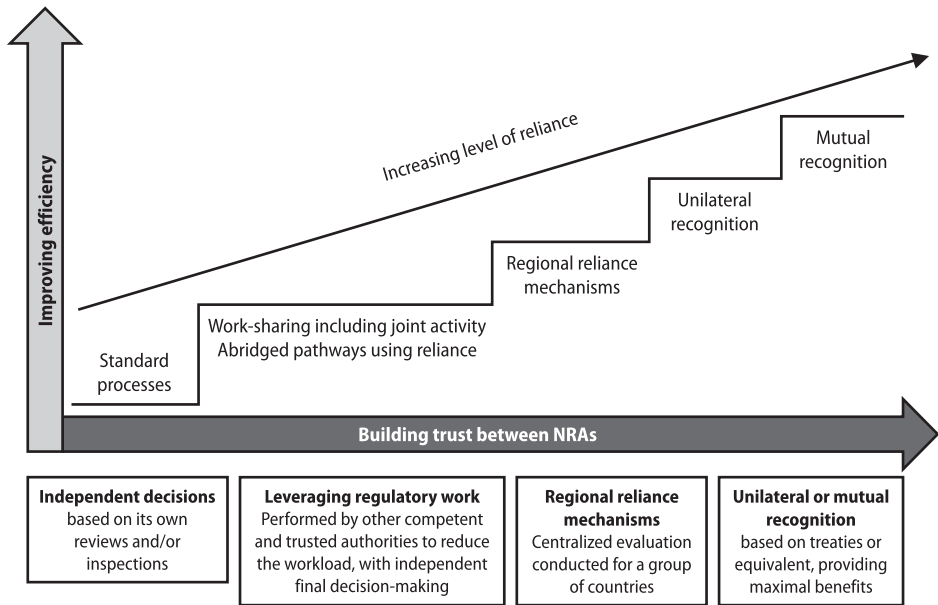
Stringent regulatory authority. A regulatory authority which is: (a) a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission, the US Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency (as before 23 October 2015); or (b) an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before 23 October 2015); or (c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015) (3).

Work-sharing. A process by which NRAs of two or more jurisdictions share activities to accomplish a specific regulatory task. The opportunities for work-sharing include joint assessment of applications for authorization of clinical trials or marketing authorizations, joint inspections for good practices, joint post marketing surveillance of the quality and safety of medical products, joint development of technical guidelines or regulatory standards and collaboration on information platforms and technology. Work-sharing also entails exchange of information consistent with the provisions of existing agreements and compliant with each agency's or institution's legislative framework for sharing such information with other NRAs. A joint activity is a form of work-sharing whereby a regulatory task is conducted by two or more NRAs in collaboration in order to share their assessments, benefit from each other's expertise and discuss any shortcomings of the data evaluated. For example, a joint assessment is a procedure in which the same application is submitted simultaneously to two or more NRAs so that they conduct their evaluations in parallel and share their scientific assessments (e.g. the different modules for quality, nonclinical and clinical data can be assigned to different NRAs for review). The NRAs participating in a joint assessment can combine their lists of questions or deficiencies to the manufacturer and base their respective independent regulatory decisions on the outcome of these assessments. Similarly, a joint inspection is one in which two or more NRAs share the activities and assessments performed during an inspection.

5. Key concepts

Fig. 1 illustrates some of the key concepts explained in the document, notably how NRAs can gain efficiency in regulatory operations and how to avoid duplication by using reliance approaches.

Fig. 1
Applied PDCA cycle



5.1 Reliance versus recognition

Reliance may take many forms and be applied to varying degrees in recognizing or taking account of the assessments, decisions or other authoritative information of other authorities and institutions. Recognition may be seen as a special and more formalized approach to reliance, whereby one regulatory authority recognizes the decisions of another regulatory authority, system or institution, obviating additional regulatory assessment to reach its own decision. Recognition usually requires formal and binding legal provisions.

5.2 Unilateral versus mutual reliance or recognition

Reliance and recognition may be unilateral, for example, when a country chooses to rely on or formally recognize an assessment from another country unilaterally and without reciprocity. In other cases, mutual recognition may be based on binding mutual agreements or treaties negotiated at the level of governments. Such agreements take considerable time and resources to set up, as the regulatory systems involved must be mutually assessed and shown to be equivalent before agreement can be reached. A demonstration of the equivalence of regulatory systems is usually a prerequisite for mutual reliance or recognition. Work-sharing and joint activities are examples of mutual reliance.

5.3 Life cycle approach

The concept of reliance for regulation of medical products should be applied throughout the life cycle of medical products and in all regulatory functions (see 3. Scope). While reliance approaches are widely used for the initial authorization of medical products, they should also be used for vigilance and other post-authorization activities (e.g. post approval changes, inspections and lot release), in view of the substantial regulatory resources required for evaluating safety and post-approval changes during a product's life cycle. Review of post approval changes to a product that was approved by a different authority may present challenges. Assuring "sameness of product" (see 4. Glossary) is essential for the use of reliance. If an NRA has relied on another NRA's assessment for its initial approval, use of similar reliance measures for post approval changes and vigilance activities is beneficial, as long as the sameness of the product from the initial authorization is maintained. This also avoids the situation in which different changes are accepted in originating and in receiving countries over time.

5.4 Risk-based approach

Each NRA should define its own strategy for an appropriate risk-based approach to reliance, which includes factors such as the type and source of products evaluated, the level of resources and expertise available in the NRA, the public health needs and priorities of the country and opportunities for reliance. Using marketing authorization as an example, four different reliance based regulatory pathways and levels of reliance could be envisaged, with increasing degrees of assessment by the relying NRA:

- verification of sameness of the medical product to ensure that it is the same as that assessed by the reference regulatory authority (see section 7.1.4 Sameness of a product in different jurisdictions). Sameness should always be verified in any of the reliance approaches listed here.
- confirmation of the applicability of the assessment outcomes of another authority for regulatory decision making in the national context, for example, in terms of legal and regulatory settings, benefit–risk assessment, co-morbidities, unmet medical needs, risk management plans and any quality-related specificities such as climatic zones for product stability. In case of differences, such as in target population, epidemiology and other features of the disease, medicines used concomitantly and other factors that can substantially affect the benefit–risk profile of a medicine, as well as quality parameters, especially in relation to the stability under different climatic conditions, appropriate evidence should be provided by the manufacturer.
- abridged assessment of data on quality, safety and efficacy or performance, taking into account information in the assessment reports of the reference regulatory authority; and

- joint assessment or work-sharing between two or more regulatory authorities. This may take various forms, including a primary review by one authority followed by a joint assessment session to finalize the report and comments or distribution of the modules (quality, non-clinical and safety or efficacy) between the authorities.

Regardless of the approach, it is expected that the timelines will be shorter than the standard timelines and resources will be used more effectively when reliance is used. The reduction in timelines will depend on the level of reliance and any additional assessment required locally. It is important that the timeline established for reliance procedures should be sufficient for the relying authority to properly review the assessment of the reference authority and perform the necessary local assessments, including of local labelling, product sameness and the applicability of the data to the country.

Similar reliance-based regulatory pathways can be used for other regulatory functions, such as inspection, lot release or import testing.

5.5 Regional reliance mechanisms

In some regions, medical products can be assessed centrally in a regional regulatory system. In some regional reliance mechanisms, the regional decision is binding on the member states (e.g. European Union). In others, regional decisions are recommendations that member states take into consideration when making national regulatory decisions (e.g. the Southern African Development Community collaborative procedure ZAZIBONA [Zambia, Zimbabwe, Botswana and Namibia; initial participants in the Southern African Development Community collaborative procedure for joint assessment of medicines], the Gulf Health Council and the Caribbean Regulatory System).

6. Principles of good reliance practices

In developing a strategy on the use of reliance in regulatory functions and activities, an NRA should consider the needs and characteristics of the national health and regulatory systems. A decision to practise reliance should consider existing capacity, regulatory systems' needs, the availability of an authority on which the NRA can rely with confidence and how reliance could complement the capacity to increase efficiency and make optimal use of resources. Reliance is not a lesser form of regulatory oversight but rather a strategy for making the best use of the available resources in any setting. This would allow the allocation of resources to other regulatory functions, such as in-country vigilance and post authorization activities, thereby increasing the effectiveness of local regulatory oversight. In addition, reliance can result in more evidence-based, better-quality decisions.

The following principles are meant to complement and extend the basic principles of GRP. They are based on the principles presented in the concept note and recommendations on regulatory reliance principles of PAHO and the Pan American Network for Drug Regulatory Harmonization (7).

6.1 Universality

Reliance applies to all NRAs, irrespective of their levels of maturity or resources. Lack of resources or capacity are not the exclusive drivers for reliance. Different NRAs use reliance for different reasons. Some use it to increase or build in-house capacity when there is the requisite expertise but not enough to perform their regulatory work as efficiently as they would like. Others use reliance to gain expertise that they do not have locally. Reliance is relevant for all resource settings.

6.2 Sovereignty of decision-making

The decision to practise reliance and how best to do so rests with the national health regulatory authority. Reliance does not imply dependence; it is not an agency outsourcing its decision-making authority or responsibility. In applying reliance in daily practice, NRAs maintain independence, sovereignty and accountability in regulatory decision-making.

6.3 Transparency

Transparency is a key enabler to adopting new, more efficient ways of conducting regulatory operations, both locally and internationally. NRAs should be transparent about the standards, processes and approaches they adopt in implementing reliance measures. The basis and rationale for relying on a specific entity should be disclosed and fully understood by all parties. NRAs should engage with all stakeholders, including industry, to ensure the appropriateness and awareness of reliance processes.

Furthermore, NRAs should conduct transparent regulatory operations and decision-making, not only as a fundamental principle of GRP but also to build trust and maximize opportunities for cooperation and reliance as part of a shared regulatory community responsibility. Transparency measures should be encouraged through the publishing and sharing of regulatory information to facilitate information exchange among NRAs. NRAs that seek to act as reference agencies are encouraged to issue public assessment reports in a common language to document their regulatory decisions. Relying NRAs should use such reports as the primary source of information for assessments. If no public assessment reports are available or when additional information of a confidential nature is required, the manufacturer should provide an assessment report when available to them. If the relying NRA requests non public assessment reports from a reference agency, they may be provided with the consent of the manufacturer, if necessary.

6.4 Respect of national and regional legal bases

Reliance practices should be coherent with national and regional legal frameworks and policies on medical products, supported by clear mandates and regulations that ensure efficient implementation of reliance as part of government policy on good regulation.

The reasons for adopting such legal frameworks should be the efficiency and capacity to be gained and not minimization of resources for regulatory functions. Use of reliance does not obviate the need for a capable local regulatory authority; on the contrary, it should be used to maintain and build local capacity for regulatory decision-making. When regulations do not make explicit provision for the application of reliance, it may be adopted through interpretation of existing regulations, if the legal framework does not explicitly preclude application of reliance approaches by the NRA. Reliance can be implemented through policy change, as long as it is broadly consistent with national legislation. If application of reliance is prohibited, revision of the legislation should be considered within a reasonable timeframe.

6.5 Consistency

Reliance on an assessment or decision from another authority should be established for specific, well-defined categories of products and processes. The scope of regulatory activities in which reliance may be practised should be clearly defined, and the practise of reliance should be transparent and predictable. Thus, reliance should be expected to be applied consistently for products and processes in the same categories.

6.6 Competence

Implementation of reliance approaches requires that NRAs have the necessary competence for critical decision-making. Introduction of the reliance approach usually requires the involvement of senior regulatory staff, managers and experts who are competent to make the best use of foreign information in the local context. NRAs should maintain the appropriate scientific expertise of their staff for activities in which they do not apply reliance, such as monitoring local adverse events, market surveillance and control, national labelling and product information activities and for oversight of locally manufactured products.

Equally, the authorities being relied upon should have and maintain competence and operate within a robust, transparent regulatory system based on international standards and guidelines, as well as GRP, and a well-functioning quality management system (11). Competence may be benchmarked through transparent processes for developing trust and building confidence in the reference authorities.

7. Considerations

A number of considerations can guide reliance approaches and facilitate their implementation. These include general aspects, barriers that NRAs may have to overcome and enablers for implementing reliance approaches. The non-exhaustive list of considerations below will be further elaborated in case studies, practice guides and the reliance repository.

Reliance is encouraged in any setting when supported by a common legal or regulatory framework in a regional regulatory system, by bilateral agreements, by mutual recognition agreements or on a purely voluntary, networking or ad-hoc basis. It is recommended that reliance be based on the original assessment. In some cases, however, it may be based on a decision made by reliance on another assessment.

7.1 General considerations

7.1.1 Reliance anchored in a national regulatory authority strategy

Application of reliance should have not only a legal basis that supports or at least does not preclude it (see section 6. Principles of good reliance practices) but should also be anchored in high-level national policy and the NRA strategy endorsed by senior management. This is necessary to provide a mandate for, direction to and expectations of NRA staff, to guide them in their daily work. The strategy should be detailed in procedures and integrated into processes to ensure the maximum benefits. It should include a sustainable funding model when implementing reliance, so that it does not negatively impact the financial sustainability and competence of the NRA. The strategy should be published in order to make it accessible and understandable to external stakeholders. Implementation of reliance should be supported by training and periodic reviews to ensure that the standards are being maintained, to assess whether the objectives are being met and to revise it when warranted.

NRAs that practise reliance should establish and publish a list of reference regulatory authorities, with the criteria used in identifying them. They should decide and establish the criteria they will use for selecting reference authorities, such as application of international standards, long standing recognition in the international community, proximity and commonality of medical products. To qualify reference regulatory authorities or specific oversight of a regulatory function, an NRA may refer to an assessment by an independent organization (e.g. WHO benchmarking, WHO-listed authority, International Organization for Standardization accreditation, the Medical Device Single Audit Program, PIC/S).

WHO encourages NRAs to monitor and evaluate the impact of regulatory reliance, including its benefits, in their country and region and to share their experiences with other regulatory authorities. When possible, the impact should be measured specifically, and the NRA should establish the metrics they will use to measure the impact of using reliance in regulatory decision-making and the time for conducting the assessment. The metrics may include costs saved, efficiency in the number of products reaching the market or time to market, and redirection of scarce resources to areas of higher regulatory risk. NRAs should consider methods for sharing best practices and experience in establishing reliance arrangements in international forums for regulation of medical products to increase understanding of the opportunities and challenges of reliance, subject to agreement with the other party(s) involved and information disclosure requirements.

7.1.2 Cultural change

Use of reliance approaches means moving to a more innovative, effective way of working, based on trust and relying on the outputs of other NRAs. The benefits must be understood and supported at operational level, and the staff who are expected to implement reliance approaches must contribute to their development. This will require engagement, willingness, effective preparation, messaging and support from management and peers on the importance of reliance in better addressing workload pressures without minimizing the rigor of regulatory work or losing scientific or regulatory competence or capacity. Use of assessments and information from other trusted regulatory authorities can help build capacity and competence (e.g. through exposure to the reviews and decisions of the reference authority, networking, twinning, staff visits and exchanges). Furthermore, as effective use of such information in the local context requires skill, ability and experience, the skill set and competence necessary to practise reliance will have to be developed in the NRA workforce.

Senior management, reviewers, inspectors and other staff should build confidence and trust in the work done by other NRAs or trusted authorities. This will take time and require a change in the culture of the relying NRA. The experience of regulatory authorities and systems that already practise reliance should be leveraged to promote acceptance and avoid pitfalls. Trust should also be built with the public, health care professionals and the industry by assuring them that reliance offers more efficient regulatory oversight.

7.1.3 Flexibility in approach: “one size doesn’t fit all”

In accordance with the principles outlined above, reliance strategies should be tailored to the needs of the national health and regulatory systems. NRAs may choose to rely on others in routine regulatory oversight and/or in special circumstances, such as a public health emergency. Reliance offers flexibility to NRAs. When adopting reliance, whatever the approach, the NRA should consider its capacity, establish clear goals and efficient processes and ensure that the standards and criteria are transparent and well established.

7.1.4 Investment of resources and time in implementing reliance

As stated above, reliance should increase the efficiency of a regulatory system in a country or region. Nevertheless, implementation of reliance approaches will first require investment of resources and time for activities such as legislative changes, preparation of guidance documents and approaches, pathways and processes, building confidence by preparing parallel or joint reviews supported by staff exchanges, training staff, dialogue with industry and other stakeholders and establishment of or access to information-sharing platforms, communication links and networks with other NRAs.

7.1.5 “Sameness” of a product in different jurisdictions

A critical aspect of the application of reliance is verification of the “sameness” of a medical product (see 4. Glossary and section 5.4 Risk-based approach) in different jurisdictions. Reliance can be practised only if the NRA that intends to use a foreign assessment as the basis for its own assessment and regulatory decision making has the assurance that the medical product being assessed is essentially the same as the one submitted to the reference NRA. The role of the manufacturer is essential to confirm the sameness of a product and to provide the same documentation to different NRAs, except for additional country-specific information submitted for review, such as product stability data according to the stability zone and the local product label. The manufacturer should confirm in the application that the product is the same and that the application contains essentially the same information, taking into consideration any potential national requirements. If the application is not submitted simultaneously to the agencies, the manufacturer should highlight any new information about the product acquired since the application was submitted to the reference agency, with the corresponding assessment.

7.1.6 The role of industry

Industry plays a crucial role in successful use of reliance mechanisms by NRAs. While industry widely supports reliance as a concept and practice that can increase efficiency, it must have clear guidance on its application and see meaningful benefits. Industry support and stringent adherence to the factors that validate the reliance process are essential for filing applications in several countries or regions to ensure the sameness of products submitted to reference regulatory authorities and relying NRAs. They should share complete, unredacted information.

Review and discussion of pilot programs to quickly adapt and improve guidance will be key to benefit from key learnings and improve implementation. Collaboration and dialogue among all stakeholders participating in regulatory reliance activities will help to create and build trust, which is the foundation of regulatory reliance. Transparent publication of an NRA's reliance framework and strategies, including the metrics used and benefits achieved, will encourage industry to support and promote the reliance approach.

7.1.7 Reliance in a public health emergency

In case of a public health emergency, reliance approaches are even more essential and should be given more importance in order to accelerate access to the medical products required.

7.2 Potential barriers

7.2.1 Lack of political will

Lack of political will and government support can make it difficult for NRAs to implement or facilitate reliance in their daily practice, even if a legal basis is established that supports (or does not preclude) reliance and if NRAs support reliance as a strategy and approach.

7.2.2 Lack of accessible information and confidentiality of information

Lack of access to complete assessments of reference regulatory authorities can be a major barrier to effective reliance. Reference regulatory authorities should make their assessments and other regulatory information publicly available. Non-public regulatory reports might be available directly from the manufacturer when the company is able to access these reports from the reference regulatory authority. If this is not possible, the relying NRA should approach the reference regulatory authority. In these cases, arrangements among NRAs on the exchange of confidential information would facilitate the reliance process.

Sensitive, non-public information in unredacted assessment or inspection reports can also be shared between regulatory authorities upon request. This may include confidential commercial information, trade secrets or personal information. In some circumstances, the sharing of such information may require the consent of the manufacturer. Sharing of personal information may also require consent from individuals in order to comply with data protection regulations. Given the sensitivity of such non-public information, NRAs may require that confidentiality agreements be signed that govern the exchange, management and disclosure of such information to ensure that the confidentiality of the information is protected by the relying NRA. Such information should always be exchanged through secure channels or on information-sharing platforms.

7.2.3 Other barriers

Additional potential barriers include issues such as lack of a common language, difficulties in or the cost of translation, differences in national regulatory requirements and evidentiary standards, lack of regulatory alignment of product risk classifications, inconsistent practices regarding modifications to medical devices (including in-vitro diagnostics), the lack of acceptance of foreign clinical data and real world evidence, the level of detail in regulatory reports, different levels of competence and, as previously noted, internal resistance and insufficient knowledge of the reference regulatory authority and how it operates. All such factors should be considered in developing appropriate reliance strategies, as will be further elucidated in the additional guidance documents to follow.

7.3 Enablers

7.3.1 Trust

Trust is a critical element, as reliance requires confidence that the regulatory outcome is based on strong regulatory processes and standards and is, thus, trustworthy. Consequently, initiatives to foster trust among regulatory authorities are essential. Trust develops with increasing familiarity and understanding of what is behind regulatory outputs. Confidence can be built throughout the organization by sharing information, including the standards applied to regulatory decisions, working together and learning each other's ways of working, which then leads to effective use of reliance in regulatory work. Trust can be built in phases, starting with exchange of assessment reports and moving to work-sharing or joint assessments. Regulatory authorities may consider initiating reliance processes with applications for medical products of lower risk.

In addition, industry and other stakeholders must trust regulatory authorities, for example, to respect the confidentiality of information.

7.3.2 Convergence and harmonization

Convergence and harmonization of requirements, standards and guidelines are important enablers of regulatory cooperation and reliance. The more similar requirements, standards and guidelines are, the greater the opportunity for collaboration and reliance. Use of the ICH Common Technical Document (CTD) and the electronic CTD (eCTD) as a common format for regulatory submissions around the globe is one example of how harmonization can facilitate and enable reliance.

Differences in standards and practices, however, do not prevent one authority from relying on another, particularly when the relying authority has limited capacity and expertise. The system on which an NRA relies should be at least equivalent to or superior to the standards it applies. As a matter of good practice, NRAs should rely on assessments or decisions from reference regulatory authorities that apply international standards and guidelines.

7.3.3 Information-sharing and dialogue among regulators

Information-sharing is an essential part of reliance, and NRAs are encouraged to share information and good practices with other NRAs. Increasing dialogue among regulators is seen in the growing number of international initiatives such as the International Pharmaceutical Regulators Programme and in networks for sharing regulatory information and work such as the Pan American Network for Drug Regulatory Harmonization, the Southeast Asia Regulatory Network, regulatory networks in the Regional Economic Communities under the African Medicines Regulatory Harmonisation (AMRH) Initiative and the Association of Southeast Asian Nations (ASEAN) Pharmaceutical Products Working Group, the International Coalition of Medicines Regulatory Authorities, the Caribbean Community and Common Market's

(CARICOM) Caribbean Regulatory System, the Western Pacific Region Alliance of NRAs for Medical Products and others, which greatly facilitate reliance.

Scientific and technical events, such as the International Conference of Drug Regulatory Authorities, ICH and PIC/S, are platforms for disseminating regulatory information and for building knowledge and trust among NRAs.

7.3.4 Economic or legal integration

When there is economic or legal integration in a region or a group of countries, reliance is facilitated and strengthened by the existing mutual provisions. Examples are the Asia–Pacific Economic Cooperation (APEC), ASEAN, CARICOM, the European Union, the Eurasian Economic Union, the Gulf Cooperation Council, the Pacific Alliance, the Regional Economic Communities in Africa and the Southern Common Market (MERCOSUR).

7.3.5 Engagement of stakeholders

All relevant stakeholders, including industry, health care professionals, policy-makers and the public, should be engaged and informed in order to increase their understanding and acceptance of reliance approaches and the clear benefits they present for all parties. Communication and engagement with stakeholders should be tailored to each target audience.

8. Conclusions

Reliance is being practised by a growing number of regulatory authorities as a means of improving the effectiveness and efficiency of regulation of medical products. It allows NRAs to make the best use of resources, build expertise and capacity, increase the quality of their regulatory decisions, reduce duplication of effort and, ultimately, promote timely access to safe, effective and quality assured medical products. Adoption of reliance measures whenever possible, in a well structured framework underpinned by national or regional policies and strategies, will allow regulators to focus their resources on activities that contribute to public health that cannot be undertaken by others.

Reliance represents a “smarter” form of regulatory oversight, based on constructive regional and international collaboration, that will facilitate and promote convergence and the use of common international standards and guidelines, resulting in more predictable, faster approval to improve access to quality-assured medical products for patients worldwide.

Reliance does not represent a less stringent form of regulatory oversight or outsourcing of regulatory mandates, nor does it compromise independence. On the contrary, a decision to “regulate through reliance” is the hallmark of a modern and efficient regulatory authority.

NRAs are encouraged to include reliance-related provisions as part of their flexible regulatory pathways, and reliance should be considered in all regulatory functions of the life cycle of a medical product, as appropriate.

The principles and considerations presented in this document should be considered in implementing regulatory reliance frameworks or strategies. Effective implementation of reliance will benefit not only NRAs but also patients, health care providers and industry.

While reliance may be viewed as particularly useful for low-resourced regulatory authorities, it is equally relevant for well-resourced NRAs. Reliance is an approach to be used by all NRAs and should therefore become an integral part of regulatory operations.

References

1. Good regulatory practices: guidelines for national regulatory authorities for medical products. Draft working document. Geneva: World Health Organization; 2016.
2. Definition of a mutual recognition agreement. Paris: Organization for Economic Co-operation and Development; 2020.
3. Definition of stringent regulatory authority. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report (WHO Technical Report Series, No. 1003). Geneva: World Health Organization; 2017:34–5 (<https://iris.who.int/bitstream/handle/10665/258720/9789241210034-eng.pdf?sequence=1&isAllowed=y>, accessed 29 January 2021).
4. Policy evaluating and publicly designating regulatory authorities as WHO-listed authorities. Draft working document. Geneva: World Health Organization; 2019.
5. WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems. Geneva: World Health Organization; 2020 (<https://iris.who.int/bitstream/handle/10665/341243/9789240020245-eng.pdf?sequence=1>, accessed 29 January 2021).
6. A framework for evaluating and publicly designating regulatory authorities as WHO-listed authority, Interim list of national regulatory authorities. Geneva: World Health Organization; 2020 (<https://www.who.int/initiatives/who-listed-authority-reg-authorities>, accessed 29 January 2021).
7. Pan American Health Organization, Pan American Network for Drug Regulatory Harmonization. Regulatory reliance principles: concept note and recommendations. Ninth Conference of the Pan American Network for Drug Regulatory Harmonization (PANDRH) (San Salvador, 24 to 26 October, 2018. Washington DC: Pan American Health Organization; 2019 (<https://iris.paho.org/handle/10665.2/51549>, accessed 29 January 2021).
8. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. Geneva: World Health Organization; 2020 (<https://iris.who.int/bitstream/handle/10665/340323/9789240020900-eng.pdf?sequence=1>, accessed 29 January 2021).
9. History of PIC/S. Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme; 2020 (<https://picscheme.org/en/history>, accessed 29 January 2021).
10. Outcome of WHO survey on reliance. International Pharmaceutical Regulators Programme; 2019 (<http://www.iprp.global/news/outcome-who-survey-reliance>, accessed 29 January 2021).

11. WHO guideline on the implementation of quality management systems for national regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report (WHO Technical Report Series, No. 1025). Geneva: World Health Organization; 2020: Annex 13:273–327 (<https://iris.who.int/bitstream/handle/10665/331814/9789240001824-eng.pdf?sequence=1&isAllowed=y>, accessed 29 January 2021).

Appendix 1

Examples of use of reliance

Regulatory reliance can take many forms and encompasses a wide range of regulatory approaches and practices that involve two or more regulatory authorities. It may be limited to a discrete regulatory process or function or comprise the full scope of regulatory functions throughout the life cycle of a medical product. Many examples around the world illustrate current use of reliance and the diverse ways in which NRAs leverage the work of others. The examples below illustrate the points raised in the GRelP, to show use of reliance in different regulatory functions. The list is not exhaustive but an illustration of current global practices in reliance. It may be replaced in the future by a comprehensive repository of reliance approaches to be established as a part of a toolbox of GRelP.

A1. Clinical trials

Work-sharing in the assessment of clinical trials is being used in some regions, such as the Voluntary Harmonisation Procedure in the European Union (1) and the African Vaccine Regulatory Forum (AVAREF) (2). By assessing clinical trial applications together, NRAs and, in some cases, ethics committees in different countries can benefit from the assessments performed by the different participating countries with a view to facilitating and ensuring the robustness of the clinical trials application assessment process across countries. The AVAREF platform has been instrumental in building the expertise and capacity of regulators and ethics committees, promoting the use of international standards and expediting clinical trial assessments and decisions for medical products of high public health interest in both emergency and other circumstances. A guideline and a platform for joint assessment of applications for clinical trials as well as guidelines for site inspections for good clinical practices have been set up to facilitate product development, regulatory decision-making and access to promising new medical products (3).

A2. Marketing authorization

A2.1 Abridged regulatory pathways with reliance for initial marketing authorization

Several procedures are available through regulatory authorities or the WHO prequalification programme for use of an abridged regulatory pathway by a relying NRA. The European Union Article 58 (also referred to as European Union Medicines for all) (4), the Swissmedic Marketing Authorisation for Global Health Products (5) procedures and the WHO collaborative procedure (CRP) for accelerated registration (CRP) (6) are

three examples of abridged regulatory pathways in which reliance is used to facilitate the registration of medical products.

The European Union Article 58 and the Swissmedic Marketing Authorisation for Global Health Products not only facilitate national registration but also provide an opportunity for experts from NRAs to both observe and participate in assessment and scientific advice procedures, thus building their capacity and establishing confidence in the processes.

The CRP facilitates the assessment and accelerates national registration of WHO-prequalified medical products and medicines approved by a stringent regulatory authority. The CRP provides unredacted reports on the assessment, inspection and performance evaluation (in the case of in-vitro diagnostics) upon request (and with the consent of the manufacturer) to participating NRAs, primarily in low- and middle-income countries. The procedures are detailed in WHO guidelines, which also include guidance on how NRAs can make the most efficient use of the reports in reaching their own decisions, as participating NRAs are expected to reach a decision on marketing authorization within 90 calendar days (regulatory time). The CRP has been successful in both accelerating decisions in countries and building the capacity of regulatory authorities.

The WHO certificate of a pharmaceutical product (CPP) is also used as a reliance tool, in lieu of full or partial assessment for marketing authorization (7). NRAs are encouraged to consider use of electronic CPP. These certificates are being used in lieu of a full or partial review, accelerating assessment in many countries such as Benin, Bolivia, Cameroon, Congo, Cuba, Curaçao (Kingdom of the Netherlands), Guinea, Haiti, Honduras and China, Hong Kong SAR.

A2.2 Quality information

Many NRAs, and the WHO Prequalification programme, recognize certificates of suitability for monographs in *The European Pharmacopoeia* (8) for active pharmaceutical ingredients (APIs) as validation of the quality of a certain API. Some countries also recognize confirmation of API prequalification by the WHO Prequalification programme for APIs (9). These two examples provide assured mechanisms of reliance and also reduce the documentation requirements for countries that rely upon or recognize those certificates. When a certificate of suitability for the monographs of *The European Pharmacopoeia* or confirmation of prequalification of an API is issued, the receiving NRA need not duplicate the API assessment but can focus on sections not covered by either document.

A2.3 Work-sharing

The Australia–Canada–Singapore–Switzerland United Kingdom ACCESS Consortium (10) was formed in 2007 by “like-minded” medium-sized regulatory authorities to promote work sharing for greater regulatory collaboration and alignment of regulatory

requirements. The ACCESS Consortium explores opportunities to share information and work in areas such as biosimilar products, complementary medicines, generic medicines, new prescription medicines, medical devices and information technology. The Consortium capitalizes on each country's strengths, addresses gaps in science, knowledge and expertise and leverages resources to expedite risk assessment, while maintaining or raising quality and safety standards. The Consortium builds on international networks, initiatives and mechanisms to advance work- and information-sharing throughout the life cycles of health products.

A2.4 Joint assessments

Joint assessments can be beneficial to NRAs by spreading the workload, building capacity through broader experience and expertise and helping to build trust in each other's assessments and decision making processes. Similarly, industry can benefit from a common review and a single set of questions, saving both resource and time as compared with separate interactions. In view of these benefits, several joint assessment initiatives have been introduced into regional regulatory networks, sometimes driven by the higher-level priorities of economic blocs seeking to create common markets. Examples of joint assessment initiatives include those in the Regional Economic Communities in Africa (East African Community (11)), ZAZIBONA (12) in the Southern African Development Community, the Economic Community of West African States/West African Health Organization (13)) and the ASEAN Joint Assessment Coordinating Group (14).

A2.5 Unilateral recognition

The Mexican Federal Commission for Protection against Sanitary Risk unilaterally recognizes marketing authorizations from certain reference regulatory authorities (15).

A2.6 Mutual recognition

The European Union is an example of highly integrated regulatory cooperation, and its many regulatory pathways depend heavily on work-sharing, recognition and other forms of reliance. The approval of medicines is based on a single assessment system, so that an assessment report from any agency in the European Union network can be used as a basis for reliance by other regulators. In this case, a strong, common legal framework and harmonized regulatory standards shared by all European Union countries has enabled and facilitated reliance and recognition (16).

A3. Post-approval changes

In accordance with the same principles as for initial marketing authorization, reliance can also be applied broadly in assessing post-approval changes already approved by NRAs considered to be reference authorities. In the case of CRP, for example, WHO

informs the participating NRAs about any variations in prequalified products approved by the WHO Prequalification team (6).

The Health Sciences Authority in Singapore applies a verification route with shortened times for approving post-approval changes to quality and product labels, to increase leverage of reference agencies' assessments, minimize duplication of effort and increase efficiency as part of work that includes effective life cycle management of registered therapeutic medicinal products. To qualify, the proposed changes must be identical to those approved by one of the Authority's five reference agencies, with proof of the approval and the approved product label of that reference agency (17).

A4. Testing and lot release

A4.1 Network of Official Medicines Control Laboratories

The network of official medicines control laboratories supports regulatory authorities in controlling the quality of medicinal products on the market. Collaboration within the General European Official Medicines Control Laboratories Network (GEON) (18) makes the best use of resources by pooling resources and avoids duplication of work and testing. Some of the main goals of the GEON are to ensure mutual recognition among its members of tests conducted by national official medicines control laboratories, coordinate activities among official medicines control laboratories and facilitate sharing of knowledge and work.

A4.2 Lot release and quality monitoring of vaccines and other biological products

Launched in 2017, the WHO National Control Laboratory Network for Biologicals (WHO-NNB) (19) brings together national control laboratories and NRAs of vaccine-producing and vaccine recipient countries, WHO contract laboratories, manufacturers' associations, WHO regional offices and other stakeholders, including donors. WHO-NNB ensures effective use of global resources by providing a platform and infrastructure for collaboration and exchange of information on quality and technical aspects. Its main objective is to facilitate access to and the availability of prequalified vaccines (and other biotherapeutic products) through reliance on batch releases by NRAs and national control laboratories that are members of WHO-NNB, thereby reducing redundant testing and encouraging more cost-effective testing and more effective regulatory oversight.

A5. Pharmacovigilance

Exchanges and sharing of data are critical in pharmacovigilance. More than 100 Member States share data on the safety of medical products in the WHO database of individual case reports of safety, VigiBase, developed and maintained by the Uppsala Monitoring Centre (20). Member States use this database (and thereby each other's data)

as a single source of pharmacovigilance information to confirm and validate any signals of adverse events associated with medicines and vaccines that they have observed. In Regulation EU No 1235/2010 (21), the European Union introduced the concept of a supervisory authority for pharmacovigilance, to be responsible for verifying on behalf of the Union that the marketing authorization holder for a medicinal product satisfies the pharmacovigilance requirements as per European Union legislation.

Countries in the Region of the Americas have been preparing joint assessments of periodic safety updates and risk management plans. Coordinated by Health Canada, pairs of countries have completed evaluation reports for several products. The reports are made available on a regional platform with access restricted to the pharmacovigilance focal points of the NRAs.

A6. Inspections

Governments and NRAs in various regions have made mutual recognition agreements so that they can rely on each other's inspections, avoiding duplication of work and making the best use of resources. These include agreements between the European Union (22) and Australia, Canada, Japan, Switzerland and the United States and ASEAN mutual recognition agreements (23).

PIC/S is a non-binding, informal cooperative arrangement among regulatory authorities in the field of good manufacturing and good distribution practices of medicinal products for human or veterinary use and, more recently, also in good clinical and good vigilance practices (24). Its aim is to facilitate cooperation and networking among competent authorities and regional and international organizations, thus increasing mutual confidence in inspections. PIC/S has issued guidance on inspection reliance, outlining a process for desk-top assessment of compliance with good manufacturing practices (25). Reliance is an important aspect of desktop assessments of compliance with relevant good practice guidelines and requirements, as described in WHO guidance (26).

The OECD operates a system for mutual acceptance of data in the assessment of chemicals (including pharmaceuticals), in which data generated in any member country in accordance with OECD test guidelines and the principles of good laboratory practice are accepted by any other member country for assessing products for the protection of human health and the environment (27).

A7. Examples of medical devices

Reliance is prevalent in the regulation of medical devices, including in-vitro diagnostics. For example, the Medical Device Single Audit Program (28) was developed under the auspices of the International Medical Device Regulators Forum (IMDRF). Under this Program, the regulatory authorities of Australia, Brazil, Canada, Japan and the United States have pooled their resources into a robust system of oversight by third party

auditing organizations, which, in turn, audit the quality management systems of medical device manufacturers. The Program permits an auditing organization to conduct a single regulatory audit that satisfies the requirements of the regulatory authorities that participate in the Program. The pooled resources are used to establish and maintain oversight of auditing organizations, resulting in more effective use of limited regulatory resources. A single audit programme allows regulatory authorities to leverage resources efficiently and to streamline the regulatory process without compromising public health and to promote better aligned, more consistent regulatory requirements.

The IMDRF has also issued guidance for exchanges of information on the safety of medical devices among participating NRAs (29). The system reports incidents that represent a serious threat public health beyond national borders. The IMDRF provides consistent terminology for reporting and coding adverse events for categorized reporting (30).

These activities are just two examples of the work of IMDRF in harmonization, convergence and reliance in the area of medical devices. Other examples are optimizing standards for regulatory use (31), essential principles of the safety and performance of medical devices (32) and requirements for the competence, training and conduct of regulatory reviewers (33).

In Singapore, medical devices and in vitro diagnostics that have been authorized through specific pathways in Australia, Canada, Europe, Japan or the United States are eligible for abridged evaluation. To qualify, the proposed intended use must be identical to that approved in the reference country. Typically the documentation includes proof of approval from the reference regulatory authority and summary technical documents to satisfy requirements for supporting documentation (34). Additionally, Australia recognizes registrations and certifications from notified bodies designated by the medical device regulators of Health Canada, European member states, the Pharmaceuticals and Medical Devices Agency of Japan, the US Food and Drug Administration and organizations participating in the Medical Device Single Audit Program (35).

A8. Examples of public health emergencies

WHO developed the “emergency use assessment and listing” mechanism as a risk-based procedure for assessing and listing unlicensed vaccines, therapeutics and in-vitro diagnostics for use primarily during public health emergencies of international concern but also in other public health emergencies when appropriate.

PAHO has developed guidance for NRAs and regulatory systems on practical ways of implementing reliance for emergency use of medicines and other health technologies in a pandemic (36).

References to Appendix 1

1. Clinical trials facilitation groups. Guidance document for sponsors for a voluntary harmonisation procedure (VHP) for the assessment of multinational clinical trial applications. Heads of Medicines Agencies; 2016 (https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2016_06_CTFG_VHP_guidance_for_sponsor_v4.pdf, accessed 29 January 2021).
2. The African Vaccine Regulatory Forum. Brazzaville: World Health Organization Regional Office for Africa; 2020 (<https://www.afro.who.int/health-topics/immunization/avaref>, accessed 29 January 2021).
3. GCP inspection guide. Joint review guideline. In: AVAREF tools. Brazzaville: World Health Organization Regional Office for Africa; 2020 (<https://www.afro.who.int/publications/avaref-tools>, accessed 29 January 2021).
4. Human regulatory. Marketing authorisation. Medicines for use outside the European Union. European Medicines Agency. Amsterdam. European Medicines Agency; 2019 (<https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/medicines-use-outside-european-union>, accessed 29 January 2021).
5. The Swissmedic Marketing Authorisation for Global Health Product (MAGHP) Procedure. Bern: Swissmedic; 2017 (<https://www.swissmedic.ch/swissmedic/en/home/about-us/development-cooperation/marketing-authorisation-for-global-health-products.html>, accessed 29 January 2021).
6. Collaborative procedure for accelerated registration. Geneva: World Health Organization, Prequalification of Medical Products; 2020 (<https://extranet.who.int/prequal/vitro-diagnostics/collaborative-procedure-accelerated-registration>, accessed 29 January 2021).
7. Model certificate of a pharmaceutical product. Geneva: World Health Organization; 2020.
8. Background & legal framework. Certificate of suitability to the monographs of the European Pharmacopoeia. Strasbourg: Council of Europe, European Directorate for the Quality of Medicines & Healthcare; 2020 (<https://www.edqm.eu/en/certification-background-77.html>, accessed 29 January 2021).
9. Active pharmaceutical ingredients. Geneva: World Health Organization; 2020 (<https://extranet.who.int/pqweb/medicines/active-pharmaceutical-ingredients>, accessed 29 January 2021).
10. The ACCESS Consortium. Australian Government. Department of Health. Therapeutic Goods Administration (<https://www.tga.gov.au/international-activities/australia-canada-singapore-switzerland-united-kingdom-access-consortium>); Government of Canada (<https://www.canada.ca/en/health-canada/services/drugs-health-products/international-activities/australia-canada-singapore-switzerland-consortium.html>); Health Sciences Authority (<https://www.hsa.gov.sg/international-collaboration/therapeutic-products/acsc>); Swissmedic: <https://www.swissmedic.ch/swissmedic/en/home/about-us/international-collaboration/multilateral-co-operation-with-international-organisations---ini.html>; MHRA: <https://www.gov.uk/government/news/uk-medicines-regulator-joins-up-with-australia-canada-singapore-and-switzerland-regulators>; all accessed 29 January 2021.
11. Medicines and Food Safety Unit. Arusha: East African Community; 2020 (<https://www.eac.int/health/71-sector/health/191-219-23-medicines-and-food-safety-unit>, accessed 29 January 2021).
12. Alternative/Expedited process to register medicines via the ZAZIBONA collaborative process. Gaborone: Southern African Development Community; 2015 (http://www.rffa.co.za/wp-content/uploads/2015/10/ZaZiBoNa-Registration-Pathway_v01_09062015.pdf, accessed 29 January 2021).

13. Regional joint assessment procedure for medicine registration and marketing authorization of medical products. Bobo Dioulasso: West African Health Organization; 2019.
14. ASEAN cooperation on standards and conformance to facilitate trade in the region. Jakarta: Association of Southeast Asian Nations; 2020 (<https://asean.org/asean-economic-community/sectoral-bodies-under-the-purview-of-aem/standards-and-conformance/>, accessed 29 January 2021).
15. Patel P, McAuslane N, Liberti L. R&D briefing 71: Trends in the regulatory landscape for the approval of new medicines in Latin America. London: Centre for Innovation in Regulatory Science; 2019 (<http://docplayer.net/146295622-Trends-in-the-regulatory-landscape-for-the-approval-of-new-medicines-in-latin-america.html>, accessed 29 January 2021).
16. Medicinal products. EudraLex – EU legislation. EudraBook V1 – May 2015 / EudraLex V30 – January 2015. Brussels: European Commission; 2020 (https://ec.europa.eu/health/documents/eudralex/cd/index_en.htm, accessed 29 January 2021).
17. Therapeutic products guidance. Guidance on therapeutic product registration in Singapore (TPB-GN-005-005). Chapter H. Minor variation (MIV) application submission. Singapore: Health Sciences Authority; 2019 (https://www.hsa.gov.sg/docs/default-source/hprg/therapeutic-products/guidance-documents/guidance-on-therapeutic-product-registration-in-singapore_jan2019.pdf, accessed 29 January 2021).
18. General European OMCL Network (GEON). Strasbourg: Council of Europe, European Directorate for the Quality of Medicines & Healthcare; 2020 (<https://www.edqm.eu/en/general-european-omcl-network-geon>, accessed 29 January 2021).
19. WHO-National Control Laboratory Network for Biologicals (WHO-NNB). Geneva: World Health Organization; 2016 (<https://www.who.int/teams/regulation-prequalification/regulation-and-safety/laboratory-networks-and-services/regulatory-harmonization/who-nnb>, accessed 29 January 2021).
20. VigiBase. Uppsala: Uppsala Monitoring Centre; 2020 (<https://www.who-umc.org/vigibase/vigibase/>, accessed 29 January 2021).
21. Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products. Off J Eur Union. 2010;L348/1 (<https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF>, accessed 29 January 2021).
22. Mutual recognition agreements (MRA). Amsterdam: European Medicines Agency; 2020 (<https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/mutual-recognition-agreements-mra>, accessed 29 January 2021).
23. ASEAN mutual recognition arrangements. Jakarta: Association of Southeast Asian Nations (<https://asean.org/asean-framework-agreement-on-mutual-recognition-arrangements/>, accessed 29 January 2021).
24. Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (<https://picscheme.org/en/picscheme>, accessed 29 January 2021).
25. Guidance on GMP Inspection Reliance. PIC/S; 2018 (<https://picscheme.org/docview/2475>, accessed 29 January 2021).

26. Guidance on good practices for desk assessment for compliance with good manufacturing practices, good laboratory practices and good clinical practices for marketing authorization of medical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report (WHO Technical Report Series, No. 1010). Geneva: World Health Organization; 2018: Annex 9 (<https://www.who.int/docs/default-source/medicines/norms-and-standards/current-projects/trs1010-annex9--desk-assessment.pdf>, accessed 29 January 2021).
27. Mutual acceptance of data (MAD). Paris: Organisation for Economic Co-operation and Development; 2020 (<https://www.oecd.org/chemicalsafety/testing/mutualacceptanceofdatamad.htm>, accessed 29 January 2021).
28. Medical devicesingleauditprogram (MDSAP). SilverSpring (MD): FoodandDrugAdministration; 2020 (<https://www.fda.gov/medical-devices/cdrh-international-programs/medical-device-single-audit-program-mdsap>, accessed 29 January 2021).
29. Medical devices: post-market surveillance: national competent authority report exchange criteria and report form. Singapore: International Medical Device Regulators Forum; 2017 (<http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-170921-pms-ncar-n14-r2.pdf>, accessed 29 January 2021).
30. IMDRF Adverse Event Terminologies Working Group. IMDRF terminologies for categorized adverse event reporting (AER): terms, terminology structure and codes. Singapore: International Medical Device Regulators Forum; 2020 (<http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-200318-ae-terminologies-n43.pdf>, accessed 29 January 2021).
31. IMDRF Standards Working Group. Optimizing standards for regulatory use. Singapore: International Medical Device Regulators Forum; 2018 (<http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-181105-optimizing-standards-n51.pdf>, accessed 29 January 2021).
32. IMDRF Good Regulatory Review Practices Group. Essential principles of safety and performance of medical devices and IVD medical devices. Singapore: International Medical Device Regulators Forum; 2018 (<http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-181031-grrp-essential-principles-n47.pdf>, accessed 29 January 2021).
33. IMDRF Good Regulatory Review Practices Group. Competence, training, and conduct requirements for regulatory reviewers. Singapore: International Medical Device Regulators Forum; 2017 (<http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-170316-competence-conduct-reviewers.pdf>, accessed 29 January 2021).
34. Overseas reference regulatory agencies. Registration overview of medical devices. Singapore: Health Sciences Authority; 2019 (<https://www.hsa.gov.sg/medical-devices/registration/overview#toggle=togglepanel-overseas-reference-regulatory-agencies>, accessed 29 January 2021).
35. Comparable overseas regulators for medical device applications. Canberra: Therapeutic Goods Administration, Department of Health; 2019 (<https://www.tga.gov.au/comparable-overseas-regulators-medical-device-applications>, accessed 29 January 2021).
36. Reliance for emergency use authorization of medicines and other health technologies in a pandemic (e.g. COVID-19). Washington DC: Pan American Health Organization; 2020 (<https://iris.paho.org/handle/10665.2/52027>, accessed 29 January 2021).

7.2 Good practices of national regulatory authorities in implementing the collaborative registration procedures for medical products

Annex 6, WHO Technical Report Series, 1019, 2019

1. Background	936
2. Aims and objectives	937
3. Scope	938
4. Glossary	938
5. Key principles	940
6. Essential elements of a registration system (in the context of collaborative registration procedures)	942
References	956
Appendix 1 An example of information to applicants for registration via the WHO collaborative registration procedure	958
Appendix 2 Verification for product submitted under the WHO collaborative procedure	960
Appendix 3 Abridged/abbreviated review for product submitted under the WHO collaborative procedure	964
Appendix 4 Additional information to be included in the screening checklist	980
Appendix 5 Example of a national regulatory authority reliance model approach: information, documentary evidence and assessment activity	982
Appendix 6 Model acknowledgement or approval letter for variations of products registered through the WHO collaborative procedure	984

1. Background

In 2014, the 67th World Health Assembly resolution, WHA67.20, recognized that

effective regulatory systems are an essential component of health system strengthening and contribute to better public health outcomes, that regulators are an essential part of the health workforce, and that inefficient regulatory systems themselves can be a barrier to access to safe, effective and quality medical products (1).

Nonetheless, regulators, globally, and in particular low- and middle-income countries, face an increasingly complex regulatory environment, with limited resources and a need to avoid duplication by communicating, collaborating, cooperating and forming coalitions to ensure product quality, safety and efficacy, as well as supply-chain security.

To this end, collaborative registration procedures (CRPs) with a view to accelerating national registrations and the regulatory life-cycle of products prequalified by the World Health Organization (WHO), or approved by reference stringent regulatory authorities (SRAs), have been developed and implemented (2, 3). Based upon WHO's experience with the collaborative procedure for WHO prequalified pharmaceutical products and vaccines (2), and the pilot collaborative procedure of products approved by SRAs (3), it is possible to facilitate and accelerate national registration processes using this approach in the management of registrations and post-registration regulatory product life-cycle, based on reliance on the expertise and regulatory outcomes of recognized reference authorities.

Available assessment and inspection reports of reference SRAs or the WHO Prequalification Team (PQT), in addition to the registration dossiers, can facilitate and accelerate the adoption of national regulatory decisions by assuring national regulatory authorities (NRAs) of the positive benefit–risk of a product and its identical quality with the product already approved elsewhere, while allowing them to reflect their own judgement on the benefit–risk balance as it relates to their specific country situation and the legislation in place. This contributes substantially to savings in regulatory resources, improvements in the quality of regulatory decisions and faster availability of needed therapies for patients.

Nevertheless, it has been evident from experiences with the CRPs for products prequalified by WHO and pilot SRA collaborative registration, that it is critical to have clear NRA procedures to support acceleration of the availability of medical products, without compromising their quality, safety and efficacy, as well as providing an opportunity to harmonize dossier requirements and submission expectations.

Additionally, WHO has been facilitating regional collaborative procedures in the context of medicines regulatory harmonization in various regions. The regional mechanisms mobilize the existing regional resources to accelerate access to medical products through work-sharing and joint activities. These regional collaborative

registrations have been established and supported in collaboration with their partners, in the East African Community, the Southern African Development Community, the Economic Community of West African States, the Caribbean Community and Common Market and the Association of Southeast Asian Nations. Similar initiatives are being developed for other regional economic communities and CRP can serve as an instrument to facilitate regional work-sharing.

2. Aims and objectives

This guideline is intended to serve as the NRAs' best practices model for implementing CRP and reliance and/or risk-based approaches in their overall marketing authorization system for medical products, and it should be read in conjunction with the full text of the collaborative procedures (2, 3). The document also outlines the recommended approaches a NRA should take to process different types of applications, based on prior decisions and documentary evidence from the PQT, reference authorities and regional collaborative procedures.

The objectives of the document are to:

- describe the practical steps for NRAs to implement the collaborative procedure for prequalified products, SRA-approved products, or products from other reference authorities and regional harmonization;
- provide a resource for NRAs to effectively and efficiently implement collaborative reliance-based procedures for medical products, including vaccines.

This guideline is complementary to and consistent with the principles already elaborated in the draft guideline *Good regulatory practice: guidance for national regulatory authorities for medical products* (4). Furthermore, it supplements the guidance and best practices guidelines for marketing authorizations, which include *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for national medicines regulatory authorities* ("The Blue Book") (5), *Good review practices: guidelines for national and regional regulatory authorities* (6), and the *Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions* (7). These guidelines and best practices promote interagency communications, in order to facilitate greater regulatory convergence, thus increasing regulatory efficiency and quality of decisions, and improving patient access.

It should be remembered that WHO focal persons (as specified on the WHO website (8)) can be approached at any time, to provide additional explanations and assistance in the implementation of and practice of the collaborative procedure (Procedure) or other reliance approaches.

3. Scope

This guideline is focused mainly on the collaborative procedure for WHO-prequalified pharmaceutical products and vaccines and the collaborative procedure for pharmaceutical products and vaccines approved by SRAs. In addition, the principles, practical steps and tools described in this guideline may apply to a stand-alone setting outside the collaborative registration approach, for example, where the NRA specifies other authorities as reference authorities for its own reliance purposes. Although, the published Procedures apply for pharmaceutical products and vaccines, the general principles may also apply to medical devices, including in vitro diagnostics, for which the collaborative procedure guideline is under development.

This document provides recommendations to NRAs that are participating in the Procedures. Nonetheless, reliance or risk-based approaches follow the principles of good regulatory practices (GRP) and are also applicable and practised among the well-resourced and mature regulatory agencies. This enables a greater alignment and convergence with international standards for the NRAs, while they can also maximize efficient use of their own resources. Moreover, the NRAs are able to focus on value-adding activities and therefore reduce the burden of duplication of work done by trusted authorities and duplication of work for applicants/manufacturers.

In the case of national applications for registration of products assessed and prequalified by WHO or registered by reference authorities, it is possible that national applications can be submitted by other persons/legal entities that act on behalf of manufacturers with WHO-prequalified products or products approved by reference authorities. It is necessary to consider these options, and existing CRPs includes arrangements for such situations. If the applicant for national registration is not the same as the manufacturer with the WHO-prequalified or reference authority-approved product, the manufacturer with the WHO-prequalified or reference authority-approved product confirms to the NRA and WHO/reference authority by an authorization letter that the applicant is acting for, or pursuant to rights derived from, the manufacturer with the WHO-prequalified or reference authority-approved product and that they agree with the application of the procedure in the country concerned.

Note: The CRPs cover initial registrations and variations/post approval changes.

4. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

abridged review. A limited independent assessment of specific parts of the dossier, or submission for suitability of use under local conditions and regulatory requirements, while relying on prior assessment and inspection outcomes from a

reference authority or trusted institution to inform the local decision. The abridged review is based on assessment reports, and good manufacturing practices (GMP) inspection reports of reference authorities, plus specific parts of the *Common Technical Document* (CTD) (for example, stability data in Module 3 of the CTD (9)).

abbreviated review. See abridged review.

collaborative procedure (Procedure). The collaborative procedure to accelerate the national registration of prequalified pharmaceutical products and vaccines, or the collaborative procedure to accelerate the national registration of products approved by stringent regulatory authorities (10, 11). The collaborative registration procedures cover initial registrations and post-registration variations/post-approval changes.

dossier. The regulatory submission package submitted to the national regulatory authority as an application for marketing authorization in line with the applicable country requirements and requirements specified in the respective Procedure guidelines (2, 3).

manufacturer. Any person or legal entity engaged in the manufacture of a product subject to marketing authorization or licensure; or any person or legal entity that is an applicant or holder of a marketing authorization or product licence where the applicant assumes responsibility for compliance with the applicable product and establishment standards.

participating authority or participating national regulatory authority. A NRA that voluntarily agrees to implement this collaborative procedure and accept the task of processing applications for registration of WHO-prequalified pharmaceutical products and vaccines, in accordance with the terms of the Procedure. A list of participating authorities is posted on the WHO/PQT website, for pharmaceutical products (12) and for vaccines (13).

recognition. The routine acceptance of the regulatory decision of another regulator or other trusted institution. Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B.

reliance. An act whereby a regulatory authority in one jurisdiction may take into account or give significant weight to work performed by another regulator, or other trusted institution, in reaching its own decision.

reference authority. A regulatory authority that agrees to provide outcomes of its regulatory expertise (especially assessment and inspection reports) to applicants/authorization holders or inspected manufacturers; agrees to sharing of these documents with national regulatory authorities; and provides, under specified conditions in line with the principles of the Procedure, support to other parties involved in the Procedure.

stringent regulatory authority. The authority as defined by the interim definition in 2017 (10) and updated in 2018 (11).

verification. The procedure by which a regulatory authority only validates the product or submission, and ensures that the product for local marketing is equal or

similar to that approved by the reference authority or trusted institution. Verification may be on the basis of assessment reports, GMP inspection reports and/or a certificate of pharmaceutical product of a reference authority.

5. Key principles

5.1 Risk-based approach

It is regulatory best practice for NRAs to implement quality risk management (14). In this respect, the NRAs should allocate resources and a level of effort that is proportionate to the level of risk. For example, the quality, safety and efficacy of a product prequalified by WHO, or approved by a reference authority, may be considered demonstrated compared to a product with no such prior reviews and/or approvals; therefore, the level of effort required to reach a final regulatory decision by a NRA should be differentiated accordingly.

5.2 Optimum use of available resources

Assessment activities should be aligned with resources available to the NRA. In addition, NRAs should be able to recognize their capabilities, limitations and the most efficient and effective approach to ensure that the patients are served and protected with the available resources. This includes removing duplication and identifying elements in the benefit–risk assessment that are critical in the local context. For innovative products, this may mean bridging the benefit–risk assessment done by reference SRAs to the local population, suitability of use in the local context, or stability data that suit the local climatic conditions.

5.3 Ensuring the “sameness” of products

The core principle for collaborative registrations is to ensure identical products (or that where differences exist, these are clearly stated) between the NRA and the reference NRAs, regardless of the approaches or assessment activities conducted by the NRA. The same pharmaceutical product or same vaccine is defined in the Procedures (2, 3), as characterized by:

- the same qualitative and quantitative formulation;
- the same manufacturing site(s)¹ for the drug substance and finished product, including specific block(s)/unit(s), manufacturing chain,

¹ The sameness of the manufacturing sites for active pharmaceutical ingredients (APIs) and finished pharmaceutical product (FPPs) means that the specific site must be approved by the PQT or reference authority for the specific product under consideration, and included as part of the marketing authorization in the reference country. Any additional sites, regardless of GMP status, are not acceptable under this procedure. Any changes or variations to include additional sites should be approved by the PQT or the reference authority before inclusion in the submission to the participating NRAs.

processes, control of materials and finished product, and, in the case of vaccines, also by the same batch-release scheme;

- the same specifications for the excipient(s), drug substance and finished product;
- the same essential elements of product information for pharmaceutical products, and, in the case of vaccines, by the same product information, packaging presentation and labelling.

Notwithstanding the principle and definition of the same product under the Procedures, the general principles in this guideline may be applied in other cases where the information is partly the same, but some differences between the products exist and are clearly stated and acceptable to the NRA. In those cases, the NRA should take additional precautions or steps, such as full review of corresponding data not assessed by the reference NRA, or inspecting the additional sites, as the case may be, while relying on shared information where sameness is applicable.

5.4 Compliance with nationally legislated regulatory requirements

Submissions and documentary evidence should be consistent and they should comply with applicable national legal and regulatory requirements. Collaborative registrations, or reliance approaches, do not substitute compliance with applicable national requirements; however, NRAs are encouraged to update, where applicable, any legal or regulatory requirements in line with international best practices and harmonized requirements.

5.5 Flexibility to allow national regulatory authorities to adapt to their situations

No one size fits all; the best practices should permit each NRA to adapt and suit their own circumstances; for example, the practical steps and tools should be applicable across the maturity levels of NRAs, national strategies or procedures. It should be remembered that internationally harmonized practices and standards facilitate work-sharing and improve the compliance of applicants/manufacturers.

6. Essential elements of a registration system (in the context of collaborative registration procedures)

6.1 National regulatory authority agreement to participate in collaborative procedures of WHO-prequalified pharmaceutical products and vaccines or products approved by stringent regulatory authorities

To responsibly decide on participation in the CRP, the management of interested NRAs should have a good understanding of the principles of the procedure (2, 3) and be aware of its benefits and feasibility, as well as commitments that are associated with participation. Proper study of the procedure is necessary. It is useful to understand to what extent current practices and policies permit the implementation of the process and how the participation corresponds with the NRA's developmental plans. The NRA management should be especially assured that there are no legal barriers preventing participation or hampering effective implementation of the procedure. This is not normally the case, as the CRP only represents the availability of additional expertise for NRA consideration in its decision-making process. Any pending issues can be clarified with the WHO focal person prior to a formal agreement on participation.

To successfully operate the procedure from the beginning, and to be able to inform local applicants about registration in this respect, it is important to prepare registration pathways for prequalified and reference SRA-approved products and to consider the following factors, especially those presented next.

The selection of focal persons who are responsible for communication with WHO and with reference national regulatory authorities

Optimally, focal persons for the registration agenda should be selected among NRA technical staff who are experienced with the registration process, from the submission of applications to adoption of decisions, with post-registration regulatory activities. They should also be able to communicate with colleagues who are responsible for the end-to-end registration process, including staff responsible for all administrative steps, inspection, post-approval changes, pharmacovigilance and laboratory testing.

Focal persons for inspection activities should preferably be experienced GMP inspectors who are involved in inspection planning and in communication with other departments in the NRA and inspectorates in other countries.

It is important that focal persons are motivated and able to communicate in English; and that they understand the NRA application tracking process and have access to the internet. It is up to the focal persons to regularly collect and communicate to WHO, or reference SRAs, the relevant Procedure-related information, and share such information obtained from WHO or reference SRAs with responsible NRA units.

National regulatory authority application tracking systems

NRAs should adapt existing tracking systems, or implement appropriate tracking systems for applications for registration, that enable easy identification and monitoring of progress and timelines of all applications considered under CRP and other NRA pathways. All the NRA staff that are responsible for different aspects of a product throughout the life-cycle management should have access to the tracking systems.

The adoption of provisions to organize the Procedure process and meet the prescribed timelines

This may include some adaptation of the application screening process; changes in assessment practice; recording of applications in NRA databases and tracking systems; new timelines for certain registration steps; modified staff responsibilities; and/or arrangements of technical committee meetings. Adequate resources should be available to implement the Procedure, especially with regard to the capacity of involved personnel, access to a shared network, and communication with WHO and reference NRAs. In line with GRP, the changes should be reflected in relevant standard operating procedures (SOPs) and staff should be appropriately trained in the Procedure, registration pathway, and the process for reliance on outcomes from other regulatory authorities or PQT, as well as risk management science (risk-based approaches) and change management.

Regulatory fees

Regulatory fees for the Procedure applications should be decided by the NRA and this information should be publicly available to the applicants.

Information to applicants

Manufacturers should be properly informed about the existence of the new process; scope of the products for which this is applicable; possible deviations from standard national requirements; differences from current registration practices; and the benefits that come with participation. An example of information to applicants for registration is included in Appendix 1. A focal person should be identified who would respond to Procedure-specific questions and assist those submitting their first Procedure applications.

Communication

When informing WHO about participation in the Procedure(s), the NRA should mention the date it is prepared to implement the Procedure(s) and to accept the first applications for this/these registration pathway(s).

MedNet is an information platform where WHO or SRA assessment and inspection outcomes, and additional confidential information, are shared. Focal persons are invited, by WHO, to this internet-based communication platform, after it receives a

duly signed agreement for participation. Each focal person must create their personal access passcode, in order to enter the shared information site. If requested, WHO can assist in MedNet learning. In the case of regional cooperation, other information platforms can be used.

6.2 Registration pathways

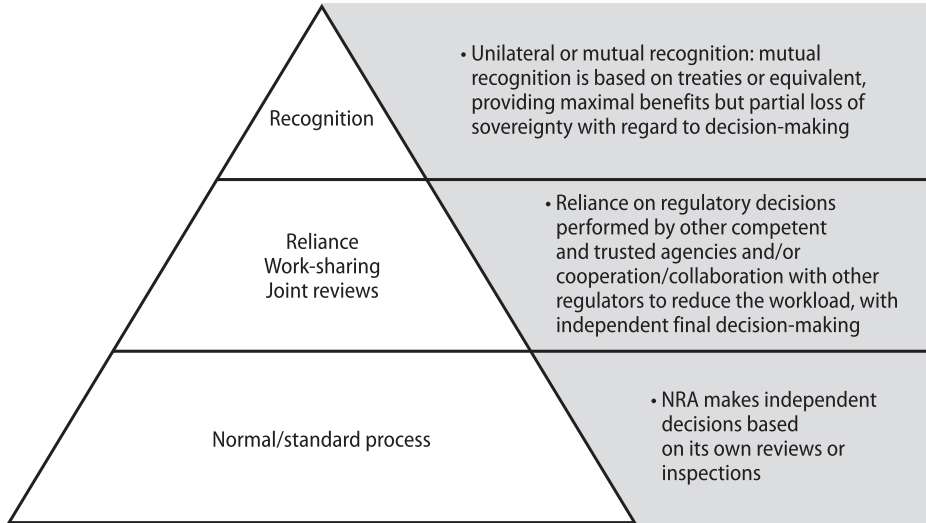
NRAs should define and establish clear registration pathways, for example, for products with prior approval from reference SRAs; WHO-prequalified products; products through joint reviews or work-sharing; normal reviews; and fast-track mechanisms. This information enables manufacturers/applicants to select the most appropriate pathway and to provide the necessary documentary evidence applicable for each pathway as part of the dossier submission.

In-line with GRP, a robust registration system incorporates principles of good risk management that ensures that the level of control and resource allocation is proportionate to the level of public health risk associated with specific products. In this regard, NRAs should classify applications submitted for registration, based on the level of potential public health risk for each product. The risk class of a specific product may be determined by factors such as the route of administration; dosage form; formulation; development level (that is, new API or multisource product); competence of the companies, including compliance with regard to GMP; applicable WHO and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, as demonstrated from past inspections; prior approval from reference authorities or WHO prequalification; and the scope of information available from the reference authorities or the PQT.

Fig. A6.1 shows an example of registration pathways for a NRA. At the base of the model is the normal registration pathway where the NRA independently performs all assessment and inspection activities in order to reach its own decision. Following this are different levels of cooperation or collaboration with other regulators, ranging from joint activities, work-sharing, reliance and, ultimately, recognition. It is important to note that the level of effort decreases as one goes up the pyramid, from independent full assessment at the base of the pyramid to complete reliance on decisions by others (recognition) at the top of the pyramid.

NRAs may define the combination of these approaches and should clearly state the approaches applicable for collaborative registrations, that is, for products prequalified by WHO and for products approved by reference SRAs. NRAs should state the reference authorities for which recognition or reliance is applicable. It is suggested that where a list of reference authorities is stated, at the very least it should include the established reference SRAs.

Fig. A6.1

Model for registration pathways for national regulatory authorities (NRAs)

NRAs may define the combination of these approaches and should clearly state the approaches applicable for collaborative registrations, that is, for products prequalified by WHO and for products approved by reference SRAs. NRAs should state the reference authorities for which recognition or reliance is applicable. It is suggested that where a list of reference authorities is stated, at the very least it should include the established reference SRAs.

6.3 Organization of assessment activities

NRAs should also consult the other applicable WHO publications that provide detailed arrangement for assessments (5, 6).

A NRA has several options for organizing its assessment activities, based on its legal and regulatory framework, development plans and capabilities. The approaches described next may be adopted by the NRA.

Verification

Verification is not a scientific assessment but an administrative process to reach a regulatory decision, based on registration or authorization by a reference NRA or WHO prequalification. The NRA formalizes its decision by approving the product or submission and ensures the product for local registration and marketing conforms to the product as prequalified by WHO and approved by the reference NRA. This may require a policy, or a regulatory provision to facilitate the NRA to apply this approach. Verification should

be applied where conformity with requirements of the reference authority or institution is sufficient to meet the requirements of the receiving authority or institution. This may apply to all or part of the submission.

Abridged/abbreviated review

Abridged/abbreviated review is a limited assessment of suitability of use under local conditions and regulatory requirements, while relying on prior assessment and inspection outcomes from the reference NRA or the PQT to inform the local decision. This approach focuses on value-adding activities in addition to the NRA's assessment activities and avoids duplication of the work already done by others. Desk review of inspection reports may be considered as a form of abridged/abbreviated review.

Note: These two options (verification and abridged reviews) are not mutually exclusive, as some NRAs may implement a combination of these approaches for the Procedures, where applicable. For example, some NRAs may recognize the PQT outcomes, since they address programmatic suitability for the countries for which prequalified products are mainly intended for use, while approvals from reference NRAs may require a combination of verification and abridged/abbreviated reviews to address the local context (e.g. benefit–risk in the local population; stability to allocate the storage conditions; shelf-life at the storage conditions prevailing in the country; risk management plans; and suitability of information for patients/health professionals, where applicable). Other special access mechanisms introduced by the reference SRA may address the local context in their review process, thereby enabling verification to be applicable in those cases.

The NRA should clearly identify the type of products and applications suitable for an abridged/abbreviated review or verification, as well as the abbreviated review timelines associated with those. To facilitate implementation, registration pathways, different templates and procedures, including SOPs, should be in place to differentiate products or applications by the type of assessment to be conducted, that is, verification, abridged/abbreviated review, and /or full review. Additionally, the assessors should be trained accordingly. Sample templates for verification and abridged/abbreviated review are provided in Appendices 2 and 3, respectively.

Secondary review

NRAs may perform secondary reviews of the shared assessment and inspection outcomes from the PQT or reference NRA. Moreover, this approach may be essential where the NRA is involved or participates in the initial reviews, for example, joint reviews between the NRA and the PQT or in special access mechanisms by reference SRAs that have provisions for NRA participation. As a result, the NRA's input may be incorporated into the final decision of the PQT or the reference SRA, thereby facilitating a concurrent regulatory decision where a parallel submission has been made.

Full review

For full review, a NRA is capable, and has the resources and expertise, to carry out a full assessment of quality, preclinical and clinical data (safety and efficacy) of products with no prior approval elsewhere. This route is not recommended for the collaborative procedures, as it is considered a duplication of effort.

Verification, abridged review, and secondary reviews facilitate better resource management for the NRAs, shorten timelines compared with a full review and could improve the quality of the review. More importantly, the quality and availability of the full reports from the reference authorities are key to this process.

The NRA reserves the right to re-route any application to the normal review process if the application does not fulfil the intent of the verification or abridged/abbreviated or secondary review process, and the applicants should be made aware of this.

6.4 The effectiveness of risk-based review strategies

What metrics should be used to determine the effectiveness of risk-based review strategies in addressing the intended problems of volume, capacity and review effort, without compromising quality?

Timelines

NRAs should set timelines that take into account the level of reliance or different registration pathways, for example, recognition, reliance, work-sharing/joint reviews and full assessment. The timelines should be based on the NRA's existing resources and benchmarking with other NRAs. Tracking mechanisms should be in place, and these should be able to track and account for the regulator's time and applicant's/manufacturer's time during the review process. Information on a predefined time for receipt of questions and provision of answers should be defined by the NRA. Typically, this is defined as 30 calendar days for the applicant/manufacturer to respond or provide additional information.

For the Procedures, the recommended timelines are specified in the Procedure, that is, the NRA should reach a decision within 90 days of the regulatory time and communicate such decision to the applicant within 30 days of reaching it. The NRAs are encouraged to streamline national processes as outlined in Sections 6.2 and 6.3.

The timelines are also affected by the quality of the submissions and the number of review cycles.

Other metrics

Other metrics that could be useful for reliance models or the Procedure include: the proportion of products approved/disapproved/withdrawn through these risk-based approaches, relative to the total approvals; the number of review cycles relative to completion of assessments; and review effort and quality of decisions.

The NRA should be able to track these metrics for each registration pathway, to assess the relative efficiencies and effectiveness of the adopted pathways; to evaluate not only accelerated decision-making, but also the impact on regulatory burden and quality of regulatory decisions; and to identify areas for improvement.

6.5 Steps of the common regulatory pathway

In principle, the CRP follows the key steps of a national registration process; however, certain steps can be simplified. According to NRA practice, the points presented next should be considered and incorporated into internal SOPs.

Procedure initiation

When the Procedure commencement date is announced by a NRA, the Procedure is applicable to new submissions to the NRA, or for products pending registration in the NRA. In situations where the applicant wishes to apply the Procedure to an application that is already pending within the NRA, the applicant should first update the dossier to ensure that the technical part of the information is the same as that approved by the PQT or reference NRA, and any deviations should be clearly stated. It is up to the NRA to decide whether or not it is more convenient to switch to the Procedure to complete the registration or to grant registration via the normal pathway, and inform the applicant accordingly (e.g. when the assessment is finished and registration is imminent).

Each applicant initiates the Procedure by submitting CRP-specific documents as part of a registration application. The correct fees should be paid and the date of receipt of the dossier/application recorded by the NRA.

Dossier format and content

Dossiers should be submitted in the appropriate format, as required by the respective NRAs, that is, hard copies, electronic format in portable document format (PDF), or electronic common technical document (eCTD), as applicable. Notwithstanding the submission format to the respective NRAs, the content of the dossier should enable verification of the sameness of the products as those of the PQT or the reference NRAs. The dossiers should be updated to include all variations approved by the PQT or reference NRA before the national submission. A current quality information summary (QIS or QIS-SRA(crp)) should be provided, where applicable, subject to exceptions in line with the PQT product-specific procedures. Additional NRA-specific documents should be included, such as application forms, product information and labelling in national format, if required. For detailed guidance on submission format and content, please refer to Section 4.2 in reference (2) and Section 4.1 in reference (3).

Screening to validate the application

The NRA should properly screen the applications, to ensure that the product is eligible for the Procedure and that all the required documentation is provided, as per the NRA procedures and CRP process. Use of a checklist is recommended (Appendix 4). The submission of the dossier should be recorded using the existing procedures for storage and management of applications. Formal deficiencies in the submitted application and the dossier should be communicated to the applicant, in line with the national practice. The screening should be performed quickly (e.g. within 2 days) and applicants should be given a defined time to respond (e.g. 30 days).

Decision on the Procedure and informing WHO

Having a complete valid CRP application, the NRA promptly decides whether or not to apply the Procedure, marks in its records that the product is being processed under the CRP, and promptly informs WHO accordingly. In the case that the NRA decides to register the product in line with the Procedure, the PQT or reference NRA shares assessment and inspection reports, typically within 30 days of receipt of the request and/or expression of interest from the applicant to participate in the CRP. This starts the 90-day regulatory period in which NRAs should decide on the registration in line with the Procedure.

Processing the application

To maximize the benefits of the PQT or reference NRA outcomes, the NRA is recommended to follow the risk-based review process, that is, to verify that the prequalified or reference NRA-approved product and national submissions are the same, and review country specific requirements, for example, prescribing and labelling information. The need for a special risk management plan follow-up should be considered. Appendix 2 is a template for verification, representing a simplified process to verify product similarity. Appendix 3 is a template for an abbreviated/abridged review, which includes verification of detailed requirements and limited scientific assessment to suit the local context, as required. Where applicable, as per country procedure, the report is tabled for consideration by a competent technical committee as soon as practicable, and within 90 calendar days of the Procedure.

Inspections

If the NRA inspectorate is involved in assessing compliance with GMP and other practices, and in data verification, the inspectors have available PQT or reference NRA inspection reports to facilitate the development of their judgement. It is advisable to organize a desk-review process instead of on-site inspections (7).

Laboratory testing

Preregistration laboratory testing of submitted samples is not recommended during CRPs. Instead, post-registration risk-based testing is recommended. The NRA should assess whether it is feasible to perform independent testing in its laboratories, or whether special arrangements or partnerships are necessary. WHO advice can be sought in relation to quality testing, and results from WHO-organized testing for prequalified products, including lot-release testing results for vaccines, can be shared. In other words, for vaccines, reliance on testing done by national quality control laboratories from reference authorities should serve as the basis for CRPs.

Product information

Prescribing and labelling information should be submitted in the standard national format. In the case of labelling, a mock-up presentation is normally sufficient instead of a definitive printed package of the product to be marketed, which may be difficult to produce before registration. Indications should be checked against national therapeutic guidelines, when applicable. The content of the product information should correspond to the information approved by the PQT or reference NRA. Different information content must be justified and can represent a deviation from prequalification or approval by the reference NRA. For prequalified vaccines, the product information and labelling submitted to the NRA should be the same as that approved by the PQT.

Communication with applicants

After the NRA review process, issues to be communicated to WHO, the reference NRA, or the applicant are summarized and communicated through the normal communication procedures of the NRA. Should the applicant fail to respond in time or to provide other necessary cooperation, the NRA is entitled to terminate the procedure and to process the application in line with normal registration procedures. Such termination is communicated to the applicant and to WHO or the reference NRA.

Decision on registration and communication to WHO

The NRA may decide to refuse to register or issue a registration. Reasons for refusal and/or conditions for registration, including post-registration commitments, should be formally prepared and concurrently shared with the applicant and WHO within 30 days of the decision. The registration number, date, clock-stop days and – if applicable – deviations from the PQT or reference NRA decisions, should be notified to WHO and the reference NRA, as applicable.

Regulatory time measurement

The regulatory registration time for the purpose of the Procedure starts on the day on which the assessment and inspection reports are shared, or when a valid submission is

received by the NRA (whichever is later), and ends on the date of registration. In the event of queries being raised, the clock should stop until the applicant has addressed the concern. Clock-stop time is not included in the registration time.

6.6 The focus of reviews in abridged/abbreviated assessments

The level of abridged review may vary depending on the type of product, for example, generic versus innovative product, or prescription versus non-prescription medicine, vaccines versus chemical entities, or the collaborative procedure, that is, based on WHO prequalification or reference NRA approval, or through special access mechanisms.

Quality review

Reliance is generally straightforward, as quality standards are often common across major jurisdictions, and those determined by the PQT or reference SRA are considered adequate for most NRAs. Nonetheless, applicant/manufacturer filing strategies may complicate reliance mechanisms, owing to potential differences in indications and data and quality specifications for different markets. Notwithstanding this, the QIS or QIS-SRA(crp) is a useful document to facilitate the verification or abridged review for quality documentation, subject to exceptions as per Section 6.5, “Dossier format and content”. It allows the applicant to clearly state differences, if any, for example, storage conditions and shelf-life for reference NRA approvals and easy verification of product sameness, thereby saving significant NRA resources in verification or abridged reviews. Verification or abridged reviews may focus on:

- *for APIs/drug substances*: general properties that enable identification of the potential impact of critical quality attributes on the performance of the finished product/drug product (e.g. pKa, solubility, particle size distribution, polymorphism, where relevant); manufacturing site; manufacturing process (e.g. for APIs, purification crystallization, micronization; for drug substances, producing cell line, cell banks, purification methods, presence of viral inactivation steps); quality standards and specifications and test methods of the API/drug substance; container closure system; retest period; and storage conditions;
- *for biological substances*: the description of the molecule, including features such as glycosylation/post-translational modifications; “artificial” modifications (amino-acid substitutions, pegylation); and molecular size.
- *for FPPs/drug products*: description; unit and batch formula; production batch sizes; manufacturing site; manufacturing process; quality standards and specifications and test methods of the excipients and FPP/drug product; container closure system; shelf-life, including in-use period; and local storage conditions.

Note: In some cases, for example, approvals by reference SRAs, the NRAs may need to perform an additional independent review of stability data if the climatic conditions, or container closure system, and consequently the stability data, are not the same, but this does not preclude reliance on other quality aspects under the Procedure.

Clinical review

The NRAs should ensure the indications are consistent with national treatment guidelines, where applicable. For the collaborative procedure for reference SRA-approved innovative products, reliance tends to be more challenging, notwithstanding the same dataset that had been reviewed by the reference SRA, as the benefit–risk may not be identical in the different populations or settings. Additionally, with the adoption of various facilitated registration mechanisms for innovative medicines, including conditional approvals or rolling submissions, the NRAs may not have similar registration pathways to facilitate approvals of such products. With this in mind, the concept of the bridging report (15) is recommended for the CRP for products approved by SRAs, to address differences in the target population relative to the population in the clinical trials; epidemiology and other features of the disease; concomitantly-used medicines; and, hence, the interaction potential; local therapeutic and diagnostic modalities; and other factors that can substantially lead to a different benefit–risk balance. A risk management plan should be reviewed from the point of view of local relevance.

Post-approval changes

Post WHO prequalification or reference NRA authorization, commitments should be considered and the relevant ones may be included in the local NRA registration decision. The applicants should be committed to reflect or at least notify post-approval changes. Deviations of the locally registered product from the PQT- or reference authority-approved product should be reported.

A model example of information, documentary evidence and assessment activity of a NRA applying the reliance model is provided in Appendix 5.

6.7 Managing product differences

Some differences could exist between the application dossiers, in particular for SRA-approved products. These should be clearly stated, and, in some cases, the NRA has to perform its own assessments of such data where the proposed changes were not covered in the original submission/assessment performed by reference SRA. Some common potential differences are highlighted below for illustrative purposes:

- different presentations without changing the packaging materials;
- regional labelling requirements;
- storage conditions and shelf-life.

Any change beyond the above would result in the product being considered different from the prequalified product or that approved by the reference NRA.

6.8 Managing variations/post-approval changes

Post-approval changes (variations) require significant resources for both manufacturers and the NRAs and pose a significant threat to the continued supply of quality-assured medicines and vaccines in the target countries. More specifically, it is generally reported that it takes 2–4 years to complete approval of moderate to major change(s) in every country where a global product is registered. Consequently, these long regulatory approval timelines not only make the supply chain complex, with different versions of the product required to supply multiple countries, but also consume substantial resources for both manufacturers and NRAs.

To ensure the absence of deviations between the WHO-prequalified product, or reference NRA-approved product and the NRA-registered product, variations should only be submitted to the NRA after acceptance by the PQT or approval by reference NRAs, to ensure sameness of the products throughout the product life-cycle.

While it is expected that many NRAs have the expertise and capacity to review variations, there is significant risk associated with reviewing variations to a product approved by a different authority. Variations should be reviewed by the originating authority, to avoid the possibility/likelihood of different changes being accepted in the originating and receiving countries over time. This results in the product in the receiving country no longer being the same as that approved by the originating authority, that is, different from the product for which safety, efficacy and quality have been established.

The *WHO general guideline on variations to multisource pharmaceutical products* (16) provides a recommendation for expanding the capacity of individual NRAs through work-sharing and recognition of the decisions of other NRAs in the network, and convergence of regulatory requirements, thus avoiding unnecessary repetition of evaluations of the same variation by multiple NRAs.

Categorizations and management of variations

Variation terminology, fees and administrative requirements are subject to national regulations. Variations to the product that have been registered by the CRP registration pathway should first be submitted to the PQT or reference NRA for assessment. Post-approval variations differ, depending on the CRP route followed. The PQT will only categorize variations for prequalified products on a product-specific basis (17, 18), while accepting SRA-approved variations and their categorization.

Once approved by the PQT or reference NRA, the applicant may implement the change and notify the NRA of such immediately (within 30 days). Variations submissions to NRAs should clearly indicate that the product has been registered by the CRP registration pathway, with same dossier, including any additional information

based on PQT or reference NRA assessment, and evidence of such approval by submission of the “PQT or reference NRA approval letter” (for minor or major variations) or PQT or reference NRA acknowledgement email (for notifications). The PQT or reference NRA will share the variation outcomes with the NRA, for variations that require prior approval.

To monitor the post-prequalification changes and to verify the compliance of manufacturers in submissions of variations, participating NRAs can benefit from visiting the PQT or reference NRA’s website. WHO or reference NRA public assessment reports are continually updated with regard to the lists of approved variations.

The notifications that affect administrative information relevant to WHO or the reference NRA only are not included. Such administrative changes relevant for individual participating NRAs should be submitted in line with national legislation and guidance. As regards reference NRA-approved products, classification of variations may somewhat deviate from the PQT scheme, but similar principles of variation management should be followed, benefiting as much as possible from publicly available information.

Processing variations by the national regulatory authorities and communication to WHO

Like the assessment during the registration process, the NRA may consider performing verification based on the shared assessments of the variation by the PQT or reference NRA, instead of independent review, and issue an acknowledgement of receipt or approval within 30 days.

If a change is rejected by the NRA, this should be communicated to the applicant with an explanation for the rejection. As appropriate, there should be an opportunity for dialogue between the NRAs, WHO and the applicant, as necessary, with the aim of resolving the NRA’s concerns with the application. Any significant deviations resulting in the NRA-registered product not being the same as the PQT- or reference NRA-approved product should be communicated to WHO and the reference NRA within 30 days, at which point the corresponding product is no longer considered to be in the CRP process.

Non-administrative changes submitted only to the NRA should not be approved or accepted unless justified. If the NRA decides to approve/accept a variation that is not approved or accepted by the PQT or reference NRA, the NRA should record the differences between the PQT- or reference NRA-approved and national product. The NRA informs WHO of such variations if they are major, for updates in the online list of products registered through the collaborative procedure. Depending on the nature of such variations, the product can be treated as different from the prequalified or the reference NRA product in the given parameters. As already discussed, in such cases when the NRA-registered product is no longer considered the same as the PQT- or reference NRA-approved product, the product is no longer considered to be in the CRP process.

6.9 Registration renewals: national regulatory authority and WHO actions

Renewals

The validity of registration and renewal of registration by the NRA will be based on the existing guidelines for renewal of registration of products applicable in each NRA. The renewal process represents a good opportunity to review whether all applicants' commitments were satisfied and to verify consistency (e.g. verifying all approved variations; requalification in the case of a prequalified pharmaceutical product; renewal or changes to the conditions of registration in the reference NRA are up to date for the nationally registered product) between the PQT, reference SRAs and national registration conditions.

Withdrawals, de-registrations, suspensions and de-listings

In cases where a prequalified product is withdrawn from prequalification by the manufacturer, it is suspended or de-listed by the PQT, who will then promptly, through the restricted-access website, and subject to the above-mentioned obligations of confidentiality and restrictions on use, inform the relevant participating NRA accordingly, providing the reasons for the withdrawal whenever required to do so. The same procedure applies for products registered through the collaborative procedure for SRA-approved products.

If a participating NRA de-registers or suspends the registration of a prequalified or SRA-approved product for any reason, the participating NRA informs the PQT or reference SRA thereof (together with the reason for this decision). The information should be provided without delay whenever product quality, safety or efficacy is concerned, and, in other cases, within 30 working days. A participating NRA is encouraged to consult the PQT or reference SRA before adopting a decision about de-registration or suspension of registration of a WHO-prequalified or SRA-approved product.

Other matters

In the event of a Notice of Concern (NoC) issued by the PQT or reference SRA for a site (GMP, good clinical practices [GCP] and good laboratory practices [GLP] issues) on a product registered under the procedure, the NRA should follow the position of the PQT or reference SRA, unless justified to decide otherwise. Reasons for not following the PQT or reference SRA decision should be communicated to the PQT or reference SRA.

References

1. Resolution WHA67.20. Regulatory system strengthening for medical products. In: Sixty-seventh World Health Assembly, Geneva, 19–24 May 2014. Geneva: World Health Organization; 2014 (https://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R20-en.pdf, accessed 15 February 2019).
2. Collaborative procedure between the World Health Organization (WHO) Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fiftieth report. Geneva: World Health Organization; 2016: Annex 8 (WHO Technical Report Series, No. 996; <https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>, accessed 15 February 2019).
3. Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization; 2018: Annex 11 (WHO Technical Report Series, No. 1010; <https://iris.who.int/bitstream/handle/10665/272452/9789241210195-eng.pdf?sequence=1&isAllowed=y>, accessed 15 February 2019).
4. Good regulatory practices: guidelines for national regulatory authorities for medical products. Geneva: World Health Organization; 2016.
5. Marketing authorization of pharmaceutical products with special references to multisource (generic) products: a manual for national medicines regulatory authorities (NMRAs), 2nd ed. Geneva: World Health Organization; 2011 (https://apps.who.int/iris/bitstream/handle/10665/44576/9789241501453_eng.pdf?sequence=1, accessed 15 February 2019).
6. Good review practices: guidelines for national and regional regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-ninth report. Geneva: World Health Organization; 2015: Annex 9 (WHO Technical Report Series, No. 992; https://iris.who.int/bitstream/handle/10665/176954/9789240693968_eng.pdf?sequence=1&isAllowed=y, accessed 15 February 2019).
7. Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization 2018 (WHO Technical Report Series, No. 1010; <https://iris.who.int/bitstream/handle/10665/272452/9789241210195-eng.pdf?sequence=1&isAllowed=y>, accessed 15 February 2019).
8. World Health Organization. Collaborative procedure for accelerated registration.
9. ICH harmonisation for better health. M4: The Common Technical Document (<https://www.ich.org/products/ctd.html>, accessed 15 March 2019).
10. Definition of stringent regulatory authority. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-first report. Geneva: World Health Organization; 2017:34–5 (WHO Technical Report Series, No. 1003; <https://iris.who.int/bitstream/handle/10665/258720/9789241210034-eng.pdf?sequence=1&isAllowed=y>, accessed 15 February 2019).
11. Definition of “stringent regulatory authority”. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization; 2018:43–4 (WHO Technical Report Series, No. 1010; <https://iris.who.int/bitstream/handle/10665/272452/9789241210195-eng.pdf?sequence=1&isAllowed=y>, accessed 15 February 2019).

12. World Health Organization. Essential Medicines and Health Products: prequalification of medicines (<https://extranet.who.int/prequal/medicines>, accessed 15 February 2019).
13. World Health Organization. Immunization standards. Revised procedure for expedited review of imported prequalified vaccines for use in national immunization programmes.
14. ICH harmonised tripartite guideline. Quality risk management Q4. Step 4 version. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2005 (<https://www.ich.org/page/quality-guidelines>, accessed 15 February 2019).
15. Appendix 6: Requirements for provision of a bridging report for reference SRA-approved pharmaceutical product and vaccines for consideration of registration in participating countries. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization; 2018: Annex 11 (WHO Technical Report Series, No. 1010; <https://iris.who.int/bitstream/handle/10665/272452/9789241210195-eng.pdf?sequence=1&isAllowed=y>, accessed 16 February 2019).
16. WHO general guidance on variations to multisource pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fiftieth report. Geneva: World Health Organization; 2016: Annex 10 (WHO Technical Report Series, No. 996; <https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>, accessed 15 February 2019).
17. WHO guidelines on variations to a prequalified product. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-seventh report. Geneva: World Health Organization; 2013: Annex 3 (WHO Technical Report Series, No. 981; https://iris.who.int/bitstream/handle/10665/81144/WHO_TRS_981_eng.pdf?sequence=1&isAllowed=y, accessed 15 February 2019).
18. Guidance on variations to a prequalified vaccine. Geneva: World Health Organization; 2015.

Appendix 1

An example of information to applicants for registration via the WHO collaborative registration procedure

Registration of WHO-prequalified pharmaceutical products and vaccines/products approved by stringent regulatory authorities (SRAs) through the collaborative registration procedure

Since [date], [name of the NRA] participates in the World Health Organization (WHO) collaborative registration procedure (CRP) for WHO-prequalified pharmaceutical products and vaccines/collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities (SRAs), and accepts applications for registration in line with this procedure (hereinafter referred to as “the Procedure”).

This Procedure serves to facilitate and accelerate the registration of products that have already been assessed and listed as prequalified by the WHO Prequalification Team (PQT)/SRAs. Detailed information about the CRP can be obtained at: <https://extranet.who.int/prequal/medicines/collaborative-procedure-accelerated-registration>.

All applicants for national registration of WHO prequalified products/SRA-approved products are encouraged to use this registration route. With this pathway, **finalization of the valid application is expected within 90 days of regulatory time**. Subject to [name of the NRA]’s previous agreement, the Procedure is also applicable to pending WHO prequalified products/SRA-approved products already in national registration. Specific arrangements may be necessary.

[Name of the NRA] reserves the right to use the standard national registration route or to switch to it during the CRP, in case of specific products (for example, products not included in national treatment/vaccination guidelines) or lack of the applicant’s cooperation.

Applicants wishing to use this registration route should:

1. Notify WHO/the SRA of their intention to use this Procedure for registration of a particular product by sending the appropriate notification form (Appendix 2/ Appendix 3 Part B) to WHO/the SRA, as outlined on the WHO website. If the applicant for national registration is different from the manufacturer with a prequalified product/SRA-approved product, the mutual agreement between the applicant and the manufacturer is necessary and the notification to WHO/the SRA has to be sent by the manufacturer.

2. Follow the national guidance to applicants for registration, available at [*insert reference for national guideline*]. More importantly, the following should be considered:
 - a. The national Application form and requirements on samples and labelling stay in place.
 - b. “WHO Collaborative Procedure”/“SRA Collaborative Procedure” should be indicated as the proposed registration pathway in the national application form or in the covering letter.
 - c. The Expression of Interest form (Appendix 3 Part A/Appendix 7 of the Procedure), as outlined on the WHO website, has to be submitted.
 - d. The technical content of the dossier has to correspond exactly to that submitted and currently approved by the PQT/SRA and as specified in the corresponding Procedure guidelines. The dossier has to be updated to reflect all post-prequalification variations approved by the PQT/SRA and accompanied by the appropriate current quality information summary (QIS)/QIS-SRA(crp). All variations still pending at the PQT/SRA have to be notified, and deviations from the prequalified product have to be clearly declared in the expression of interest form (Appendix 3 Part A/Appendix 7 of the Procedure).
 - e. Additional, country specific requirements are: _____

2. A fee of _____ per product is charged for new applications considered under this procedure.

In situations where the applicant wishes to apply the Procedure to an application that is already pending with [*name of the NRA*], the applicant should first update the dossier to ensure that the technical part of the information is the same as that currently approved by the PQT/SRA, as applicable.

The post-prequalification variations should be submitted to [*name of the NRA*] within 30 days from the PQT/SRA approval. The PQT/SRA approval letter should be attached.

In case of questions/requests related to the CRP, the [*name of the NRA*] focal person’s contact information is as follows: [*name of the NRA focal person for the CRP and their contact information*].

Appendix 2

Verification for product submitted under the WHO collaborative procedure

Note [instructions on using the template]: This template is provided for verification of products to be registered nationally through the WHO collaborative procedure for prequalified products, or products approved by reference stringent regulatory authorities (SRAs). National regulatory authorities (NRAs) are free to modify the template as they deem fit, to suit their specific requirements.

1. Product details

Dossier aspects to verify	
Proprietary product name	
International Nonproprietary Name (INN) of the active pharmaceutical ingredient (API)/ drug substance, strength, pharmaceutical form	
Applicant	
Date of application	
Application number (assigned by NRA)	
Type of product/registration	
Reference authority	
Declaration from the applicant	

2. Product quality

Dossier aspects to verify	Comments (including confirmatory statements of sameness)
Marketing status in reference SRA or WHO prequalification status	
Name and complete address of the applicant	
Name and complete address (including specific unit/blocks) of the API/drug substance manufacturer(s)	

Table *continued*

Dossier aspects to verify	Comments (including confirmatory statements of sameness)			
Name(s) and complete address(es) (including specific unit/blocks) of the manufacturer(s) of the finished pharmaceutical product(s) [FPP(s)] or biological drug products(s) (DP(s)), including the final product release if different from the manufacturer				
Description (visual appearance)				
Composition	Component and quality standard	Function	Quantity per unit (mg)	%
	Total			
Specifications for the finished product				
Container closure system (including pack sizes, container size or volume)				
Stability summary and conclusions (including the storage statement and shelf-life)				
Lot/batch-release documents				
Assessor's comments on the product quality				

3. Product information

Dossier aspects to verify	Comments
Is the information for the health-care professional provided as approved by the reference SRA or WHO Prequalification Team (PQT)?	
Is the information for the patient/user (patient information leaflet) provided as approved by the reference SRA or PQT?	
The information does not contradict national therapeutic guidelines	
Assessor's comments on the product information	

4. Labelling

The following minimum information appears on the label:

Dossier aspects to verify	Comments
Is the labelling of outer packaging (as final packaging or mock-up presentation) provided as approved by the reference SRA or PQT?	
Additional information on outer packaging as per national requirements	
Is the labelling of internal packaging (as final packaging or mock-up presentation) provided as approved by the reference SRA or PQT?	
Additional information on internal packaging as per national requirements	
Assessor's comments on the product labelling	

5. Applicant commitments to the WHO Prequalification Team or reference stringent regulatory authority

State any commitments by the applicant to WHO or to the reference SRA that may require follow up.

Examples:

- The applicant undertook to continue long-term testing of [*INN of API*] for a period of time sufficient to cover the whole provisional retest period [*period ending month/year*].

- The applicant undertook to continue long-term testing of [*FPP reference number, trade name [INN of API], strength, pharmaceutical form*] for a period of time sufficient to cover the whole provisional shelf-life [*period ending month/year*].
- The applicant committed that three consecutive production batches would be prospectively validated and a validation report – in accordance with the details of the validation protocol provided in the dossier – would be made available as soon as possible, for evaluation by assessors or for verification by the WHO inspection team.

6. General national regulatory authority review comments

7. Assessment of responses to [*list of questions/list of outstanding issues/request for supplementary information*]

For each question:

Question:

Response from the applicant:

Assessment of response:

Appendix 3

Abridged/abbreviated review for product submitted under the WHO collaborative procedure

Note [instructions on using the template]: This template is provided as a recommended approach including a combination of the verification and abridged review of products to be registered nationally through the WHO collaborative procedure for prequalified products, or products approved by reference stringent regulatory authorities (SRAs). National regulatory authorities (NRAs) are free to modify the template as they deem fit, to suit their specific requirements. The assumption is that the NRA has access to the final assessment outcomes from WHO or the reference SRA in the form of assessment and inspection reports, including the quality information summary (QIS), to facilitate the abridged review. This template does not cover situations where the NRAs have no access to this confidential information in order to enable the verification of the specific product quality-related outcomes from WHO or the reference SRA. The different sections, for example, quality, clinical, product information and labelling, as well as risk management plans (RMPs), may be separated into different templates, especially where different teams/disciplines are involved in the review process.

1. Product details

Dossier aspects to verify	
Proprietary product name	
International Nonproprietary Name (INN) of the active pharmaceutical ingredient (API) or drug substance, strength, pharmaceutical form	
Applicant	
Date of application	
Application number (assigned by NRA)	
Type of product/registration	
Reference authority	
Declaration from the applicant	

2. Product quality

Dossier aspects to verify	WHO Prequalification Team (PQT) or reference SRA submission	NRA submission	Comments
Name and complete address of the applicant			
Name(s) and complete address (including specific blocks/units) of the manufacturer(s) of the finished pharmaceutical product(s) [FPP(s)] or biological drug products(s) (DP(s)), including the final product release if different from the manufacturer			
Drug substance or active pharmaceutical ingredient (name, manufacturer)			
Name of API/drug substance			
General properties that may affect the performance of the finished product (for example, polymorphism, solubility in physiological media)			

Table *continued*

Dossier aspects to verify	WHO Prequalification Team (PQT) or reference SRA submission	NRA submission	Comments
Name and address(es) (including specific blocks/units) of the manufacturer(s) of the API(s)/drug substance			
Control of the API/drug substance (including the specification reference number, version and date – the copy of the specification may be included as an attachment to the report)			
Analytical procedures (including the analytical procedure reference number, version and date – the copy of the analytical procedure may be included as an attachment to the report)			
Container closure system			

Table continued

Dossier aspects to verify		WHO Prequalification Team (PQT) or reference SRA submission				NRA submission				Comments
Stability summary and conclusions (including storage statement and re-test period)										
Finished pharmaceutical product (FPP)/drug product (DP)										
Description										
Composition	Component and quality standard	Function	Quantity per unit (mg)	%	Component and quality standard	Function	Quantity per unit (mg)	%		
	Total				Total					

Table continued

Dossier aspects to verify	WHO Prequalification Team (PQT) or reference SRA submission		NRA submission		Comments
Manufacturer (name, address (including specific block/unit) and responsibility)					
Commercial batch size and batch formula	Proposed commercial batch size(s) (for example, number of dosage units)		Proposed commercial batch size(s) (for example, number of dosage units)		
	Component and quality standard (and grade, if applicable)	Quantity per batch (kg/batch)	Component and quality standard (and grade, if applicable)	Quantity per batch (kg/batch)	
	Total		Total		

Table *continued*

Dossier aspects to verify	WHO Prequalification Team (PQT) or reference SRA submission	NRA submission	Comments
Narrative description of the manufacturing process (no need to compare the whole manufacturing process – one can just look at the blank master production document reference number, version and date, together with information on the site)			
Control of FPP/DP (state the specification reference number, version and date – a copy of the specification may be included as an attachment to the report)			
Analytical procedures (including the analytical procedure reference number, version and date-- a copy of the analytical procedure may be included as an attachment to the report)			

Table *continued*

Dossier aspects to verify	WHO Prequalification Team (PQT) or reference SRA submission	NRA submission	Comments
Container closure system (including pack sizes, container size or volume)			
Stability summary and conclusions (including the storage statement and shelf- life)			
Lot/batch-release documents			
Assessor's comments on the product quality			

3. Clinical safety and efficacy

Pharmacokinetic/safety/efficacy-related information used for PQT or reference SRA approval		
Type of study	"X" in appropriate box	Comparator product, where applicable
Bioequivalence/comparative pharmacokinetics		
Biowaiver based on Biopharmaceutics Classification System (BCS) biowaiver		
Additional strength biowaiver		
Clinical data		
Comparative pharmacodynamic and potential immunogenicity (for biologicals)		
Other (please specify)		
Assessor's comments on pharmacokinetic/safety/efficacy-related information		

Bioequivalence/comparative pharmacokinetics			
Dossier aspects to verify	PQT or reference SRA submission	NRA submission	Comments
Study #			
Study title			
Clinical facility (or the contract research organization)			

Table *continued*

Bioequivalence/comparative pharmacokinetics			
Dossier aspects to verify	PQT or reference SRA submission	NRA submission	Comments
Bioanalytical laboratories			
Number of patients/ volunteers			
Test product (name, manufacturer, batch number, batch size, location of multipoint dissolution data in physiological media and release media, if different)			
Reference product (name, manufacturer, source, batch number, expiry date)			
Results (geometric ratio and the 90% confidence intervals for the PK parameters)			
Assessor's comments on bioequivalence/ comparative pharmacokinetics			

Relevant clinical studies			
Dossier aspects to verify	PQT or reference SRA submission	NRA submission	Comments
Study ID			
Number of study centres/ locations			
Design			
Study posology			
Study objective			
Subjects by arm entered/ completed			
Duration			
Population included in the study (age, sex, ethnicity, severity of disease)			
Diagnosis including criteria			
Primary endpoint			
Assessor's comments on relevant clinical studies			

4. Clinical data

Note: The benefit–risk profile of SRA-approved products in other markets could differ, as their use in other markets is not always considered in the SRA review process. In this respect, the SRA assessment does not always confirm the availability of data and questions that are relevant for use in other environments. For this reason, the SRA assessment reports can be considered incomplete. Therefore, the NRA has to address this local context or suitability in a local environment as part of the review process under the WHO collaborative registration procedure (CRP).

Product information	Comments
Proprietary product name	
International Nonproprietary Name (INN) of the API/drug substance, strength, pharmaceutical form	
Chemical class (new molecular entity [NME]/therapeutic biological product, existing APIs/drug substance, new salt or ester, new dosage form, new combination product, amongst others)	
Pharmacological class	
Proposed indications, dosing regimens, age groups (confirm whether these are the same as approved by the reference SRA, WHO guidelines or national treatment guidelines)	
Existing alternatives to the proposed product for the same indication(s)	
Clinical pharmacology	
Justification for the dose/dose regimen (in the target population)	
Absorption, distribution, metabolism and excretion (ADME) (applicability in the target population, e.g. the pharmacokinetic effects of drug-demographic and drug-disease interactions, such as, renal impairment, hepatic impairment, should be described)	
Interaction studies (food and drug/drug interactions relevant for target countries that are not discussed in the SRA assessment report)	

Table *continued*

Product information	Comments
Pharmacodynamics	
Statistical methods for additional analysis, such as subgroup analyses and adjusted analyses	
Benefit–risk analysis	
Relevance of studied population for the target population (ethnicity, gender representation, age groups, etc.) as regards demonstration of safety and efficacy	
Relevance of SRA-approved conditions of use (proposed indications, dose and directions of use) as regards epidemiology and disease pattern in the target countries, as well as other implications for efficacy and safety, for example, feasibility of monitoring and precautionary measures (such as, microbial resistance testing or therapeutic drug monitoring) (applicants should have evaluated the effects of major demographic factors [e.g. age, sex, and race] and other predefined or relevant intrinsic and extrinsic factors on efficacy [such as, disease severity, prior treatment, concomitant illness, concomitant drugs, body weight, genetic variants, renal or hepatic impairment, microbial resistance]; regional differences may need to be considered with respect to multinational clinical trials)	
The adequacy of the directions for use	
The therapeutic role of a product and its recommended use according to relevant national and international treatment guidelines	
Other related quality issues, including but not limited to, storage conditions and conditions of administration and use	
Assessor's comments on clinical data	

5. Risk management plans

Note: The benefit–risk profile of SRA-approved products in other markets could differ, as their use in other markets is not always considered in the SRA review process. In this respect, the SRA assessment does not always confirm the availability of data and questions that are relevant for use in other environments. For this reason, the SRA assessment reports can be considered incomplete. Therefore, the NRA has to address this local context or suitability in a local environment as part of the review process under the WHO collaborative registration procedure (CRP).

Product overview	Comments
Proprietary product name	
International Nonproprietary Name (INN) of the API/drug substance, strength, pharmaceutical form	
Chemical class (new molecular entity (NME)/therapeutic biological product, existing API (generic) or similar biotherapeutic product, new salt or ester, new dosage form, new combination product, amongst others)	
Pharmacological class	
Proposed indications, dosing regimens, age groups (confirm whether these are the same as approved by the reference SRA, WHO guideline or national treatment guidelines)	
Risk management plan (RMP) was provided with the submission	
Epidemiology of the indications and target population (relevance of the clinical trial population to the intended target population [inclusions, exclusions, limited numbers, trial setting, use in special populations])	
Assessment of identified and potential risks (inclusion of all important risks related to the active substance, formulation, route of administration, target population, specific subpopulations and the potential for interaction from the safety specifications)	

Table continued

Product overview	Comments
Summary of planned pharmacovigilance activities (including post-authorization safety studies) (ongoing and planned studies in the post-authorization pharmacovigilance development plan in the target population)	
Plans for post-authorization efficacy studies (if applicable)	
Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)	
To what extent does the RMP approved by the reference SRA and applicant's commitments reflect the local situation or needs?	
Summary of the RMP	
Assessor's comments on the RMP	

6. Product information

6.1 Information for health-care professionals and corresponding sections of the patient information leaflet

Note: The patient information leaflet (PIL) should fully mirror the information for health-care professionals in a user-friendly language and style. The review of the product information should take into account the local context, especially in cases where this was not accounted for in the reviews by the reference SRA. Moreover, WHO prequalification product information is specific to the expressions of interest (EOIs), that is, only taking into account the specific therapeutic indication in the EOI, while the NRA may consider broader therapeutic indications and national treatment guidelines.

Dossier aspects to verify	Comments
Is the information for the health-care professionals provided as approved by the reference SRA or PQT?	
Is the information for the patient/user (PIL) provided as approved by reference the SRA or PQT?	

Table *continued*

Dossier aspects to verify	Comments
Does the information contradict national therapeutic guidelines?	
Assessor's comments on the product information	

6.1 Labelling

The following minimum information appears on the label:

Dossier aspects to verify	Comments
Is the labelling of outer packaging (as final packaging or mock-up presentation) provided as approved by the reference SRA or PQT?	
Additional information on outer packaging as per national requirements	
Is the labelling of internal packaging (as final packaging or mock-up presentation) provided as approved by the reference SRA or PQT?	
Additional information on internal packaging as per national requirements	
Assessor's comments on the product labelling	

7. Applicant commitments to the WHO Prequalification team or reference stringent regulatory authority

State any commitments by the applicant to WHO or to the reference SRA that may require follow up.

Examples:

- The applicant undertook to continue long-term testing of [*INN of API*] for a period of time sufficient to cover the whole provisional retest period [period ending month/year].
- The applicant undertook to continue long-term testing of [*FPP reference number, trade name [INN of API], strength, pharmaceutical form*] for a period of time sufficient to cover the whole provisional shelf-life [period ending month/year].

- The applicant committed that three consecutive production batches would be prospectively validated and a validation report – in accordance with the details of the validation protocol provided in the dossier – would be made available as soon as possible for evaluation by assessors or for verification by the WHO inspection team.

8. General national regulatory authority review comments

9. Assessment of responses to [list of questions/list of outstanding issues/request for supplementary information]

For each question:

Question:

Response from the applicant:

Assessment of response:

Appendix 4

Additional information to be included in the screening checklist

Note [instructions on using the template]: This template only provides additional considerations during screening which is specific to the WHO collaborative procedure (hereinafter referred to as “the Procedure”). The assumption is that the national regulatory authority (NRA) has a standard dossier screening checklist to ensure a valid submission is provided by the applicants. This template provides additional considerations to assist the NRA in determining the suitable registration pathway and assessment level/type.

Dossier/product information
Dossier application/screening number
Applicant
Submission date
International Nonproprietary Name, strength, dosage form

Screening details

Description	Yes/no	Comments
Has the applicant submitted the applicable expression of interest (that is, cover letter and/or applicable appendices) for the Procedure?		
Has the applicant submitted a valid marketing authorization/registration data/prequalification letter from <i>(cross out where not applicable)</i> : • WHO prequalification? • Reference stringent regulatory authority (SRA; specify)¹? • Any other country?		

¹ The reference SRA is the one whose registration the applicant would like to be considered as acceptable for reliance; for example, a product could be manufactured in country A but registered in country B. Country B NRA therefore becomes the reference SRA. In some regulatory cases, the reference SRA could be the NRA in the country of manufacture.

Table *continued*

Description	Yes/no	Comments
Has the Applicant submitted the quality information summary (QIS), as approved/endorsed by the reference authority or WHO (<i>cross out where not applicable</i>): - the QIS (for prequalified products)? - the QIS-SRA (crp)?		
Has the applicant submitted the full assessment reports from the reference authority or institution ² ?		
Has the applicant submitted the full inspection reports from the reference authority or institution ¹ ?		
Has the applicant submitted the product information (information for health-care professionals and information for the patient/user), as approved by the reference authority or institution?		
Has the applicant submitted a bridging report, or justification for exemption, as applicable?		
Has the applicant submitted the risk management plan, if applicable/required?		
Has the applicant submitted the public assessment and inspection reports from the reference authority or institution, if applicable?		

² This information is required for information but not for a decision on the validity of the submission. Absence of the assessment or inspection reports in the submission from the applicant/manufacture should not constitute a failed screening or invalid submission. For example, in the WHO Prequalification Team Collaborative Procedure, the assessment and inspection reports (unredacted) are shared directly between WHO and the NRA. This may apply for other reference authorities. Thus, in these cases, the applicant/manufacture are not in possession of the reports for submission to the NRA.

Appendix 5

Example of a national regulatory authority reliance model approach: information, documentary evidence and assessment activity

Pathway	Assessment approach	Documentary evidence (supporting documentation)	Example of products	Comments
Recognition	No scientific assessment	• Certificate of pharmaceutical product (CPP) from reference stringent regulatory authority (SRA) • Public assessment and inspection reports • Assessment and inspection reports	• Products prequalified by the World Health Organization (WHO) • National regulatory authority (NRA) may specify the NRA(s) or institutions whose decision it recognizes	CPP is not applicable for prequalified products Similarity between the local context important for this pathway/approach
Reliance				
a. WHO prequalification	Verification, or abridged reviews, secondary review, or a combination	• Signed agreements/consent • Quality information summary (QIS) • Assessment and inspections reports from the WHO Prequalification Team (PQT) • WHO public assessment reports and WHO public inspection reports (publicly available from the PQT website)	Products prequalified by WHO	NRAs to review the product information for consistency with local treatment guidelines and policies; information shared directly from WHO

Table continued

Pathway	Assessment approach	Documentary evidence (supporting documentation)	Example of products	Comments
b. Reference SRA (special access mechanisms)	Verification, or abridged reviews, or combination of both	• Signed agreements/consent • QIS-SRA(crp) – endorsed by SRA • SRA assessment reports inspection reports • Public assessment and inspection reports (publicly available)	Products with scientific opinion or similar decisions to facilitate access in low- and middle-income countries	Scientific opinions, or similar SRA decisions consider the use in target settings (outside the SRA market)
c. Reference SRA	Combination of verification and abridged review	• Signed agreements/consent • QIS-SRA(crp) – endorsed by SRA • Bridging report, if applicable • SRA assessment reports, inspection reports • Public assessment and inspection reports (publicly available)	Products approved by SRA and marketed in SRA market	Information may be shared by the applicant/manufacturer; SRA approvals do not necessarily consider use in other settings
d. Other reference NRAs	Abridged reviews	NRA assessment and inspection reports QIS-SRA(crp) (potential use if all stakeholders agree)	Products approved by NRAs recognized as reference by the NRA	Direct interaction between the NRAs; no WHO facilitation
Work-sharing/ joint reviews	Full assessment as primary reviewer or rapporteur, and secondary reviewer for other products	Primary assessment reports from rapporteur	All types of products, depending on the scope of the regulatory network	
Information-sharing	Full assessment and inspections	Memorandum of understanding (MoU) between NRAs for information sharing (non-binding)	All products in the scope of the MoU or agreements between the NRAs	

Appendix 6

Model acknowledgement or approval letter for variations of products registered through the WHO collaborative procedure

Application number _____

The Managing Director

[*Name of applicant*]

[*Address*]

[*Date*]

Attention: Regulatory Affairs Manager

Dear Sir/Madam,

I refer to the application dated [*date of application*] for variation of:

Proprietary name (trade name) _____

Approved generic name(s) _____

Strength(s) per dosage unit _____

Dosage form _____

Name of authorization holder* _____

[*Must be a person or legal entity in the country in which marketing is being authorized; this letter should normally be addressed to the marketing authorization holder]

Evaluation of the application has been completed following the WHO collaborative procedure (hereinafter referred to as the Procedure). Approval of the variation under [name of legislation] is granted, subject to the conditions in this letter and its attachments. This letter and its attachments constitute the approval. The date of approval is the date of this letter. In part, this approval relies upon your assurance that: **no variations have been made other than (i) those notified in this application; (ii) changes that are permitted without notification or prior approval according to the guidelines of [name of the reference authority or institution]; and (iii) the variation is as approved by [name of the reference authority or institution].**

The conditions that apply are as follows:

General conditions applying to all products

- The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence.
- The product(s) must conform to all the details as approved by [name of reference authority or institution] in line with the Procedure requirements.
- No further changes may be made to the product without prior approval, except for changes of the type listed in [name of reference authority or institution]'s policy on "Changes to pharmaceutical aspects of registered products that may be made without prior approval". The conditions in that policy apply.

[OPTION 1: *There is no objection to the concurrent supply of changed and unchanged product.*]

[OPTION 2: *The concurrent supply of the changed and unchanged product is considered unacceptable. You should use up all existing pre-variation stock before supplying the changed product.*]

Additional specific conditions applying to this product:

[For example, "All batches of the finished product must comply with a limit of 0.5% for Impurity A"]

[_____]

[_____]

If you have any doubt as to the meaning of this letter and its attachments, you should contact the undersigned prior to marketing the product.

Yours faithfully

[*Name*]

[*Signature*]

authorized person under [*name of legislation*]

7.3 Collaborative procedure between the World Health Organization (WHO) Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines

Annex 8, WHO Technical Report Series, 996, 2016

1. Definitions	988
2. Background information	988
3. Principles of collaboration	991
4. Steps in the collaboration for national registration of a pharmaceutical product or a vaccine	997
5. Collaboration mechanisms for post-prequalification and/or post-registration variations	1002
6. Withdrawals, suspensions or delistings of prequalified pharmaceutical products or vaccines and national deregistrations	1004
References	1004
Appendix 1 National regulatory authority participation agreement and undertaking for national regulatory authority focal point(s)	1005
Appendix 2 Consent of WHO prequalification holder for WHO to share information with the national regulatory authority confidentially under the Procedure	1015
Appendix 3 Expression of interest to national regulatory authority (NRA) in the assessment and accelerated national registration, acceptance by NRA and notification of Procedure outcomes	1018
Appendix 4 Report on post-registration actions in respect of a product registered under the Procedure	1026

1. Definitions

Collaborative procedure (Procedure)¹

Procedure for collaboration between the World Health Organization (WHO) Prequalification Team (WHO/PQT) and interested national regulatory authorities (NRAs) in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines.

Participating authorities or participating NRAs

NRAs that voluntarily agree to implement this collaborative procedure and accept the task of processing applications for registration of WHO-prequalified pharmaceutical products and vaccines in accordance with the terms of the Procedure. A list of participating authorities is posted on the WHO/PQT website at <https://extranet.who.int/prequal/medicines/accelerated-registration-prequalified-fpps>.

Pharmaceutical product

Any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in human beings, or with a view to making a medical diagnosis in human beings, or to restoring, correcting or modifying physiological functions in human beings.

Vaccine

A vaccine is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, one of its surface proteins or genetically-engineered material. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it and “remember” it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

2. Background information

National assessment of applications for registration of pharmaceutical products and vaccines (marketing authorization) is the key regulatory process that enables NRAs to

¹ Collaborative procedure between the World Health Organization (WHO) Prequalification of Medicines Programme and national medicines regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products appeared as Annex 4 (WHO Technical Report Series, No. 981, 2013).

evaluate and monitor the quality, safety and efficacy of pharmaceutical products and vaccines. For most countries the approach to registration of pharmaceutical products and vaccines is a combination of two components:

- the NRA's own assessment of application documentation combined with verification of compliance with relevant good practices by inspections (mostly focusing on good manufacturing practices (GMP) and inspections of manufacturing sites) and testing of product characteristics when applicable;
- consideration by the NRA of decisions and outcomes of assessments and inspections made by NRAs in other countries, and for vaccines also official batch release by the national control laboratory performing the oversight of the vaccines.

Consideration of the outcomes of assessments and inspections by authorities, whose regulatory decisions are based on acceptable standards, substantially contributes to savings in regulatory resources and improvements in the quality of regulatory decisions, while retaining the prerogative of NRAs to conclude their assessment by sovereign decisions, which reflect their own judgement of the benefit–risk balance as it relates to their specific country situation and the legislation in place. Taking into consideration the regulatory decisions of other NRAs requires setting up a system that will permit:

- identification of reference authorities whose regulatory decisions are based on acceptable standards and identification of documents associated with such regulatory decisions, which are relevant to the regulatory environment in the country wishing to rely on such decisions;
- assurance that the product for which the decision has been taken by the reference NRA is the same (see section 3.2) as the product being assessed or, if it is not the same, that a clear understanding exists of the differences between the products subjected to assessment in the two regulatory environments;
- efficient use of available scientific expertise and human and financial resources to decide, with reasonable certainty, on the benefit–risk profile of an evaluated product when used in a given country;
- the choice by each NRA of the approaches that will make best use of the resources, workload and competence of individual NRAs.

Approaches could range from completely independent data reviews and inspections to adoption of regulatory decisions of reference authorities without any further scientific review. A pragmatic approach is to verify whether the product submitted

for registration is the same (see section 3.2) as the product already prequalified and assess only those areas which relate to use of the product in the country concerned and where failure to comply with regulatory standards could pose health risks (e.g. stability data). In the other areas, the outcomes of reference authorities may be adopted.

To enhance timely access to prequalified products in countries, to ensure that the product in countries is the same as the one which is prequalified and to provide a model for regulatory information exchange among countries, this Procedure has been developed based on the above-mentioned considerations. In line with the *Procedure for prequalification of pharmaceutical products* (1) and the *Procedure for assessing the acceptability in principle of vaccines for purchase by United Nations agencies* (2) it aims to provide a convenient tool for NRAs wishing to enhance their premarketing evaluation and registration system by taking advantage of the scientific assessment work conducted by WHO/PQT. For pharmaceutical products the present procedure is complementary to the WHO/PQT collaborative procedure with NRAs in inspection activities (<https://extranet.who.int/prequal/inspection-services>).

The collaborative procedure was first piloted in June 2012 and is currently in use for pharmaceutical products (<https://extranet.who.int/prequal/medicines/collaborative-procedure-accelerated-registration>). For vaccines another procedure for expedited review of imported prequalified vaccines for use in national immunization programmes was published in 2007 and has been implemented for national registrations since 2010. However, this procedure did not include collaborative arrangements with the NRAs. In 2010 WHO/PQT piloted an expedited registration procedure that involved sharing of the WHO/PQT assessment reports with the NRAs.

Enhanced collaboration and information exchange between NRAs and WHO/PQT benefits all partners. Subject to the agreement of the WHO prequalification (PQ) holders concerned, NRAs have access to assessment outcomes that are not in the public domain and that have been prepared in conformity with the WHO recommended standards on which the *Procedure for prequalification of pharmaceutical products* (1) and the *Procedure for assessing the acceptability in principle of vaccines for purchase by United Nations agencies* (2) are based. Such reports and relevant WHO documents help NRAs to make their decisions and also assist in training national regulatory staff. At the same time, feedback from NRAs on the information and documentation received from WHO/PQT under the Procedure allows WHO/PQT to improve its work and ensures that the outcomes of its assessments are relevant to NRAs. As a consequence patients and vaccinees benefit from this collaboration by gaining faster access to pharmaceutical products and vaccines that have been found acceptable in principle for procurement by United Nations (UN) agencies. The collaborative registration procedure can be of particular relevance when implemented for pharmaceutical products and vaccines in emergency situations.

Depending on available resources, participating authorities have the opportunity to participate in the assessment process and in inspections organized by WHO/PQT.

This collaborative procedure also benefits manufacturers of prequalified pharmaceutical products and vaccines through faster and better harmonized regulatory approvals in participating countries. This Procedure, when combined with the WHO/PQT collaborative procedure with NRAs in inspection activities, alleviates the burden of additional national inspections on manufacturers.

3. Principles of collaboration

3.1 This collaborative procedure is applicable to:

- pharmaceutical products that have been assessed and inspected by WHO/PQT in line with the procedures and standards available at <https://extranet.who.int/prequal/medicines/manufacturers> and have been found to be acceptable in principle for procurement by UN agencies as listed in the *List of WHO prequalified medicines*, available at <https://extranet.who.int/prequal/medicines>. The Procedure is not applicable to pharmaceutical products that have been listed as prequalified on the basis of approval by stringent regulatory authorities (SRAs).² For such products the principal part of the assessment has been performed by SRAs and WHO/PQT is not in possession of assessment and inspection reports that can be shared;
- vaccines that have been assessed and inspected by WHO/PQT in line with the procedures and standards available at <https://extranet.who.int/prequal/vaccines> and have been found to be acceptable in principle for procurement by UN agencies as listed in the *List of WHO prequalified vaccines*, available at <https://extranet.who.int/prequal/vaccines>. This Procedure is applicable to vaccines that successfully passed either the standard or streamlined prequalification process.

Although the Procedure mostly serves to accelerate the assessment and registration of prequalified multisource (generic) pharmaceutical products it is applicable to vaccines and any pharmaceutical product for which the safety and efficacy has been documented to WHO/PQT by the submission of preclinical and clinical data.

² Products listed as prequalified according to the procedure described in the Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 5 (WHO Technical Report Series, No. 986).

The Procedure has three major stakeholders: WHO/PQT, interested NRAs and those WHO PQ holders or applicants³ who agree that this Procedure is used for applications for national registration of their WHO-prequalified product submitted to an NRA.

3.2 WHO/PQT and participating authorities receive applications for the same pharmaceutical product or vaccine. Within the context of this Procedure, the same pharmaceutical product or same vaccine is characterized by:

- the same product dossier;⁴
- the same manufacturing chain, processes, control of materials and finished product, and in the case of vaccines also by the same batch release scheme;
- the same active ingredient and finished product specifications;
- the same essential elements of product information for pharmaceutical products,⁵ in the case of vaccines by the same product information, packaging presentation and labelling.

3.3 WHO/PQT, with the agreement of the WHO PQ holder, shares the full outcome of prequalification assessments, inspections and, if relevant, also results of laboratory testing, including final assessment and inspection reports, with participating authorities, under appropriate obligations of confidentiality and restrictions on use (see below).

As regards sharing the outcomes of assessments, inspections and results of laboratory testing, only data owned by the WHO PQ holder and WHO are shared. Sharing of any other data (e.g. related to a closed part of the Active pharmaceutical

³ If the applicant for national registration is not the same as the WHO PQ holder, the WHO PQ holder must confirm to the NRA and WHO/PQT by an authorization letter (as per the template annexed to Appendix 3, Part A) that the applicant is acting for, or pursuant to rights derived from, the WHO PQ holder and that the WHO PQ holder agrees with the application of the procedure in the country concerned.

⁴ Submission of dossiers in common technical document (CTD) format as required by WHO/PQT is considered a standard. In exceptional situations data can be organized differently in line with specific national or WHO requirements; however, the technical data included in the dossier must be the same. There may be country-specific differences in administrative data, or if required by NRAs under exceptional circumstances, additional technical data can be provided (e.g. bioequivalence with a country-specific comparator).

⁵ The essential elements of product information include in particular the indications, contraindications, posology (dosing), special warnings and precautions for use, adverse reactions, storage conditions, primary packaging and shelf life. Differences in brand name, the name of applicant or WHO PQ holder, language, format and degree of detail of the product information, labelling of internal and external packaging, among others, are not considered essential for the purposes of this Procedure. The language of the product information may be different as long as the information content is the same as that approved by WHO/PQT.

ingredient master file) is subject to additional agreement of the data owners concerned.

- 3.4 For the purpose of this collaborative procedure, participating authorities accept the product documentation and reports in the format in which they are routinely prepared by WHO in accordance with the *Procedure for prequalification of pharmaceutical products* (1) and the *Procedure for assessing the acceptability in principle of vaccines for purchase by United Nations agencies* (2). It should be noted, however, that participating authorities may require applicants to comply with specific requirements for local regulatory review. Each participating authority should make such specific requirements public.
- 3.5 Fees to be paid by the applicants to participating authorities continue to follow standard national procedures. Similarly, the submission by manufacturers of samples for laboratory testing – if required – continues to follow standard procedures as defined in national legislation and/or as defined by NRAs. Participating authorities are advised to refrain from preregistration laboratory testing. Results from the laboratory testing organized in the course of prequalification assessment or inspections will be included in the information package available to each participating authority.
- 3.6 Consistent with the terms of Appendix 1, Part A and Appendix 3, Part B, each participating authority commits itself:
 - to treat any information and documentation provided to it by WHO/PQT pursuant to this Procedure as confidential in accordance with the terms of Appendix 1, Part A, and to allow access to such information and documentation only to persons⁶
 - who have a need to know for the purpose of the assessment and accelerated registration of the product in question in the country and any post-registration processes that may be required,
 - who are bound by confidentiality undertakings in respect of such information and documentation which are no less stringent than those reproduced in Appendix 1, Part A;
 - to issue its national regulatory decision on registration of a given prequalified product (whether positive or negative) within 90 calendar

⁶ This includes the focal point(s) and all other persons in the NRA who have access to any information and documentation provided by WHO/PQT.

days⁷ of regulatory time.⁸ If the applicant takes a long time to complete missing parts of the documentation without any justification, to provide additional data or to respond to other queries raised by NRAs, or if the applicant fails to provide the NRA with necessary information and cooperation, the NRA is entitled to terminate the Procedure and switch to the normal registration process. Such termination is communicated to the applicant and to WHO/PQT using Appendix 3, Part C.

These commitments are provided by each participating authority to WHO/PQT in writing by entering into the agreement for participation in this Procedure as reproduced in Appendix 1, Part A and are reconfirmed for each pharmaceutical product or vaccine for which collaboration is sought (see Appendix 3, Part B).

Each participating NRA nominates a maximum of three focal points and specifies their areas of responsibility (inspections, assessment of pharmaceutical products, assessment of vaccines). These focal points will access the restricted-access website through which WHO/PQT will communicate all confidential information and documentation. Upon justified request of an NRA to WHO/PQT, the number of focal points can be increased.

Focal points designated by the NRA must sign the undertaking reproduced in Appendix 1, Part B before they will be granted access to the restricted-access website. Any change in designated focal points must be communicated to WHO/PQT in writing without delay and must be accompanied by an undertaking (Appendix 1, Part B) signed by the new focal point(s).

- 3.7 The decision whether or not to register a given product in a particular country remains the prerogative and responsibility of each participating authority. Accordingly a participating authority may come to a different conclusion from that reached by WHO/PQT or can decide to discontinue the Procedure for a specific product. Within

⁷ Participating authorities should issue their national regulatory decisions at the earliest opportunity after being given access to the confidential information and documentation on a given prequalified product. Although a time limit of 90 days of regulatory time is defined in the Procedure, the decision should normally be taken within 60 days. This deadline can be extended to a maximum of 90 days if predefined dates of technical or decision-making meetings do not allow a participating authority to issue its decision within 60 days. If a participating authority does not issue its decision within 90 days of regulatory time and does not communicate valid reasons for the delay to WHO/PQT, WHO/PQT can follow up with the head of the NRA to clarify the situation. The timeline should be reduced as much as possible to facilitate access to products needed in case of emergency situations.

⁸ Regulatory time starts after a valid application for the registration according to the Procedure has been received and access to the confidential information has been granted (whichever is the later) and continues until the date of decision on registration. The regulatory time does not include the time granted to the applicant to complete missing parts of the documentation, provide additional data or respond to queries raised by NRAs.

30 calendar days of having taken its decision, the participating authority reports this decision to WHO/PQT, together with the dates of submission and registration and, if applicable, any deviations from the WHO/PQT's decision on prequalification and the reasons for such deviations⁹ and/or any decision to discontinue the Procedure for a specific product. It does so through the restricted-access website by completing the form in Part C of Appendix 3 or providing the same information in another format. The NRA provides a copy of the completed form or the information to the applicant.

- 3.8 Participation by WHO PQ holders/applicants is voluntary, through the submission to a participating NRA of the expression of interest reproduced in Part A of Appendix 3. For each product such participation will be subject to the WHO PQ holder/applicant accepting the terms of this Procedure, including the confidential exchange of information and documentation between WHO/PQT and the NRA (see Appendix 2).

The WHO PQ holder/applicant can cease participation in this Procedure at any time provided that he or she informs WHO/PQT and the participating NRAs in writing of his or her decision. In such a case the NRA shall cease all use of the information disclosed to it for the respective product(s) as per the terms of the participation agreement (see Appendix 1).

- 3.9 The requirements and procedures in case of a variation (as defined in WHO guidelines (3)) may differ between NRAs and WHO/PQT. The present collaborative procedure includes a variation procedure (see section 5) which is aimed at promoting consistency between variations accepted by WHO/PQT and variations accepted by participating authorities. There could be situations in which a manufacturer of a WHO-prequalified product submits a variation application to a participating authority and not to WHO/PQT or vice versa. In such a case the conditions of the national registration, which were initially "harmonized" with the WHO PQ decision, may become essentially different through the product life cycle. In such a case a product registered and procured in a participating country would no longer be the same as the WHO-prequalified product because the specifications, manufacturing sites and/or other essential parameters would no longer be the ones accepted by WHO/PQT. The WHO PQ holders/applicants and NRAs are expected to inform WHO/PQT of the differences and the reasons for them, if, due to inconsistencies in variations, the nationally-registered product is no longer the same as the WHO-prequalified product.

⁹ This refers to a decision not to approve the registration of a WHO-prequalified product and to a decision to approve the registration, but with deviations in indications, contraindications, posology (dosing), special warnings and precautions for use, adverse drug reactions, storage conditions and shelf life. For pharmaceutical products differences in brand name, name of applicant or WHO PQ holder, format of product information, level of detail of product information, labelling of internal and external packaging and language of product information are not considered to be deviations from the PQ conclusions.

As a result, applicants are required to submit to participating authorities without delay, at the latest 30 calendar days after acceptance of the variation by WHO/PQT, those variations which are subject to national regulatory requirements. WHO/PQT will inform the NRAs that have registered individual prequalified products, through the restricted-access website, about variations to the prequalification status of such products if and when regulatory action is deemed to be justified. Participating authorities are encouraged to follow the outcomes of the WHO variation procedures for nationally-approved WHO-prequalified products.

If a national variation procedure results in the nationally-registered product being no longer the same (see section 3.2) as the WHO-prequalified product, or in the event that a variation of a WHO-prequalified product is not followed by the same variation of the nationally registered product (in the case that the particular variation is subject to national regulatory requirements), the participating authority informs WHO/PQT of the situation by submitting the form in Appendix 4, clearly specifying the deviations. The deadline for informing WHO/PQT is 30 days after the NRA has been informed by WHO/PQT about variation outcome. The variation approved by WHO/PQT will be considered by WHO/PQT as accepted by the NRA on a non-objection basis 30 days after information-sharing, unless and until the NRA informs WHO/PQT otherwise. Other participating NRAs, which have registered the WHO-prequalified product in question pursuant to this Procedure, will be made aware of such deviations through the restricted-access website. In addition, if the fact that a WHO-prequalified product has been registered in a particular country pursuant to this Procedure has been made public, any subsequent deviations should also be made public.

- 3.10 If a prequalified product is withdrawn by the WHO PQ holder, or is suspended or delisted by WHO/PQT, WHO/PQT will inform each participating authority that has approved, or is in the process of reviewing the product pursuant to this Procedure, of the withdrawal, suspension or delisting and the reasons for taking this action, through the restricted-access website and subject to the obligations of confidentiality contained in Appendix 1, Part A. Similarly, when an NRA deregisters or suspends the registration of a prequalified pharmaceutical product or vaccine for any reason, it will inform WHO/PQT of this decision and of its reasons through the restricted-access website. Other participating NRAs which have registered the WHO-prequalified product in question pursuant to this Procedure will be made aware of such national deregistration or suspension through the restricted-access website. In addition, if the fact that a WHO-prequalified product has been registered in a country pursuant to this Procedure has been made public, any subsequent deregistration or suspension should also be made public by posting on the WHO/PQT website.

- 3.11 Participation in this Procedure does not exempt applicants for national registration and holders of national registration from the respective national regulatory requirements. Participating authorities retain the right to assess submitted data and organize site inspections to the extent they deem appropriate. WHO encourages NRAs not to perform repetitive assessment of thoroughly assessed data, but rather to focus on data verification so that they can be assured that the same product is submitted for registration as is prequalified. It is highly recommended not to reinspect the sites that have already been inspected by WHO/PQT inspection teams or by NRAs recognized by WHO as stringent and as functional with respect to inspections of vaccine manufacturing sites.
- 3.12 Sharing of information related to the Procedure between WHO/PQT, WHO PQ holders/applicants and NRAs is governed by Appendices 1, 2, 3 and 4. Completed Appendices 1 and 2 must be submitted to WHO/PQT without any change in their content. Provision of Appendices 3 and 4 can be substituted by provision of the same information by other means.

4. Steps in the collaboration for national registration of a pharmaceutical product or a vaccine

- 4.1 The applicant submits the product dossier for a WHO-prequalified pharmaceutical product or a vaccine to a participating NRA. The technical part of the dossier is updated to reflect the data as approved by WHO/PQT during the initial prequalification procedure, and consecutive variation procedures and requalification (where applicable). The applicant must provide the participating authority with:
- an application dossier complying with established national requirements, including the same technical information as that approved by WHO/PQT. To the extent that national regulatory requirements allow, the technical part of the dossier will be identical to the current version of the WHO/PQT dossier.¹⁰ In specific cases the NRA may prefer a dossier which is abbreviated in line with national requirements;
 - an expression of interest reproduced in Part A of Appendix 3;

¹⁰ In the case of vaccines that are prequalified by the “Streamlined procedure for vaccines with marketing authorization/licensing granted by eligible NRAs” (as defined in the *Procedure for assessing the acceptability, in principle, of vaccines, for purchase by United Nations agencies*. In: WHO Expert Committee on Biological Standardization: sixty-first report. Geneva: World Health Organization; 2013: Annex 6 (WHO Technical Report Series, No. 978)) the submitted data should reflect essential data submitted to the NRA that granted the authorization/licence and additional documents as provided to WHO.

- data and samples according to country-specific requirements;
- any fees that may be payable to the NRA pursuant to national requirements.

Wherever possible, to minimize the workload of the NRA and facilitate the process, applicants should ensure that they express their interest in using the Procedure (Appendix 3, Part A) to the NRA and to WHO/PQT before submitting a national application for registration. If acceptable to NRAs, not only should the technical content of the dossiers be the same, but also the format in which data are presented should closely follow the format in which dossiers are submitted to WHO/PQT, i.e. the common technical document (CTD) format. In the case of vaccines the product summary file format may be also applicable.

In situations where the applicant wishes to apply the Procedure to an application which is already pending within the NRA, the applicant should first update the dossier to ensure that the technical part of the information is the same as that approved by WHO/PQT.

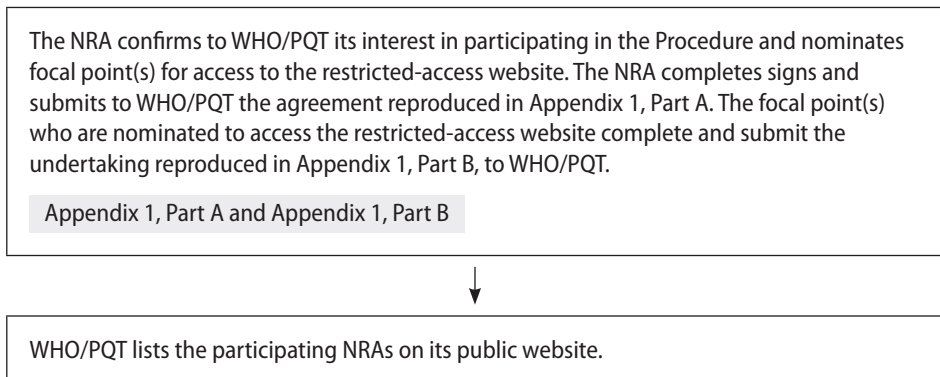
- 4.2 For each application under this Procedure, WHO/PQT is informed by the WHO PQ holder/applicant about the submission to the participating NRA by providing a completed copy of Appendix 3, Part A. The WHO PQ holder provides WHO at this time with its written consent for WHO/PQT to provide the product-related information in compliance with the applicable confidentiality requirements to the NRA of the country concerned (see Appendix 2).
- 4.3 The participating NRA informs WHO/PQT and the respective applicant of each application which it accepts or declines to include in this Procedure (Appendix 3, Part B). It is for the individual NRAs to decide whether to apply the Procedure for individual submissions. The Procedure applies only to applications that the NRA has accepted as complete.
- 4.4 Within 30 calendar days of receipt of the WHO PQ holder's consent, WHO/PQT shares the most recent product-related information and assessment, inspection and laboratory-testing outcomes through the restricted-access website with the participating authority. This information is subject to the obligations of confidentiality and restrictions on use and may include assessment report(s), variation assessment report(s) if applicable, inspection report(s) of the most recent inspection(s), the letter of prequalification or requalification and results of laboratory testing, if applicable. At the request of the participating authority, WHO/PQT provides explanations and/or more detailed information. If NRAs have significant concerns or questions which would preclude the registration of the prequalified pharmaceutical product or vaccine in their country, questions may be sent to WHO/PQT, preferably within 60 calendar days from the first

day of the regulatory time. WHO/PQT will facilitate the problem resolution in cooperation with relevant parties.

- 4.5 After receiving the information and documentation from WHO/PQT, the participating authority undertakes an accelerated assessment of the product in question. For each application, the participating authority is required to issue the relevant national decision within 90 calendar days of regulatory time.¹¹ Within 30 days of having taken its decision the participating authority reports this decision, together with an indication of the dates of submission, registration and, if applicable, the length of the non-regulatory time. The participating authority also reports any deviations from the WHO PQ conclusion and the reasons for such deviations, or, if a decision has been made to discontinue the Procedure for a product, the reasons for such discontinuation, to WHO/PQT through the restricted-access website. This report is provided to WHO/PQT using Part C of Appendix 3 and is copied to the applicant. WHO/PQT lists pharmaceutical products and vaccines registered according to this Procedure by participating NRAs on its public website. The steps in the collaboration for national registration of a pharmaceutical product or vaccine are summarized in Figure A8.1.

Figure A8.1

Flowchart showing the principal steps of the collaborative procedure



¹¹ See footnote 7.

Figure A8.1 *continued*

Registration process

The applicant submits the application for national registration of the WHO-prequalified pharmaceutical product or vaccine to the participating authority and informs the authority of its interest in following the Procedure by completing the expression of interest reproduced in Appendix 3, Part A. If the applicant for national registration is not the same as the WHO PQ holder, the WHO PQ holder confirms to the NRA and WHO/PQT by an authorization letter (as per the form annexed to Appendix 3, Part A) that the applicant is acting for, or pursuant to rights derived from, the WHO PQ holder and that the PQ holder agrees with the application of the Procedure in the country concerned.

Appendix 3, Part A



The WHO PQ holder/applicant informs WHO/PQT about the submission of its application to the NRA(s) (by providing a copy of completed Appendix 3, Part A) and, for each product and country, provides WHO/PQT with its written consent to share the product-related information and documentation, under confidential cover, with the participating authority. The WHO PQ holder completes and signs the consent form reproduced in Appendix 2 and submits it to WHO/PQT.

Appendix 2



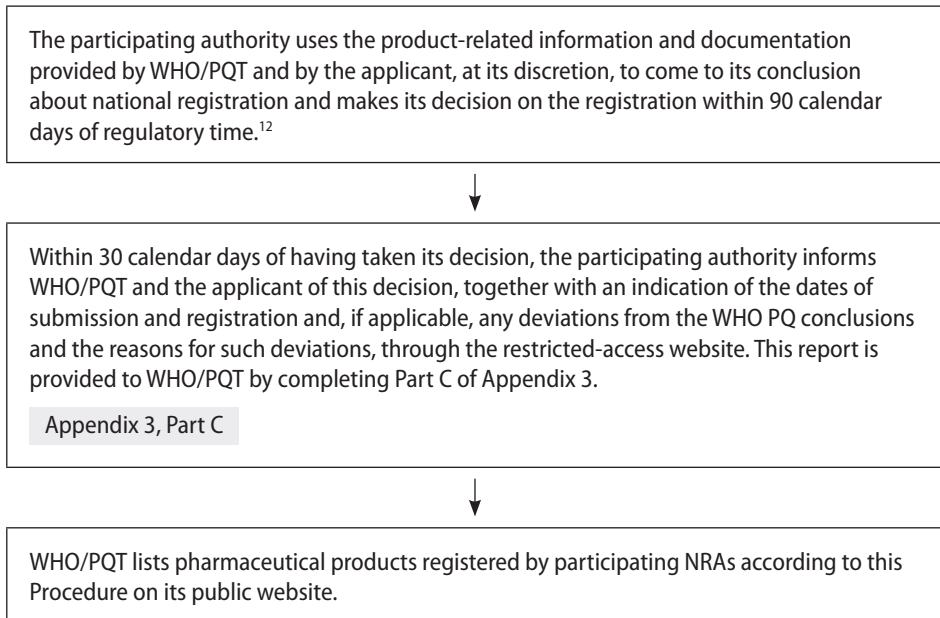
The participating authority informs WHO/PQT and the applicant of its consent to apply the Procedure to the application for registration of the product, on the understanding that the application is accepted as complete, or of its refusal by completing and signing Part B of Appendix 3.

Appendix 3, Part B

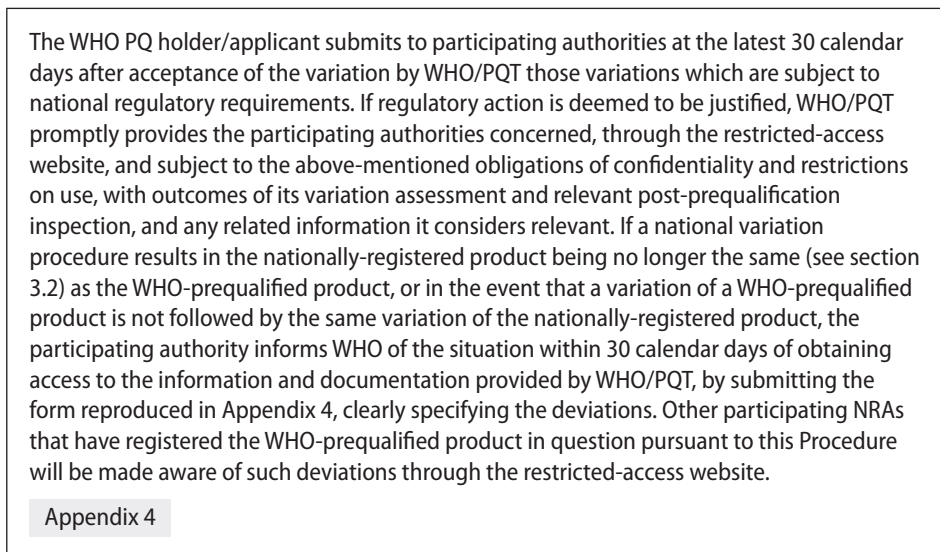


Within 30 calendar days of receipt of the WHO PQ holder's consent, WHO/PQT provides the participating authority with product-related information and documentation, and provides additional explanations, if requested, through the restricted-access website, and subject to the obligations of confidentiality and restrictions on use in place between WHO/PQT and the NRA.



Figure A8.1 *continued*

Post-registration processes



¹² See footnote 7.

Figure A8.1 *continued*

WHO/PQT informs the participating authority, through the restricted-access website, and subject to the above-mentioned obligations of confidentiality and restrictions on use, about withdrawals, suspensions or delistings of prequalified pharmaceutical products or vaccines. The participating authority informs WHO/PQT, through the restricted-access website, of national de-registration or suspension (for any reason) of a prequalified pharmaceutical product or vaccine and the reasons for doing so. Other participating NRAs which have registered the WHO-prequalified product in question pursuant to this Procedure will be made aware of such national de-registration or suspension, through the restricted-access website.

Appendix 4



WHO/PQT removes a product from the list published in line with this procedure:

- if the nationally-registered product is no longer the same (see section 3.2) as the WHO-prequalified product, or
- if the NRA deregisters a WHO-prequalified product, or
- if WHO/PQT delists a WHO-prequalified product.

WHO/PQT will also publish the reasons for the removal from the list.

5. Collaboration mechanisms for post-prequalification and/or post-registration variations

- 5.1 Those post-prequalification variations submitted to WHO/PQT, which are subject to national regulatory requirements, are expected to be submitted to any relevant participating authorities without delay at the latest 30 calendar days after acceptance of the variation by WHO/PQT. Submission of variations to NRAs should respect national regulatory requirements. Applicants for national variations should inform participating authorities that the same application for a variation is being processed by WHO/PQT.
- 5.2 WHO/PQT promptly shares the outcomes of variation assessment and of related post-prequalification inspection (if applicable), through the restricted-access website, and subject to the above-mentioned obligations of confidentiality and restrictions on use, with the relevant participating authorities, in all cases in which a variation (including “notification” according to WHO/PQT’s variation procedures (3)) requires regulatory action (e.g. where product quality, safety, efficacy or patient information materials are concerned).

Within 30 days of obtaining access to the information and documentation from WHO/PQT, each participating authority informs WHO/PQT through the restricted-access website if and to what extent a variation of a WHO-prequalified product is not followed by the same accepted variation of the nationally-registered product and, as a consequence, the nationally-registered product is no longer the same (see section 3.2) as the WHO-prequalified product. The variation approved by WHO/PQT will be considered by WHO/PQT as accepted by the NRA on a non-objection basis 30 days after information-sharing, unless and until the NRA informs WHO/PQT otherwise.

- 5.3 If a national variation procedure occurs independently of a variation submitted to WHO/PQT and results in the nationally-registered product being no longer the same (see section 3.2) as the WHO-prequalified product, the participating authority informs WHO/PQT within 30 days about the subject and outcome of this national variation procedure.
- 5.4 Deviations under 5.2 and 5.3 above may include change of source of active ingredients or starting materials, manufacturing sites, manufacturing process, product specifications, testing methods, storage conditions, shelf life, packaging material, indications, contraindications, posology (dosing), special warnings and precautions for use, adverse reactions and other changes specified in WHO/PQT guidelines (3). Differences in brand name, name of applicant or WHO PQ holder, format of product information, level of detail of product information, labelling of internal and external packaging and language of product information are not considered to be deviations from the conclusions during the prequalification of pharmaceutical products. For vaccines, such changes must be reported to WHO/PQT, which provides its opinion on the extent to which the difference represents deviation from conclusions during prequalification.
- 5.5 If a national variation procedure results in the nationally-registered product being no longer the same (see section 3.2) as the WHO-prequalified product, or if a variation of the WHO-prequalified product is not followed by a variation of the nationally-registered product and, as a consequence, the nationally-registered product is no longer the same, the WHO PQ holder will inform WHO/PQT of the differences and their reasons.
- 5.6 WHO/PQT removes a product from the list published in line with this Procedure if the nationally-registered product is no longer the same (see section 3.2) as the WHO-prequalified product.

6. Withdrawals, suspensions or delistings of prequalified pharmaceutical products or vaccines and national deregistrations

- 6.1 If a WHO-prequalified product is withdrawn by the WHO PQ holder, or if a product is suspended or delisted by WHO/PQT, WHO/PQT will promptly, through the restricted-access website, and subject to the above-mentioned obligations of confidentiality and restrictions on use, inform relevant participating authorities accordingly, providing the reasons whenever needed.
- 6.2 In the case that a participating NRA deregisters or suspends the registration of a prequalified pharmaceutical product or vaccine for any reason, the participating authority informs WHO/PQT of the decision (together with an indication of the reasons), through the restricted-access website. The information should be provided promptly whenever there are concerns about product quality, safety or efficacy and in all other cases within 30 days. A participating authority is encouraged to consult WHO/PQT before adopting a decision about deregistration or suspension of registration of a WHO-prequalified product.
- 6.3 In the case that a WHO-prequalified product is deregistered at the national level, or in the case that WHO/PQT delists a prequalified product, WHO/PQT adjusts the information about this product on its website accordingly.

References

1. Procedure for prequalification of pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 10 (WHO Technical Report Series, No. 961; https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1).
2. Procedure for assessing the acceptability, in principle, of vaccines, for purchase by United Nations agencies. In: WHO Expert Committee on Biological Standardization: sixty-first report. Geneva: World Health Organization; 2013: Annex 6 (WHO Technical Report Series, No. 978; https://iris.who.int/bitstream/handle/10665/89148/9789241209786_eng.pdf?sequence=1&isAllowed=y).
3. *For pharmaceutical products*: WHO guidelines on variations to a prequalified product. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013: Annex 3 (WHO Technical Report Series, No. 981; https://iris.who.int/bitstream/handle/10665/81144/WHO_TRS_981_eng.pdf?sequence=1&isAllowed=y), (and any updates thereto).

Appendix 1

National regulatory authority participation agreement and undertaking for national regulatory authority focal point(s)

Appendix 1, Part A

Agreement to participate in the collaborative procedure between the World Health Organization (WHO) Prequalification Team (WHO/PQT) and national regulatory authorities (NRAs) in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines

Details of NRA

Name of NRA: _____ (“the NRA”)

Postal address: _____

Country: _____ (“the Country”)

Telephone number (please include codes): _____

Email (please indicate contact details as appropriate for inclusion in the list of participating NRAs maintained on the WHO website): _____

Scope of agreement

Applicants for national registration of a particular WHO-prequalified pharmaceutical product or vaccine (hereafter referred to as “Applicants”) may express their interest to the NRA in the assessment and accelerated registration of this product (“the Product”) in the Country under the “Collaborative Procedure between WHO/PQT and NRAs in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products or vaccines” (hereafter referred to as “the Procedure”).¹

Subject to the NRA agreeing to conduct such assessment and consider such accelerated registration of the Product under the Procedure (by submitting the form reproduced in Part B of Appendix 3 attached to the Procedure to WHO/PQT through the restricted-access website), the NRA hereby confirms for each such Product that it will

¹ If the applicant for national registration is not the same as the WHO prequalification (PQ) holder, the WHO PQ holder must confirm to the NRA and to WHO/PQT by an authorization letter (as per the template annexed to Appendix 3, Part A) that the applicant is acting for, or pursuant to rights derived from, the WHO PQ holder, and that the WHO PQ holder agrees with the application of the Procedure in the country concerned.

adhere to, and collaborate with the WHO/PQT and the Applicant for registration of the Product in accordance with the terms of the Procedure.

Confidentiality of information

Any information and documentation relating to the Product and provided by WHO/PQT to the NRA under the Procedure may include but shall not necessarily be limited to:

- the full WHO/PQT assessment and inspection outcomes (reports) and if relevant, also results of laboratory testing;
- information and documentation on variations (as defined in WHO guidelines²), as well as information and documentation on any actions taken by WHO/PQT or NRAs post-prequalification of the Product;
- all such data, reports, information and documentation being hereinafter referred to as “the Information”.

As regards sharing the outcomes of assessments, inspections and laboratory testing, only data owned by the WHO PQ holder and WHO/PQT are shared. Sharing of any other data is subject to additional agreement of the data owners concerned.

WHO/PQT agrees to make such information available to the NRA through a restricted-access website exclusively for the purpose of the assessment and accelerated registration of the Product in the Country and any post-registration processes that may be required, in accordance with and subject to the terms of the Procedure (“the Purpose”). The NRA agrees to treat any Information provided by WHO/PQT as aforesaid as strictly confidential and proprietary to WHO/PQT, the WHO PQ holder/Applicant and/or parties collaborating with WHO/PQT and/or the WHO PQ holder/Applicant. In this regard, the NRA agrees to use such Information only for the Purpose and to make no other use thereof. Thus, the NRA undertakes to maintain the Information received from WHO/PQT in strict confidence, and to take all reasonable measures to ensure that:

- the Information received from WHO/PQT shall not be used for any purpose other than the Purpose;
- the Information shall only be disclosed to persons who have a need to know for the aforesaid Purpose and are bound by confidentiality undertakings in respect of such information and documentation which are no less stringent than those contained herein.

² For pharmaceutical products: WHO guidelines on variations to a prequalified product. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013: Annex 3 (WHO Technical Report Series, No. 981), (and any updates thereto).
For vaccines: <https://extranet.who.int/prequal/vaccines> (and any updates thereto).

The NRA warrants and represents that it has adequate procedures in place to ensure compliance with its aforesaid obligations.

The obligations of confidentiality and restrictions on use contained herein shall not cease on completion of the Purpose.

The obligations of confidentiality and restrictions on use contained herein shall not apply to any part of the Information which the NRA is clearly able to demonstrate:

- was in the public domain or the subject of public knowledge at the time of disclosure by WHO/PQT to the NRA under the Procedure; or
- becomes part of the public domain or the subject of public knowledge through no fault of the NRA; or
- is required to be disclosed by law, provided that the NRA shall in such event immediately notify WHO/PQT and the Applicant in writing of such obligation and shall provide adequate opportunity to WHO/PQT and/or the Applicant to object to such disclosure or request confidential treatment thereof (provided always, however, that nothing contained herein shall be construed as a waiver of the privileges and immunities enjoyed by WHO/PQT and/or as submitting WHO/PQT to any national court jurisdiction).

Upon completion of the Purpose, the NRA shall cease all use and make no further use of the Information disclosed to it under the Procedure, and shall promptly destroy all of the Information received from WHO/PQT which is in tangible or other form, except that the NRA may retain copies of the Information in accordance with its established archival procedures, subject always, however, to the above-mentioned obligations of confidentiality and restrictions on use. The Purpose for each product shall be deemed completed as soon as:

- the WHO PQ holder/Applicant discontinues participation in the Procedure for the particular product;
- the Product is deregistered by the NRA and/or delisted by WHO/PQT.

The access right of the NRA's focal point(s) to the restricted-access website will cease automatically upon the NRA ceasing to participate in the Procedure. If and as soon as an NRA focal point is replaced by a new focal point or ceases to be an employee of the NRA, such focal point's access to the restricted-access website shall automatically terminate.

The NRA agrees that it has no right in or to the Information and that nothing contained herein shall be construed, by implication or otherwise, as the grant of a licence to the NRA to use the Information other than for the Purpose.

Timelines

In respect of each Product that the NRA agrees to assess and consider for accelerated registration under the Procedure, the NRA undertakes to abide by the terms of the Procedure, including but not limited to the following timelines for processing each application:

- within 90 calendar days of regulatory time³ after obtaining access (through the restricted access website) to:
 - the data submitted to WHO/PQT for prequalification of the Product and owned by the WHO PQ holder,
 - the full WHO/PQT assessment and inspection outcomes (reports),
 the NRA undertakes to take a decision on the national registration of the Product;
- within 30 working days of the NRA's decision on national registration of the Product, the NRA undertakes to inform WHO/PQT of this decision and of any deviations from WHO conclusions during prequalification (with an indication of the reasons for such deviations) by completing and submitting the form attached as Appendix 3, Part C to the Procedure to WHO/PQT through the restricted-access website;
- if a national variation procedure results in the nationally-registered product being no longer the same⁴ as the WHO-prequalified product, or if and to the extent a variation of a WHO-prequalified product is not followed by a variation of the nationally-registered product and as a consequence, the nationally-registered product is no longer the same as the WHO-prequalified product, the NRA undertakes to inform WHO/PQT thereof (together with an indication of the reasons for such deviations) within 30 days of the conclusion of the national variation procedure or within 30 days of having received access to the information and documentation provided by WHO/PQT, as the case may be (i.e. by completing and submitting the form attached to the

³ Regulatory time starts after a valid application for the registration according to the Procedure has been received and access to the confidential information has been granted (whichever is the later) and continues until the date of decision on registration. The regulatory time does not include the time granted to the applicant to complete missing parts of the documentation, provide additional data or respond to queries raised by NRAs.

⁴ Within the context of this Procedure, the same pharmaceutical product/same vaccine is characterized by the same product dossier; the same manufacturing chain, processes and control of materials and finished product, in the case of vaccines also by the same batch release scheme; the same active ingredient and finished product specifications; and the same essential elements of product information for pharmaceutical products, in the case of vaccines by the same product information, packaging presentation and labelling.

Procedure as Appendix 4 to WHO/PQT through the restricted-access website);⁵

- the NRA undertakes to inform WHO/PQT in the case that the NRA deregisters or suspends the registration of the Product in the Country, by completing and submitting the form attached to the Procedure as an Appendix 4, to WHO/PQT through the restricted-access website, and to do so promptly if this decision is based on quality, safety or efficacy concerns, and within 30 days if this decision is based on other reasons.

Focal points for access to restricted-access website

The NRA has designated the person(s) listed below to act as focal point(s) for access to WHO/PQT's restricted-access website. The undertaking(s) completed and signed by the focal point(s) is (are) attached hereto as an Appendix to this agreement.

Any change in designated focal points must be communicated to WHO/PQT without delay in writing and will be subject to the new focal point having signed and submitted to WHO/PQT the undertaking reproduced in Appendix 1, Part B to the Procedure. The NRA also undertakes to inform WHO/PQT if and as soon as a designated focal point ceases to be an employee of the NRA.

Focal point for inspections

If applicable, this should be the same focal point as for the “WHO/PQT Collaborative Procedure with NRAs in inspection activities” (<https://extranet.who.int/prequal/inspection-services>). The same person should be designated for inspections of pharmaceutical products and vaccines.

1.

Mr/Ms/Dr

First name (and initials): _____

Surname/family name: _____

Title in NRA: _____

Email: _____

Telephone: _____

☐ A signed Undertaking is attached.

⁵ If the fact that a WHO-prequalified product has been registered in a country pursuant to this Procedure has been made public, any subsequent deviations should also be made public.

Focal point(s) for dossier assessment

For dossier assessment, different persons can be nominated for pharmaceutical products and vaccines. The same person may be nominated to be the focal point for inspections and dossier assessment. If additional person(s) are nominated for dossier assessment, please complete the details below.

2.

Mr/Ms/Dr _____ as a focal point for dossier assessment of

pharmaceutical products only ☐

pharmaceutical products and vaccines ☐

First name (and initials): _____

Surname/family name: _____

Title in NRA: _____

Email: _____

Telephone: _____

☐ A signed Undertaking is attached.

3.

Mr/Ms/Dr _____ as a focal point for dossier assessment of vaccines

First name (and initials): _____

Surname/family name: _____

Title in NRA: _____

Email: _____

Telephone: _____

☐ A signed Undertaking is attached.

Miscellaneous

The NRA agrees that WHO/PQT may list its name on the WHO/PQT website as a participant in the Procedure. Except as provided hereinbefore, neither party shall, without the prior written consent of the other party, refer to the relationship of the parties under this Agreement and/or to the relationship of the other party to the Product, the Information and/or the Purpose, in any statement or material of an advertising or promotional nature.

This Agreement shall not be modified except by mutual agreement of WHO and the NRA in writing. The NRA furthermore undertakes to promptly inform WHO/PQT of any circumstances or change in circumstances that may affect the implementation of this Agreement.

The parties shall use their best efforts to settle amicably any dispute relating to the interpretation or execution of this Agreement. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the parties or in the absence of agreement, with the UNCITRAL Arbitration Rules in effect on the date of this Agreement. The parties shall accept the arbitral award as final.

It is agreed furthermore that nothing contained in this Agreement shall be construed as a waiver of any of the privileges and immunities enjoyed by WHO under national and international law, and/or as submitting WHO to any national court jurisdiction.

Agreed and accepted for pharmaceutical products and vaccines.

For the NRA

Signature: _____

Name: _____

Title: _____

Place and date: _____

Attachments:

Signed Undertaking(s) of NRA focal point(s) (Appendix 1, Part B)

Appendix 1, Part B

Undertaking for NRA focal point(s)

The undersigned:

Mr/Ms/Dr

First name (and initials): _____

Surname/family name: _____

Title in NRA: _____

Name of NRA: _____ (“the NRA”)

Country: _____ (“the Country”)

Email: _____

Telephone: _____

Applicants for national registration of WHO-prequalified pharmaceutical products or vaccines (hereafter referred to as “Applicants”) may express their interest to the national regulatory authority (NRA) in the assessment and accelerated national registration of such products under the “Collaborative Procedure between the World Health Organization (WHO) Prequalification Team (WHO/PQT) and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines” (hereafter referred to as “the Procedure”).⁶

Subject to the NRA agreeing to conduct such assessment and consider such accelerated registration of a WHO-prequalified product under the Procedure, WHO/PQT will communicate confidential Information (as hereinafter defined) relating to each such product to the NRA, and the NRA will communicate outcomes of the national registration procedure and post-registration actions in respect of such products to WHO/PQT, through a restricted-access website, which can be accessed only by the focal points designated by the NRA, including the undersigned. For the purpose of accessing the restricted-access website and downloading Information and uploading reports in accordance with and subject to the terms of the Procedure, WHO/PQT will provide the undersigned with a secret access code. The undersigned undertakes to treat this access code as strictly confidential and not to disclose it to any other person whatsoever. The undersigned furthermore undertakes to take all precautionary measures that may be needed to prevent any other person whatsoever from obtaining the aforesaid secret access code and from accessing the restricted-access website (i.e. except for the other designated focal points who have signed this Undertaking).

⁶ If the applicant for national registration is not the same as the WHO PQ holder, the WHO PQ holder must confirm to the NRA and to WHO/PQT by an authorization letter (as per the template annexed to Appendix 3, Part A) that the applicant is acting for, or pursuant to rights derived from, the WHO PQ holder, and that the PQ holder agrees with the application of the Procedure in the country concerned.

“Information” as aforesaid means any information and documentation relating to a WHO-prequalified product to be provided by WHO/PQT to the NRA under the Procedure, including but not necessarily limited to:

- the full WHO/PQT assessment and inspection outcomes (reports) and if relevant, also results of laboratory testing;
- information and documentation on subsequent variations (as defined in WHO guidelines⁷), as well as information and documentation on any actions taken by WHO/PQT or NRAs post-prequalification of the Product.

As regards sharing the outcomes of assessments, inspections and results of laboratory testing, only data owned by the WHO PQ holder and WHO/PQT are shared. Sharing of any other data is subject to additional agreement of the data owners concerned.

The undersigned confirms that:

1. the NRA has bound him or her to obligations of confidentiality and restrictions on use no less stringent than those contained in Appendix 1, Part A to the Procedure; and that
2. the aforesaid obligations of confidentiality and restrictions on use shall not cease on completion of the assessment and accelerated registration of any product in the Country, nor on completion of any post-registration processes that may be required, nor on the undersigned ceasing to be an employee of (or ceasing to have another relationship with) the NRA.

The undersigned shall automatically cease having the right to access the restricted-access website when the NRA designates a new focal point to replace the undersigned or when the undersigned ceases to be an employee of the NRA.

This Undertaking shall not be modified except by mutual agreement of WHO and the undersigned in writing. The undersigned furthermore undertakes to promptly inform WHO/PQT of any circumstances or change in circumstances that may affect the implementation of this Undertaking.

The parties shall use their best efforts to settle amicably any dispute relating to the interpretation or execution of this Undertaking. In the event of failure of the latter the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the parties or in the absence of agreement, with the UNCITRAL Arbitration Rules in effect on the date of this Undertaking. The parties shall accept the arbitral award as final.

⁷ For pharmaceutical products: WHO guidelines on variations to a prequalified product. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013: Annex 3 (WHO Technical Report Series, No. 981), (and any updates thereto). For vaccines: <https://extranet.who.int/prequal/vaccines> (and any updates thereto).

It is agreed furthermore that nothing contained in this Undertaking shall be construed as a waiver of any of the privileges and immunities enjoyed by WHO under national and international law, and/or as submitting WHO to any national court jurisdiction.

Agreed and accepted by the undersigned:

Signature: _____

Name: _____

Title in NRA: _____

Place and date: _____

Appendix 2

Consent of WHO prequalification holder for WHO to share information with the national regulatory authority confidentially under the Procedure

Reference is made to the attached expression of interest in the assessment and accelerated national registration under the Procedure of the following World Health Organization (WHO) prequalified pharmaceutical product or vaccine (hereafter referred to as “the Product”) in _____ [country].¹

☐ pharmaceutical product

☐ vaccine

WHO prequalification details:

WHO prequalification (PQ) reference number: _____

Date of prequalification (dd/mm/yyyy): _____

Date of requalification (if applicable): _____

WHO PQ holder:² _____

Application details:

Name of entity: _____ (“the Applicant”)

Street: _____

City and country: _____

Email: _____

Telephone: _____

The WHO PQ holder hereby consents to the WHO Prequalification Team (WHO/PQT) providing the following information and documentation to the national regulatory authority (NRA) of _____ [country] (“the NRA”) for the assessment and accelerated registration of the Product in the country under the Procedure and to freely discuss the same with the aforesaid NRA for this purpose:

¹ Please complete a separate copy of this Annex for each country.

² If the applicant for national registration is not the same as the WHO PQ holder, the WHO PQ holder must confirm to the NRA and to WHO/PQT by an authorization letter (as per the template annexed to Appendix 3, Part A) that the applicant is acting for, or pursuant to rights derived from, the WHO PQ holder, and that the PQ holder agrees with the application of the Procedure in the country concerned.

- the full WHO/PQT assessment and inspection outcomes (reports), results of laboratory testing and, if relevant, also assessment and inspections reports of other regulatory bodies, provided that these bodies gave their written consent to the use of such reports for the purpose of the Procedure;
- information and documentation on subsequent variations (as defined in WHO guidelines³), as well as information and documentation on any actions taken by WHO/PQT post-prequalification of the Product;
- all such data, reports, information and documentation being hereinafter referred to as “the Information”.

As regards sharing the outcomes of assessments and inspections, only data owned by the WHO PQ holder and WHO/PQT are shared. Sharing of any other data is subject to additional agreement of the data owners concerned.⁴

Such consent is subject to the NRA having entered into an agreement with WHO/PQT as per Part A of Appendix 1 to the Procedure and having agreed to conduct the assessment and consider the accelerated registration of the Product under the Procedure, by having submitted the form reproduced in Part B of Appendix 3 to the Procedure to WHO/PQT.

The WHO PQ holder/Applicant commits to submit post-prequalification variations to WHO/PQT and any relevant participating authorities respecting national regulatory requirements. Variations should be submitted to participating authorities at the latest 30 calendar days after acceptance of the variation by WHO/PQT. Participating authorities should be informed about the fact that the same application for a variation is being processed by WHO/PQT. If a national variation procedure results in the nationally-registered product being no longer the same⁵ as the WHO-prequalified product, or if a variation of the WHO-prequalified product is not followed by a variation of the nationally-registered product and, as a consequence, the nationally-registered product is no longer the same, the WHO PQ holder/Applicant will inform WHO/PQT of the differences and their reasons.

³ *For pharmaceutical products:* WHO guidelines on variations to a prequalified product. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013: Annex 3 (WHO Technical Report Series, No. 981), (and any updates thereto).
For vaccines: <https://extranet.who.int/prequal/vaccines> (and any updates thereto).

⁴ In the case that certain data submitted to WHO/PQT by the WHO PQ holder in relation to PQ of the Product are not in his/her ownership, the WHO PQ holder specifies such data in an annex to this declaration of consent.

⁵ Within the context of this Procedure, the same pharmaceutical product/same vaccine is characterized by the same product dossier; the same manufacturing chain, processes and control of materials and finished product, and in the case of vaccines also by the same batch release scheme; the same active ingredient and finished product specifications; as well as the same essential elements of product information for pharmaceutical products, and, in the case of vaccines, by the same product information, packaging presentation and labelling.

For the WHO PQ holder

Signature: _____

Name: _____

Title: _____

Place: _____

Date (dd/mm/yyyy): _____

Appendix 3

Expression of interest to national regulatory authority (NRA) in the assessment and accelerated national registration, acceptance by NRA and notification of Procedure outcomes

Appendix 3, Part A

Expression of interest to the national regulatory authorities (NRAs) in the assessment and accelerated national registration of a World Health Organization (WHO)-prequalified pharmaceutical product or vaccine

In line with the Procedure, the undersigned Applicant¹ expresses its interest in the application of the above-mentioned Procedure by the NRA of _____ [country] (“the NRA”) in respect of the following submission for national registration:

- ☐ pharmaceutical product
- ☐ vaccine

Application details:

Name of entity: _____ (“the Applicant”)

Street: _____

City and country: _____

Email: _____

Telephone: _____

Date of application (dd/mm/yyyy): _____

Product name in national system (if known): _____

National reference number (if known): _____

¹ If the applicant for national registration is not the same as the WHO prequalification (PQ) holder, the WHO PQ holder must confirm to the NRA and to WHO/Prequalification Team (PQT) by an authorization letter (as per the template annexed to Appendix 3, Part A) that the applicant is acting for, or pursuant to rights derived from, the WHO PQ holder, and that the PQ holder agrees with the application of the Procedure in the country concerned.

Product details for pharmaceutical products:

Active pharmaceutical ingredient(s) (API(s)) (international nonproprietary name (INN)):

Dosage form and strength:

Packaging:

Manufacturing site(s), including block(s)/unit(s), if appropriate:

Product details for vaccines:Name of vaccine:

Composition:

Packaging:

Manufacturing site(s), including block(s)/unit(s), if appropriate:

WHO prequalification details:WHO PQ reference number:

Date of prequalification (dd/mm/yyyy):

WHO PQ holder:

The Applicant confirms that the information and documentation provided in support of the above-mentioned submission for national registration is true and correct, that the product submitted for national registration is the same² as the WHO-prequalified product and that the technical information in the registration dossier is the same³ as that approved by WHO/PQT during the initial prequalification procedure, and consecutive variation procedures and requalification (where applicable). Minor differences⁴ from the

² Within the context of this Procedure, the same pharmaceutical product/same vaccine is characterized by the same product dossier; the same manufacturing chain, processes and control of materials and finished product, and in the case of vaccines also by the same batch release scheme; the same active ingredient and finished product specifications; as well as the same essential elements of product information for pharmaceutical products, and, in the case of vaccines, by the same product information, packaging presentation and labelling.

³ Only the technical data included in the dossier must be the same. There may be country-specific differences in administrative data, or if required by NRAs under exceptional circumstances, additional technical data can be provided (e.g. bioequivalence with a country-specific comparator).

⁴ As defined in section 3.2 of the Procedure, in the case of pharmaceutical products, examples of minor differences which are not considered essential may include differences in administrative information, brand name, name of applicant (provided that the applicant is acting for, and has the authority to represent the WHO PQ holder), format of product information, level of detail of product information, labelling of internal and external packaging and language of product information.

information submitted to WHO/PQT are the following: _____

Subject to the NRA agreeing to conduct the assessment and consider the accelerated registration of the Product under the Procedure, the Applicant:

1. undertakes to adhere to, and collaborate with the NRA and WHO/PQT in accordance with the terms of the Procedure; and
2. will authorize WHO/PQT⁵ to provide the NRA confidential access to the following information and documentation and to freely discuss the same with the aforesaid NRA for the above-mentioned Purpose:
 - the full WHO/PQT assessment and inspection outcomes (reports), results of laboratory testing and if relevant, also assessment and inspections reports of other regulatory bodies, provided that these bodies gave their written consent to the use of such reports for the purpose of the Procedure,
 - information and documentation on subsequent variations (as defined in WHO guidelines⁶), as well as information and documentation on any actions taken by WHO/PQT post-prequalification of the Product.

As regards sharing the outcomes of assessments and inspections, only data owned by the WHO PQ holder and WHO are shared. Sharing of any other data is subject to additional agreement of the data owners concerned.

3. authorizes the NRA to freely share and discuss all registration-related and Product-related information provided by the Applicant to the NRA, with WHO/PQT, subject to the obligations of confidentiality and restrictions on use as contained in the NRA's participation agreement and focal points' undertakings.

⁵ If the applicant for national registration is not the same as the WHO PQ holder, then the authorization to WHO/PQT must be provided by the WHO PQ holder or their legal representative.

⁶ *For pharmaceutical products*: WHO guidelines on variations to a prequalified product. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013: Annex 3 (WHO Technical Report Series, No. 981), (and any updates thereto).
For vaccines: <https://extranet.who.int/prequal/vaccines> (and any updates thereto).

- ☐ The application for national registration was submitted before the Applicant decided to apply the Procedure to the Product and therefore at the time of submission the registration dossier did not respect conditions of the Procedure. Steps taken to update the submission to the NRA to make the dossier “the same” as required by the Procedure are listed and referenced in the attached letter.
- ☐ The Applicant is not the WHO PQ holder. An authorization letter from the WHO PQ holder is attached.

For the Applicant

Signature: _____

Name: _____

Title: _____

Place: _____

Date (dd/mm/yyyy): _____

Template for authorization letter

[To be provided if the applicant is not the WHO PQ holder. Please provide a separate letter for each NRA concerned, with a copy to WHO/PQT.]

This is to confirm that _____ (*name of applicant*) seeking registration for prequalified product number _____ (*WHO PQ number*) in _____ (*name of country*) under the WHO collaborative procedure for accelerated registration of WHO-prequalified products, is acting for, or pursuant to rights derived from _____ (*name of WHO PQ holder*) and that _____ (*name of WHO PQ holder*) agrees with the application of the Procedure in the country concerned.

For _____ (*name of WHO PQ holder*):

Signature: _____

Name: _____

Title: _____

Date: _____

Appendix 3, Part B

Decision on acceptance by the NRA to apply the Procedure to a specified WHO-prequalified product and request for access to product-specific information and documentation

Please complete all fields marked *. For other fields, if there have been changes to the details as completed in Part A, please complete the relevant fields below. Where fields below are left blank, the data in Part A are considered to be valid.

Application details:

Name of entity: _____ (“the Applicant”)

Street: _____

City and country: _____

Email: _____

Telephone: _____

*Date of receipt of submission (dd/mm/yyyy): _____

Product name in national system (if known): _____

*National reference number: _____

Product details for pharmaceutical products:

Active pharmaceutical ingredient(s) (API(s)) (international nonproprietary name (INN)):

Dosage form and strength: _____

Packaging: _____

Manufacturing site(s), including block(s)/unit(s), if appropriate: _____

Product details for vaccines:

Name of vaccine: _____

Composition: _____

Packaging: _____

Manufacturing site(s), including block(s)/unit(s), if appropriate: _____

WHO prequalification details:

*WHO PQ reference number: _____

Date of prequalification (dd/mm/yyyy): _____

WHO PQ holder: _____

Please complete either section A or section B below:

☐ **Section A**

The NRA agrees to conduct the assessment and the accelerated registration of the above-mentioned product ("the Product") under the Procedure and requests access to product-specific information, in accordance with and subject to the terms of the Procedure and the Agreement between WHO/PQT and the NRA dated ____ / ____ / ____ (dd/mm/yyyy).

☐ **Section B**

The NRA has decided not to apply the Procedure to the above-mentioned Product for the following reasons: _____

*For the NRA of _____ (indicate country)

Signature: _____

Name: _____

Title: _____

Place: _____

*Date (dd/mm/yyyy): _____

Appendix 3, Part C

Notification of outcomes of national registration procedure by the NRA

Product and application details as completed in Parts A and B above apply.

Please complete either section A or section B below:

☐ Section A

Registration has been granted under the terms of the Procedure, and the above-mentioned product ("the Product") is identified as follows in the national medicines register:

Name of the Product: _____

National registration number: _____

Date of registration (dd/mm/yyyy): _____

Non-regulatory time (days): _____

Product details (if different from those specified in Parts A and B):

Product details for pharmaceutical products:

API(s) (INN): _____

Dosage form and strength: _____

Packaging: _____

Manufacturing site(s), including block(s)/unit(s) if appropriate: _____

Product details for vaccines:

Name of vaccine: _____

Composition: _____

Packaging: _____

Manufacturing site(s), including block(s)/unit(s) if appropriate: _____

Registration holder (if different from the Applicant as specified in Parts A and B):

Name of entity: _____

Street: _____

City and country: _____

Email: _____

Telephone: _____

Are the national registration conclusions different from prequalification outcomes?⁷ _____ (yes/no)

If you answered yes to the above question, please specify:

Deviation	Reason

Please specify whether registration is subject to specific commitments, the registration is provisional or conditional, use of the Product is limited by specific prescribing restrictions, or additional clinical trials or additional data are required:

☐ **Section B**

Please complete as appropriate:

☐ The application for registration of the Product was rejected for the following reasons:

☐ The collaborative procedure was discontinued for this application for the following reasons: _____

For the NRA

Signature: _____

Name: _____

Title: _____

Place: _____

Date (dd/mm/yyyy): _____

⁷ This refers to deviations in indications, contraindications, posology (dosing), special warnings and precautions for use, adverse drug reactions, storage conditions and shelf life. For pharmaceutical products differences in brand name, name of applicant/PQ holder, format of product information, level of detail of product information, labelling of internal and external packaging and language of product information are not considered to be a deviation from the PQ conclusions.

Appendix 4

Report on post-registration actions in respect of a product registered under the Procedure

- ☐ Variation of the national registration resulting in the national registration conditions being inconsistent with the WHO/PQT prequalification conclusions
- ☐ Deregistration or suspension of the registration of the product

Product details:

Product name in national system: _____ (“the Product”)

National registration number: _____

Date of registration (dd/mm/yyyy): _____

WHO prequalification details:

WHO PQ reference number: _____

Date of prequalification (dd/mm/yyyy): _____

WHO PQ holder: _____

- ☐ The national variation procedure has resulted in the nationally-registered Product being no longer the same¹ as the WHO-prequalified product.

Deviation	Reason

¹ Within the context of this Procedure, the same pharmaceutical product/same vaccine is characterized by the same product dossier; the same manufacturing chain, processes and control of materials and finished product, and in the case of vaccines also by the same batch release scheme; the same active ingredient and finished product specifications; as well as the same essential elements of product information for pharmaceutical products, and, in the case of vaccines, by the same product information, packaging presentation and labelling.

- ☐ The variation notified to the NRA by WHO/PQT has not been followed by a variation of the nationally-registered Product and, as a consequence, the nationally-registered product is no longer the same¹ as the WHO-prequalified product.

Deviation	Reason

- ☐ The Product has been deregistered or the registration of the Product has been suspended.

Deregistration: _____ (yes/no)

suspension of registration: _____ (yes/no)

Effective date: ____ / ____ / ____ (dd/mm/yyyy)

Reasons:

For the NRA

Signature: _____

Name: _____

Title: _____

Place: _____

Date (dd/mm/yyyy): _____

7.4 Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities

Annex 11, WHO Technical Report Series, 1010, 2018

1. Background information	1030
2. Glossary	1031
3. Principles of collaborative procedure	1033
4. Medicines	1035
5. Collaboration mechanisms for management of post-registration variations	1041
Appendix 1 Agreement of the national regulatory authority to participate in the collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities	1045
Appendix 2 Example of information included in the list of participating reference stringent regulatory authority(ies)	1050
Appendix 3A Manufacturer's consent for information sharing with participating national regulatory authority(ies) and the World Health Organization	1054
Appendix 3B Manufacturer's request for stringent regulatory authority's (SRA's) permission for sharing SRA-owned non-public information with participating national regulatory authority(ies) and the World Health Organization	1056
Appendix 4 Quality information summary of the finished pharmaceutical product or vaccine approved by the reference SRA (QIS- SRA (crp))	1058
Appendix 5 Proposed documentation for collaborative procedure for reference SRA-approved pharmaceutical products and vaccines	1066
Appendix 6 Requirements for provision of a bridging report for reference SRA-approved pharmaceutical product and vaccines for consideration of registration in participating countries	1071

Appendix 7	Expression of interest to national regulatory authority	1073
Appendix 8	Confidential disclosure agreement	1076
Appendix 9	Notification of an outcome of the national registration provided by the participating manufacturer to the World Health Organization	1080

1. Background information

Management of diseases known to be of major relevance to public health in countries with limited regulatory resources is often jeopardized by delayed access to new or needed therapies. Although many medicines successfully pass a regulatory review process conducted by internationally respected regulatory bodies, also known as stringent regulatory authorities (reference SRAs), or may in addition have been prequalified by the World Health Organization (WHO), local regulatory approvals tend to consume additional time and resources of national regulatory authorities (NRAs) before these therapies can be made available to patients.

To address this issue, WHO proposes a scheme for NRAs and pharmaceutical manufacturers to facilitate registrations of the vaccines and pharmaceutical products, including biotherapeutic products approved by reference SRAs.¹ WHO recognizes the scientific evaluation of medicines by reference SRAs as they apply similarly stringent standards for quality, safety and efficacy to those recommended by WHO.

Based on WHO experience with the Collaborative procedure of WHO-prequalified pharmaceutical products and vaccines,² it is possible to facilitate and accelerate national registration processes by provision of detailed assessment and inspection outcomes generated by respected regulatory bodies.³ Assessment and inspection reports of reference SRAs made available in addition to the registration dossiers can facilitate the adoption of national regulatory decisions by assuring NRAs about the positive risk–benefit profile of a product and that its quality is identical with the product already approved elsewhere. Normally, publicly available versions of assessment and inspection outcomes do not provide all the necessary information in sufficient detail to enable regulatory decisions to be adopted. Therefore, detailed assessment and inspection outcomes that include commercially sensitive data must be shared. Whether to make such information sharing possible is up to interested pharmaceutical manufacturers, which should provide consent to information exchange among reference SRAs and NRAs, to which a product is submitted for regulatory approval. Pharmaceutical manufacturers benefit from accelerated and facilitated regulatory processes. For their part, it is up to interested NRAs to provide sufficient assurance that shared data will

¹ In addition to medicines approved by the conventional marketing authorization process, the Procedure is applicable to special “approval” mechanisms like the scientific opinion process according to Article 58 of Regulation (EC) No. 726/2004, in the European Union (EU).

² Collaborative procedure between the World Health Organization (WHO) Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 8 (WHO Technical Report Series, No. 996), 263–304.

³ Under the Collaborative procedure for WHO-prequalified pharmaceutical products and vaccines, the assessments and inspections are organized by WHO, although WHO cannot be considered as a regulatory body.

be treated with necessary care and respect for confidentiality. Nonetheless, in some jurisdictions, publicly available information such as public assessment or inspection reports, and databases of compliance with good manufacturing practices (GMP) contain substantial summarized regulatory information that can facilitate the decision-making process in less well-resourced NRAs as well.

It should be stressed that the decision to apply the process for specific medicines is up to the NRAs concerned, which retain the prerogative to conclude their assessment through sovereign decisions on medicine registration within their national jurisdiction. In addition to the facilitation of regulatory decisions on needed medicines and faster access to patients, the process also represents an avenue for harmonization of regulatory requirements and capacity-building.

The Procedure is applicable in principle to all types of medicines irrespective of whether the products are of an innovative or generic nature. The procedure is also applicable to biotherapeutic products and vaccines.

2. Glossary

For the purposes of this document, the following definitions and descriptions apply. They may have different meanings in other contexts.

biotherapeutic. A biological product with the indication of treating human diseases.

collaborative procedure of reference SRA-approved pharmaceutical products and vaccines (Procedure). Registration procedure in which assessment and national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities (reference SRAs) is facilitated and accelerated by sharing of detailed assessment and inspection outcomes generated by a reference SRA.

manufacturer. Any person or legal entity engaged in the manufacture of a product subject to marketing authorization or licensure; or any person or legal entity that is an applicant or holder of a marketing authorization or product licence where the applicant assumes responsibility for compliance with the applicable product and establishment standards.

medicine. Any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in human beings, or with a view to making a medical diagnosis in human beings, or to restoring, correcting or modifying physiological functions in human beings.

participating authority or participating national medicines regulatory authority. National regulatory authority (NRA) that voluntarily agrees to implement this collaborative procedure and accepts the task of processing applications for registration of medicines approved by reference SRAs in accordance with the terms of the Procedure. A list of participating authorities is posted on the WHO Prequalification Team (WHO PQT) website (<https://extranet.who.int/prequal/medicines/collaborative-procedure-accelerated-registration>).

participating manufacturer. A manufacturer, which is a holder of a marketing authorization granted by a reference SRA for a medicine that is intended to be submitted, has been submitted or has been granted national registration by participating NRAs in line with principles of the Procedure.

participating stringent regulatory authority. A reference stringent regulatory authority that agrees to provide outcomes of its regulatory expertise (especially assessment and inspection reports) to applicants/authorization holders or inspected manufacturers, does not object to sharing of these documents with national medicines regulatory authorities and provides, under specified conditions in line with the principles of the Procedure, support to other parties involved in the Procedure.

pharmaceutical product. Any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in human beings, or with a view to making a medical diagnosis in human beings, or to restoring, correcting or modifying physiological functions in human beings.

stringent regulatory authority.⁴ A regulatory authority which is:

- a) a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission,⁵ the US Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency (as before 23 October 2015); or
- b) an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before 23 October 2015); or
- c) a regulatory authority associated with an ICH member through a legally binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015).

vaccine. A biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, one of its surface proteins or genetically-engineered material. The agent stimulates the body's

⁴ Clarification with respect to the definition of stringent regulatory authority. See WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. Geneva: World Health Organization; 2017: (WHO Technical Report Series, No. 1003), pp 34–35; and WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. Geneva: World Health Organization; 2018 (WHO Technical Report Series, No. 1010), Section 10.1).

⁵ For the European Commission, products approved via the centralized procedure by the European Medicines Agency, decentralized procedure or mutual recognition in the European Union (EU) are eligible provided the respective NRA in the EU agrees to participate as a reference SRA in the Procedure.

immune system to recognize the agent as foreign, destroy it and “remember” it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

variation. A change to any aspect of a medicine, including but not limited to, the change of use of a starting material, a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labelling and product information.

3. Principles of collaborative procedure

Principles of the procedure (same product or defined deviations, available assessment and inspection outcomes, bridging information facilitating assessment of risk–benefit profile in new target environment, post-authorization variations and commitments in line with the SRA) are applicable to any regulated product. Nonetheless, there is a difference in the nature and scope of documents to be shared for different product categories. At present, the process is applicable to reference SRA-approved (innovative and generic medicines) and vaccines. Products approved through special mechanisms such as conditional marketing authorization or under exceptional circumstances are eligible for the procedure if there is a high unmet medical need of public health importance because access to the reference SRA assessment reports would help participating NRAs to understand the acceptability of the risk–benefit profile of such products.

Participation of all parties is voluntary and should be performed in compliance with relevant applicable legislation. All reference SRAs, NRAs and holders of marketing authorization for products considered to be therapeutically important by participating NRAs are welcome to participate. WHO plays a facilitating role in this process and in monitoring of its use and refinement of the details of the conditions.

The general approach is similar to the principles of Collaborative procedure of WHO-prequalified products in terms of information sharing, utilization of shared information, management of confidentiality and time frame. Instead of the WHO PQT, reference SRAs are the generators of the basic regulatory expertise in this procedure.

The dossiers submitted for national registration are organized in line with the globally harmonized common technical document (CTD) format to maximize use of data already submitted to reference SRAs. In the case of generic medicines, the technical part of the dossier is equivalent to the WHO PQT prequalification dossier requirements. The open part of the active pharmaceutical ingredient (API) master file is considered sufficient, unless the manufacturer is informed otherwise by the respective NRA. For innovative products (i.e. new drug applications (NDAs), biologicals licence applications for vaccines or self-standing applications) the submitted dossier consists of a rather simplified version of the reference SRA dossier (unless otherwise requested by the respective NRA) to reduce the volume of submissions to a manageable level, while including all data essential for national assessments. Such pragmatic simplification also

reduces the risk of unnecessary dissemination of highly sensitive commercial information and can make the process more acceptable for pharmaceutical manufacturers.

The key role in the process is assigned to the pharmaceutical manufacturers, which conduct the procedure and organize the provision of relevant regulatory information generated by reference SRAs to participating NRAs. The conditions under which individual reference SRAs agree to make available the assessment and inspection reports for this purpose have to be confirmed with each reference SRA. It is planned that WHO will summarize the positions of willing reference SRAs as regards the availability of assessment and inspection reports and post this information on its website, similarly to the list of NRAs that have agreed in principle to apply the piloted procedure. It is expected that the reference SRAs that issued the marketing authorization will provide a certain amount of support and cooperation, if necessary (e.g. authentication of submitted documents in case of doubt). In general, to save the resources of reference authorities, the role of reference SRAs in the proposed process is minimized.

It is up to the participating NRAs to recognize which individual medicines would be eligible for registration under this procedure, considering the relevance of the medicine concerned for public health and existing NRA capacity.

Confidentiality of shared data is assured by mechanisms applied by participating parties (NRAs, reference SRAs, manufacturers and WHO). Participating NRAs make a special commitment in the respect that any information and documentation provided to them by applicants and reference SRAs (possibly mediated by WHO) pursuant to this procedure will be treated as confidential and access to this information will be allowed only to persons involved in the individual registrations who are bound by confidentiality undertakings (Appendix 1). Authorities that make such a commitment and agree to apply the principles of the Procedure will be publicly listed by WHO.

After initiation of the Procedure, switching to the normal registration process is possible, provided that the parties involved inform each other of this decision.

3.1 Principal roles of the participating parties

Participating NRAs express their interest in participating in the Procedure, their commitment to respect the principles of the Procedure and their confirmation of confidential treatment of commercially sensitive information by forwarding to WHO a completed copy of Appendix 1 to this Procedure. A focal person for communication on issues relevant for the Procedure will be designated in each participating NRA. A list of participating authorities is posted on the WHO PQT website (<https://extranet.who.int/prequal/medicines/collaborative-procedure-accelerated-registration>). For GMP requirements for the procedure, the NRAs should refer to *Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for marketing authorization of medical products* (WHO Technical Report Series, No. 1010, Annex 7, 2018). The guidelines provide the general approaches and best practices for desk assessment to verify and confirm compliance

with GMP, good laboratory practices (GLP) and good clinical practices (GCP) of foreign facilities for manufacture of finished pharmaceutical products (FPPs) and APIs, quality control laboratories (QCLs) and contract research organizations (CROs)/clinical trial sites. The desk assessment of inspection reports is mostly sufficient to eliminate the need for site inspections.

Participating reference SRAs do not object to sharing their assessment and inspection reports with applicants or authorization holders to support access to needed medicines in line with the principles of the Procedure. Conditions and mechanisms by which the information will be shared, and the extent to which additional support can be offered to the participating NRAs are notified to WHO. A list of reference SRAs that agree to share the outcomes of their regulatory expertise in line with the principles of the Procedure and detailed conditions of information sharing are posted on the WHO PQT website (<https://extranet.who.int/prequal/medicines/collaborative-procedure-accelerated-registration>). An example of such a listing is provided in Appendix 2.

Participating manufacturers submit applications to NRAs and provide the assistance necessary to finalize the application in line with the Procedure. The participating manufacturers applying for registration have a major role in the national registration process and in the post-registration phase by carrying out the Procedure and providing any additional information requested. A primary obligation of the manufacturers is to inform the NRAs when a regulatory decision is taken by the reference SRA post-authorization, e.g. relating to non-compliance with GMP, withdrawal of the product, suspension of marketing authorization, or when the product is no longer authorized or marketed in the jurisdiction of the reference SRA.

WHO assists in the execution and maintenance of the Procedure, posts lists of participating NRAs and reference SRAs (including reference SRA conditions for information sharing) on its website and collects information about the performance of the Procedure. Should the medicine be highly therapeutically relevant for WHO-supported treatment programmes, WHO actively facilitates information exchange among the reference SRAs involved and the participating NRAs. WHO provides information on products approved by participating NRAs through the facilitated registrations using the reference SRA procedure and makes it publicly available.

4. Medicines

Both innovative and generic medicines approved by reference SRAs are eligible for the Procedure. The medicines submitted for registration to the participating NRAs should be identical with medicines approved by reference SRAs. Within the context of this Procedure, identical products are characterized by the descriptions listed below. Note that should there be any deviations from this definition of “sameness”, these must be notified (e.g. different supply chain, specifications, stability or medical claims) and such

deviations can be the reason for non-applicability of the Procedure.

For this Procedure, the same medicine is characterized by:

- the same qualitative and quantitative formulation;
- the same manufacturing site(s)⁶ for API and FPP including specific block(s)/unit(s), chain, processes, control of materials and final product, and in the case of vaccines also by the same batch release scheme;
- the same specifications for excipient, API and FPP;
- the same essential elements of product information.⁷

4.1 Submissions format and content

- The dossiers submitted for national registrations are organized in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) CTD format and contain data specified in Appendix 5. The scope of submitted technical data for innovators (i.e. NDAs or self-standing applications) represents a subset of the data submitted to reference SRAs that provides sufficient assurance about product identity, quality, safety and efficacy and meeting requirements for the NRAs. To the extent possible, API quality is confirmed by existing certification schemes (e.g. certificate of suitability (CEP)). The critical quality attributes of the excipients are taken into consideration and checked. In principle, only nonclinical and clinical summaries (ICH Module 2) are submitted instead of extensive full ICH Modules 4 and 5. However, the applicants are committed to submit these modules or specific nonclinical and clinical data if asked to do so by a participating NRA. The applicant should confirm with the respective NRAs whether full Modules 4 and 5 are required at the time of submission. It may be advantageous to submit, in addition to existing overviews, a “bridging report” that provides the summarized evidence on risks and benefits and justification of the relevance of the product for the countries for which marketing authorization is sought (Appendix 6).

⁶ “Sameness” of the manufacturing sites for APIs and FPPs means that the specific site must be approved by the reference SRA for the specific product under consideration and included as part of the marketing authorization in the reference SRA country. Any additional sites, regardless of their GMP status, are not acceptable under this procedure. Any changes or variations to include additional sites should be approved by the reference SRA before inclusion in the submission to the participating NRAs.

⁷ The essential elements of product information include the indications, contraindications, posology (dosing), special warnings and precautions for use, adverse reactions, storage conditions, primary packaging and shelf life. For pharmaceutical products, differences in brand name, the name of the applicant, language, format and degree of detail of the product information, labelling of primary, secondary and tertiary packaging, among others, are not considered essential for the purposes of this Procedure. The language of the product information may be different as long as the information content is the same as that approved by the reference SRA.

- In the case of generic medicines the technical part of a dossier corresponds in Module 3 to the full scope of quality data on a finished dosage form (part 3.P) and data on the API correspond to the open part of the API master file (APIMF). Demonstrations of bioequivalence and biowaiver criteria are equivalent to the WHO PQT prequalification dossier requirements (<https://extranet.who.int/prequal/medicines>).
- In addition to technical data the applicants provide NRAs with:
 - valid assessment and inspection reports issued by reference SRAs;
 - quality information summary (QIS)-SRA(crp) (Appendix 4);
 - a declaration assuring the identity of the product with the medicine approved by the reference SRA, consent to communicate freely with the reference SRA on product-related matters, and additional commitments as specified in Appendix 7;
 - a declaration confirming same site and source including specific block(s) or unit(s) for API and FPP production;
 - commitment to conduct risk assessment or transport validation for supply of products to the NRA market, if such assessment or validation was not already covered as part of the dossier.

Should the local applicant be a different legal entity to the holder of reference SRA marketing authorization (or scientific opinion), the relationship should be clarified and agreements assuring information flow should be adjusted to reflect this situation.

Translation of documents required in the national language is the responsibility of the manufacturer. The method and extent of verification of translation accuracy are a matter of decision of individual NRAs.

Samples, if required, should be used for checks on appearance or packaging. Laboratory testing of registration samples is not recommended and random sampling and testing should be planned in the post-registration period. Mock-ups showing the graphic design of package labelling are an acceptable way to present the texts and symbols on the packaging.

Note, however, that participating authorities may require applicants to comply with specific additional national requirements. Each participating authority is encouraged to reduce the scope of specific national requirements to align them with the Procedure and harmonize its requirements with the international format and content of a regulatory dossier. Specific national requirements should be made public.

4.2 Registration process according to the Procedure

The process flow of the Procedure is shown in Figure A11.1 and described briefly below.

1. *Pre-submission phase*

- a. Manufacturers considering registrations according to the Procedure should familiarize themselves with the principles of the Procedure, which NRAs are prepared to participate in the Procedure, and the conditions under which reference SRAs that have authorized their medicine will agree to share information and provide additional prospective support.
- b. It is recommended that a participating manufacturer should confirm with the participating NRA(s) its interest in applying the Procedure for the given medicine before the submission.
- c. The manufacturer also needs to provide the reference SRA with its consent to share the relevant regulatory information with participating NRA(s). A model of the content of such consent has been proposed (Appendix 3A), but it is up to individual applicants and reference SRAs to agree on the details of the wording.
- d. In the case that the manufacturer does not have valid assessment and inspection reports available, these should be requested from the respective reference SRA. Should the manufacturer need to obtain the agreement of the reference SRA before sharing the assessment and inspection reports, such agreement should be requested. The model for the proposed content of the request is shown in Appendix 3B.
- e. In the case of medicines that are relevant for WHO-supported disease treatment programmes, the manufacturer should agree with WHO the extent of WHO's coordination and support.
- f. The manufacturer prepares the quality information summary (QIS) reference SRA (QIS-SRA (crp)) (Appendix 4) and the QIS should be verified and endorsed by the reference SRA that issued the marketing authorization.
- g. The reference SRA should provide the required documentation, e.g. assessment and inspection reports (where applicable) and endorsement of the QIS-SRA(crp) within 30 days from receipt of the request from the manufacturer or applicant. The individual reference SRAs are invited to notify WHO about their timelines and deadlines for these activities to be posted publicly on the WHO websites referenced in the Procedure.

2. *Submission for registration*

- a. The manufacturer submits the registration application to the participating NRAs within 90 days from the date of receipt of documentation from the reference SRA. Specific national requirements must be respected, but it is up to the NRAs to minimize national deviations from the internationally acceptable dossiers to the greatest extent possible. Application fees may be charged in accordance with national requirements.
- b. The registration dossier is organized in CTD format and consists of data sets as specified in Appendix 5, including valid assessment and inspection reports issued by the reference SRA and a manufacturer or applicant's declaration.
- c. In the case of submissions coordinated with WHO, the manufacturer informs WHO about applications submitted to individual NRAs and comes to an agreement with WHO as regards access to the shared data (Appendix 8).

3. *NRAs' acceptance of products for registration in line with the Procedure and registration phase*

- a. The participating NRA validates the applications and documents submitted, decides whether or not to apply the Procedure in each specific case, and informs the applicant of its decision within 30 days.
- b. Should the NRA have any doubts about the authenticity or validity of any of the assessment or inspection reports submitted, it can ask the respective reference SRA for confirmation. The way in which confirmation is organized can vary between reference SRAs. The practical way is to share recent assessment and inspection reports as archived by the reference SRA.
- c. The NRA processes an application, benefiting from shared reference SRA regulatory outcomes and assurance about the identity of the medicine with the one approved by the reference SRA. It is up to individual NRAs to decide to what extent they accept, verify or reassesses the information provided before coming to a decision. A pragmatic approach is to verify product identity and assess only those areas that relate to use of the product in the country concerned and where failure to comply with regulatory standards could pose specific health risks. For example, these might include: review of stability data for the climatic conditions appropriate to the participating NRAs, if these are different from those approved by

the reference SRA; risk management plans (RMPs); bridging report; and labelling and product information for products approved for use in reference SRA countries. Note that product approval through mechanisms such as Article 58 of the Regulation of the European Commission, Health Canada Access Programme, United States Food and Drug Administration tentative approval, or the Swissmedic Marketing Authorization for Global Health Products Procedure is already designed to address such contextual issues in the receiving countries. Participating NRAs should avoid retesting samples prior to authorization. In the other areas, the outcomes of assessments by trusted authorities are proposed to be adopted.

- d. Participating reference SRAs can be approached to provide additional explanation or justification, depending on the extent of an individual reference SRA's commitment to support the process. In the case of medicines prioritized by WHO, the Organization can arrange for responses to questions, discussion via tele- or videoconferences or joint meetings with reference SRA experts to facilitate the process.
- e. Participating NRAs issue a decision within 90 calendar⁸ days of regulatory time⁹ from acceptance of the submission for processing according to the Procedure.
- f. Granting of registrations processed according to this Procedure is notified by the manufacturer to WHO to allow it to monitor the Procedure performance. Information about registered medicines, deviations from a reference SRA decision, dates of submission and experience is notified according to Appendix 9.

⁸ Participating authorities should issue their national regulatory decisions at the earliest opportunity after being given access to the confidential information and documentation on a given product. If a participating authority does not issue its decision within 90 days of regulatory time, the reasons should be communicated to the applicant, and/or to the reference SRA, or to WHO, where applicable.

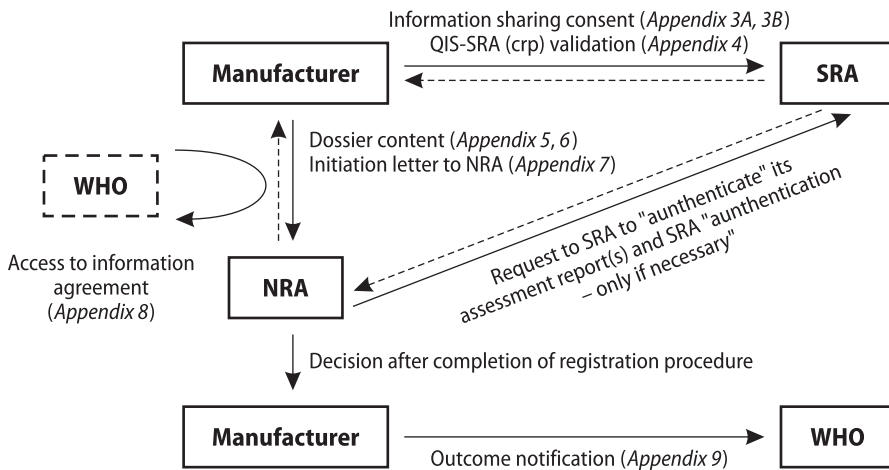
⁹ Regulatory time starts after a valid application for registration according to the Procedure has been received and access to the confidential information has been granted (whichever is the later) and continues until the date of decision on registration. The regulatory time does not include the time granted to the applicant to complete missing parts of the documentation, provide additional data or respond to queries raised by NRAs.

Figure A11.1

A summary of the steps in the Procedure and corresponding documentation

Preconditions to initiate the national registration in line with the Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities (SRAs)

- national regulatory authorities (NRAs) agree to participate and follow the principles of the procedure (*Appendix 1*)
- SRAs define conditions of their participation (*Appendix 2*)



QIS: quality information summary; NRA: national regulatory authority; SRA: stringent regulatory authority.

5. Collaboration mechanisms for management of post-registration variations

5.1 General principles

The following principles are proposed to be respected during submissions of variations to medicines and vaccines registered or submitted for registration in line with the reference SRA Procedure. These principles take into account the existing reality of non-harmonized variation processes among NRAs that participated in the pilot reference SRA Procedure. The recommended approach to handling these variations is driven by the principle of non-interference with national legislation and decision-making while facilitating national decisions on variations by provision of essential information assuring that the medicine registered by the reference SRA procedure is of equivalent quality, and in line with the latest reference SRA decisions.

These guidelines focus on all variations relevant to countries that registered the product in line with the reference SRA Procedure. Variations that were submitted or notified to the reference SRA authority should be submitted to NRAs in participating countries to assure consistency of the regulatory status of the approved products between the reference SRA and NRAs over the product life-cycle. All variations that are approved by reference SRAs before an application for registration is submitted to the participating NRAs should be submitted and clearly identified in the initial submission to participating NRAs under this Procedure. It is not necessary to submit all changes, e.g. administrative changes that are relevant for the territory of the reference SRA only, or changes affecting the quality of the product that are specific to the reference SRA region. Variations that have local relevance in participating countries, which are not submitted or notified to the reference SRA should be submitted in line with national requirements.

The cover letter submitted with each variation should clearly indicate if a variation was submitted or notified to and approved or accepted by the reference SRA, or if a variation is only a national one.

Line extensions of already registered medicines (e.g. new formulations, additional strengths, new routes of administration, changes in active substance(s)), which were submitted to the reference SRA as a new application, are not considered as variations in this document.

At present, only variations are discussed. Management of other regulatory documents such as renewal submissions and outcomes, periodic benefit–risk evaluation report (PBRER) submissions and outcomes, submissions and outcomes concerning post-authorization measures and RMP updates will be the subject of future discussions. However, national guidance should be followed, should any of these documents and regulatory information already be required under existing national regulation.

5.2 Variations that are under assessment by reference SRAs at the time of submission of an application for registration to participating NRAs

All variations under the reference SRA assessment for which a decision is expected before finalization of the collaborative Procedure (registration process is expected to be complete within 90 days), should be identified in Appendix 4. Data supporting such variations should be included in the dossier submitted with the registration application.

The applicant should confirm and attest that the information submitted to the NRA is the same as that submitted to the reference SRA for the variation, where applicable.

The applicant should notify participating NRAs of the reference SRA's decision outcome(s) (and any conditions in the case of approval) within 30 days (preferably during exchange of questions and responses between the NRA and the applicant). If an

assessment report is issued by the reference SRA, once the procedure is completed, a copy should be provided. In the case of variations not approved by the reference SRA, the applicant notifies NRAs about withdrawal (invalidation) of data related to the respective variation.

NRAs may consider reference SRA decisions on these variations during the registration process, thus avoiding the need to submit national variations immediately after the decision on registration is issued. In the case of variations not concluded by the reference SRA before the national registration is granted, the NRAs have the following options:

- consider these variations and grant registration, including conditional approval of not-yet reference SRA-approved variations; or
- defer the decision on registration until the reference SRA approval is obtained; or
- register the product based on the current reference SRA-approved conditions and await submission of variations according to section 4.3.

5.3 Variations approved by reference SRAs after national registrations are granted

Holders of registrations granted on the basis of the reference SRA Procedure are committed to keep NRAs informed about all variations or regulatory actions (e.g. urgent safety restrictions, suspensions of authorization) (Appendix 4, section 4b). The information should be provided in the form of the variation dossier submitted to the reference SRA. Holders of national registrations are required to submit variations that have been approved (or accepted in the case of notification) by the reference SRA to relevant¹⁰ participating authorities without delay at the latest 30 calendar days after the reference SRA's decision has been made. Should national legislation in a participating country require additional data or samples which are not practical to submit within 30 calendar days, the variation should be submitted as soon as possible, with a plausible explanation. There is no need to submit variations that have not been approved or accepted by the reference SRA.

The same data as submitted and approved by the reference SRA should be submitted to NRAs. The applicant should therefore confirm and attest that the information (variation dossier) submitted to the NRA is the same as that submitted to the reference SRA for the variation where applicable. In the case that an assessment report has been issued, this should be submitted with the copy of the reference SRA

¹⁰ Relevant variations are those variations that could impact quality, safety and efficacy in the receiving country. Examples of non-relevant variations include addition of a manufacturing site only for the market in the SRA's region.

decision or other document confirming the final position of the reference SRA. In the case that the variation modifies information submitted to the NRA in the reference QIS-SRA (crp), a new updated reference QIS-SRA (crp) should be submitted. The reference SRA should provide the required documentation, e.g. assessment and inspection reports (where applicable), and endorsement of the QIS-SRA (crp) within 30 days from receipt of the request from the manufacturer or applicant.

The NRAs should rely on the decision of the reference SRA to the extent possible, using expedited review pathways similar to the initial marketing authorization process under the reference SRA collaborative procedure. National decisions on such variations submitted in line with the reference SRA Procedure should not be taken by participating NRAs later than 30 calendar days following submission.

If the NRA disagrees with a notification, it should communicate this to the manufacturer within 30 days following the submission. Otherwise the notification shall be deemed accepted.

Should a participating NRA receive an application from a manufacturer for a variation that has not been previously approved by the relevant reference SRA (and it is not a case of deviation as described below in section 4.4), the product could deviate from the reference SRA-approved version and such variation merits special attention from the NRA.

The NRAs should make every effort to align their decisions. WHO can assist in such situations and mediate in communication between the parties involved.

5.4 Variations in conditions of registration, which deviate from those approved by the reference SRA approval

Deviations from the reference SRA's approved product characteristics, approved data and product information are possible provided the product is still considered – in principle – the same as the one approved by the reference SRA. All deviations from the conditions approved by the reference SRA should be identified in Appendix 4. All variations that differ from those approved by the reference SRA are subject to specific national variation guidelines in the participating countries QIS: quality information summary; NRA: national regulatory authority; SRA: stringent regulatory authority.

Appendix 1

Agreement of the national regulatory authority to participate in the collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities

Coordinated by the World Health Organization (WHO)

Details of national medicines regulatory authority (NRA)

Name of NRA: Click here to enter text. _____ (“the NRA”)

Postal address: Click here to enter text. _____

Country: Click here to enter text. _____

Telephone number (please include codes): Click here to enter text. _____

Email: Click here to enter text. _____

Scope of agreement

Applicants for national registration of a pharmaceutical product or vaccine approved by a stringent regulatory authority (reference SRA) (hereafter referred to as “Applicants”) may express their interest to the NRA for the assessment and accelerated registration of this product (“the Product”) in the country under the “*Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities*” (hereafter referred to as “the Collaborative procedure of reference SRA approved products” or “the Procedure”).¹

Subject to the NRA agreeing to participate in the Procedure and conduct such assessment and consider such accelerated registration of the product under the Procedure, the NRA hereby confirms for each such product that it will adhere to, and collaborate with, the Applicant for marketing authorization of the product and if relevant with the respective reference SRA and WHO in accordance with the terms of the Procedure.

¹ If the applicant for national registration is not the same as the reference SRA registration/marketing authorization holder, the reference SRA registration holder must confirm to the NRA with an authorization letter that the applicant is acting for, or pursuant to rights derived from, the reference SRA registration holder, and that the reference SRA registration holder agrees with the application of the Procedure in the country concerned.

Confidentiality of information

Any information and documentation relating to the product and provided by the Applicant or reference SRA to the NRA under the Procedure may include but shall not necessarily be limited to:

- the registration dossier as defined by the Procedure
- the full reference SRA assessment and inspection outcomes (reports);
- information and documentation on variations, as well as information and documentation on any actions taken by the reference SRA after national registration of the Product;
- all such data, reports, information and documentation being hereinafter referred to as “the Information”.

As regards sharing the outcomes of assessments and inspections, full reference SRA assessment and inspection reports are shared by Applicants with participating NRAs with the agreement of the respective reference SRA. Should any data in the assessment and inspection report be hidden for whatever reason, the nature and scope of missing data will be clearly indicated. Sharing of any data by the reference SRAs is subject to consent of the data owner.

The Applicant and reference SRA agree to make the Information available to the NRA exclusively for the purpose of the assessment and accelerated registration of the Product in the Country and any post-registration processes that may be required, in accordance with and subject to the terms of the Procedure (“the Purpose”). The NRA agrees to treat any Information provided by the Applicant and reference SRA as aforesaid as strictly confidential and proprietary to the Applicant, parties collaborating with the Applicant and/or reference SRA as relevant. In this regard, the NRA agrees to use such Information only for the Purpose and to make no other use thereof. Thus, the NRA undertakes to maintain the Information received from the Applicant and reference SRA in strict confidence, and to take all reasonable measures to ensure that:

- the Information received from the Applicant or reference SRA shall not be used for any purpose other than the Purpose;
- the Information shall only be disclosed to persons who have a need to know for the aforesaid Purpose and are bound by confidentiality undertakings in respect of such information and documentation, which are no less stringent than those contained herein.

The NRA warrants and represents that it has adequate procedures in place to ensure compliance with its aforesaid obligations.

The obligations of confidentiality and restrictions on use contained herein shall not cease on completion of the Purpose.

The obligations of confidentiality and restrictions on use contained herein shall not apply to any part of the Information which the NRA is clearly able to demonstrate:

- was in the public domain or the subject of public knowledge at the time of disclosure by the Applicant or reference SRA to the NRA under the Procedure; or
- becomes part of the public domain or the subject of public knowledge through no fault of the NRA; or
- is required to be disclosed by law, provided that the NRA shall in such event immediately notify the reference SRA and the Applicant in writing of such obligation and shall provide adequate opportunity to the reference SRA and/or the Applicant to object to such disclosure or request confidential treatment thereof.

Upon completion of the Purpose, the NRA shall cease all use and make no further use of the Information disclosed to it under the Procedure, and shall promptly destroy the Information received from the Applicant and the reference SRA, which is in tangible or other form and is not archived in accordance with archival procedures established by the NRA. The Purpose for each product shall be deemed completed as soon as:

- the reference SRA authorization holder/Applicant discontinues participation in the Procedure for the particular product;
- the Product is deregistered by the NRA and/or ceases to be authorized by reference SRA.

The NRA agrees that it has no right in or to the Information and that nothing contained herein shall be construed, by implication or otherwise, as the grant of a licence to the NRA to use the Information other than for the Purpose.

Should WHO staff or external experts independent on the Applicant or NRA be provided with an access to the Information in order to coordinate the Collaborative reference SRA procedure or provide an expert opinion, an access to the Information shall be subject to a confidentiality undertaking.

Timelines

In respect of each Product which the NRA accepts to assess and consider under the Procedure, the NRA undertakes to abide by the terms of the Procedure, including but not limited to the following timelines for processing each application:

- within 90 calendar days of regulatory time² after obtaining the assessment and inspection outcomes (reports) and validated QIS-SRA as well as receipt of validated submission, the participating NRA undertakes to take a final decision on the national registration of the Product;
- within 30 calendar days of regulatory time after obtaining the assessment outcomes (reports) and evidence of approval for variations and validated QIS-SRA (where applicable) as well as receipt of data submitted to the reference SRA for the variations, the participating NRA undertakes to take a final decision on the variation of the Product.

Miscellaneous

The NRA agrees that WHO may list its name on the WHO-PQT website as a participant in the reference SRA Procedure. Except as provided hereinbefore, neither party shall, without the prior written consent of the other party, refer to the relationship of the parties under this Agreement and/or to the relationship of the other party to the Product, the Information and/or the Purpose, in any statement or material of an advertising or promotional nature.

This Agreement shall not be modified except by mutual agreement of WHO and the NRA in writing. The NRA furthermore undertakes to promptly inform WHO/PQT of any circumstances or change in circumstances that may affect the implementation of this Agreement and its participation in the Procedure. This Agreement can be invalidated by a written note from the NRA to WHO. Validity of this Agreement expires at termination of the Procedure, which will be publicly announced.

Focal point(s) for communication

The NRA has designated the person(s) listed below to act as a focal point(s) for communication concerning the Procedure.

Title: _____

Name: _____

Position: _____

Email: _____

Telephone: _____

² Regulatory time starts after a valid application for the registration according to the Procedure has been received and access to the confidential information has been granted (whichever is the later) and continues until the date of decision on registration. The regulatory time does not include the time granted to the applicant to complete missing parts of the documentation, provide additional data or respond to queries raised by NRAs.

Title: _____

Name: _____

Position: _____

Email: _____

Telephone: _____

Agreed and accepted

For the NRA

Signature: Click here to enter text. _____

Name: Click here to enter text. _____

Title: Click here to enter text. _____

Place and date: Click here to enter text. _____

Appendix 2

Example of information included in the list of participating reference stringent regulatory authority(ies)

Details of reference stringent regulatory authority (SRA) agreeing to proceed, in principle, in line with conditions of the Procedure	Provision of consent or “no objection statement” to share the assessment and inspection reports issued by the reference SRA	Agreement to authenticate the reference SRA-issued assessment and inspection reports on request of participating NRAs, which have received an application for registration according to the Procedure	Provision of additional explanation with scientific justification of granting authorization to NRAs, which have received an application for registration according to the Procedure	Reference SRA position on post-registration management of medicines registered by participating NRA using the Procedure
Name and address of reference SRA Focal point for communication in matters related to the Procedure	Example 1 (EMA – current situation) EMA does not object to MAHs of centrally authorized medicines and holders of scientific opinions according to European Union Article 58 using final assessment and inspection reports in support of national registrations.	Example 1 (EMA – current position) It is expected that requests for authentication of documents will be exceptional. Subject to previous agreement with MAH (see Appendix 3 of the Procedure) the EMA can provide to the requesting NRA the full assessment reports or other relevant assessment documents.	Possible, on the understanding that these situations are exceptional and that such a request is channelled by WHO or the respective NRA, not by the manufacturer.	For example, the EMA supports the obligation of MAHs to keep national regulators informed of due major variations or line extensions; however, for the Procedure the EMA would suggest to focus on initial applications.

Table continued

Details of reference stringent regulatory authority (SRA) agreeing to proceed, in principle, in line with conditions of the Procedure	Provision of consent or “no objection statement” to share the assessment and inspection reports issued by the reference SRA	Agreement to authenticate the reference SRA-issued assessment and inspection reports on request of participating NRAs, which have received an application for registration according to the Procedure	Provision of additional explanation with scientific justification of granting authorization to NRAs, which have received an application for registration according to the Procedure	Reference SRA position on post-registration management of medicines registered by participating NRA using the Procedure
	However, when documents are provided to authorities in third countries by the MAH or holder of scientific opinion, personal information needs to be redacted. The “no objection statement” is provided by the EMA on request of individual MAHs. The request has to specify each NRA with which the assessment and inspection reports will be shared. The “no objection statement” is normally issued within 10 days.	As regards inspection reports, it is expected that the applicant will forward the latest inspection report(s) for the manufacturing site(s) to the participating NRA. Communication with the relevant Member State authority might be necessary to confirm authenticity of the inspection reports.		

Table *continued*

Details of reference stringent regulatory authority (SRA) agreeing to proceed, in principle, in line with conditions of the Procedure	Provision of consent or “no objection statement” to share the assessment and inspection reports issued by the reference SRA	Agreement to authenticate the reference SRA-issued assessment and inspection reports on request of participating NRAs, which have received an application for registration according to the Procedure	Provision of additional explanation with scientific justification of granting authorization to NRAs, which have received an application for registration according to the Procedure	Reference SRA position on post-registration management of medicines registered by participating NRA using the Procedure
	Example 2 (hypothetical reference SRA) Reference SRA does not object to MAHs of centrally authorized medicines and holders of scientific opinions according to Article 58 using final assessment and inspection reports in support of national registrations. However, when documents are provided to authorities in third countries by the MAH or holder of scientific opinion, personal information needs to be redacted.			

Table continued

Details of reference stringent regulatory authority (SRA) agreeing to proceed, in principle, in line with conditions of the Procedure	Provision of consent or “no objection statement” to share the assessment and inspection reports issued by the reference SRA	Agreement to authenticate the reference SRA-issued assessment and inspection reports on request of participating NRAs, which have received an application for registration according to the Procedure	Provision of additional explanation with scientific justification of granting authorization to NRAs, which have received an application for registration according to the Procedure	Reference SRA position on post-registration management of medicines registered by participating NRA using the Procedure
	The general statement confirming reference SRA position and conditions for sharing of the final assessment and inspection reports are made publicly available at www			

EMA: European Medicines Agency; MAH: marketing authorization holder; NRA: national regulatory authority; SRA: stringent regulatory authority as stipulated by WHO.

Appendix 3A

Manufacturer's consent for information sharing with participating national regulatory authority(ies) and the World Health Organization

Date: _____ dd/mm/yyyy _____

To: _____

RE: <SRA> sharing of non-public information concerning <Product> with the <NRA(s)> and the World Health Organization (WHO)¹

Dear [<SRA>],

On behalf of <manufacturer>, the <MAH> in <SRA country/region> of the above-referenced regulated product, I authorize the <SRA> to share the information described below ("Information") only with <NRA focal point – contact person/function> and WHO <contact person/function> solely for the purpose of the *Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities* <date; version>. Confidentiality agreements are in place between <manufacturer> and WHO.

I understand that the Information may contain confidential commercial or financial information or trade secrets that are exempt from public disclosure. I agree to hold <SRA> harmless for any injury caused by <SRA>'s sharing of the Information with the <NRA> and WHO under the terms set out herein.

Information authorized to be shared with the <NRA> and/or WHO:

- all available quality data on <Product>;
- all available nonclinical data on <Product>;
- all available clinical data on <Product>;
- any other document reasonably requested by the <NRA or WHO> during the evaluation procedure;
- all other information regarding GxP inspections and <Product> assessment.

¹ During the *Collaborative procedure in national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities* (WHO Technical Report Series No. 1010, 2018) WHO plays a facilitating role.

Authorization is given to <SRA> to provide the Information without deleting confidential, commercial or financial, or trade secret information.

As indicated by my signature, I am authorized to provide this consent on behalf of <manufacturer> and my full name, title, address, telephone number and email address are set out below for verification.

Yours sincerely,

Name: _____

Title: _____

Address: _____

Manufacturer: _____

Email: _____

Telephone number: _____

Fax number: _____

cc:

Appendix 3B

Manufacturer's request for stringent regulatory authority's (SRA's) permission for sharing SRA-owned non-public information with participating national regulatory authority(ies) and the World Health Organization

Date: _____ dd/mm/yyyy _____

<manufacturer>

RE: Request to <SRA> for a permission to <manufacturer> to share <SRA>'s non-public information concerning <Product> with the <NRA(s)> and the World Health Organization (WHO)¹

Dear <reference SRA>,

<Manufacturer> as a <MAH> of the <SRA> authorized <Product>, hereby requests the <reference SRA's> permission to share <SRA>-owned non-public information concerning <Product> for the purpose of the *Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities* assisted by WHO.

The information to be shared consists of

<SRA> final GxP inspection reports for Product <date; version>;

<SRA> Product assessment reports; and

<SRA> <other, please specify> documents/reports that may be needed in the context of this Procedure.

The information will be shared with the <NRA(s)> and WHO.

Yours sincerely,

Name: _____

Title: _____

SRA: _____

¹ During the *Collaborative procedure in national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities* (WHO Technical Report Series No. 1010, 2018), WHO plays a facilitating role.

Address: _____

Email: _____

Telephone number: _____

cc:

Appendix 4

Quality information summary of the finished pharmaceutical product or vaccine approved by the reference SRA (QIS- SRA (crp))

Foreword

Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities

The WHO *Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities* define a template for a simplified quality information summary (QIS) to outline the key quality parameters of a product approved by a stringent regulatory authority (reference SRA) for WHO prequalification. It was realized that this simplified QIS can be a useful instrument for sharing (under appropriate conditions of confidentiality) the essential quality parameters characterizing each medicine approved by SRAs in order to accelerate national decisions on registration. However, experience with the pilot-testing of the reference SRA *Collaborative procedure* revealed that the simplified WHO QIS does not contain certain data which would facilitate verification of “sameness” of the product for the purpose of the collaborative registration of reference SRA-approved medicines. Therefore the information content of the template was extended to the form of the “QIS-SRA (crp)”.

The QIS-SRA (crp) template should be completed by the applicant and verified by the reference SRA, ideally in the initial stage of the collaborative process, when the applicant (market authorization holder (MAH)) requests the reference SRA's cooperation and grants consent to information sharing. Should data in the application for national registration deviate from data approved by the reference SRA, these should be clearly indicated and summarized in section B10. The QIS-SRA (crp) should be submitted as a part of the application for national registration together with other documents stipulated in the collaborative procedure for products approved by reference SRA. A copy should also be provided in Word format.

Whenever any variation to the approved product that affects the QIS-SRA (crp) has been approved by the reference SRA, the QIS-SRA (crp) should be revised (using track-changes mode) and resubmitted to the relevant regulatory authorities in Word format together with the regulatory letter or other relevant document confirming approval of the variation under consideration.

The QIS-SRA (crp) is specifically designed for the purpose of the SRA collaborative procedure and should not be confused with other formats of QIS that are used for the purpose of WHO prequalification.

When completing the QIS-SRA (crp) template, this covering Foreword should be deleted.

QUALITY INFORMATION SUMMARY OF THE FINISHED PHARMACEUTICAL PRODUCT OR VACCINE APPROVED BY THE REFERENCE SRA (QIS-SRA(crp))

A. Pharmaceutical product or vaccine subject to reference SRA collaborative procedure

A1 Reference SRA

A2. Product registration/authorization number assigned by the reference SRA

Information as currently approved by the reference SRA

A3. Proprietary name of finished pharmaceutical product (FPP) in the reference SRA country/region

A4. Innovator or multisource (generic) FPP

A5. Name of the holder of the reference SRA marketing authorization and official address

A6. International Nonproprietary Name (INN) of active pharmaceutical ingredient(s) (API(s)), including form (salt, hydrate, solvate, etc.)

A7. Dosage form and strength

A8. Product description (as in Product information, e.g. white, film-coated, capsule-shaped tablets debossed with "X" and score line on one side and plain on other side)

A9. Primary and secondary packaging material(s) and pack size(s) (all pack types)

A10. Storage conditions (as in Product information)

A11. Shelf life of FPP (including in-use periods, where applicable)

A12. Names of all approved manufacturers of FPP, physical address(es) of manufacturing site(s) (and unit if applicable), including intermediates, primary packaging site and release testing (indicate function of each site)

A13. FPP storage conditions and duration over which stability, as reported to the reference SRA, was established (e.g. $30 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$ for 24 months, $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$ for 6 months):

Long-term (real time in months)	
Intermediate (duration in months)	
Accelerated (duration in months)	

B. Information that is considered confidentialia

Information as currently approved by the reference SRA

B1. Names of all approved API manufacturers, physical address(es) of manufacturing site(s) (and unit if applicable), including intermediates, contractors and release testing (indicate function of each site)

B2. Active pharmaceutical ingredient master file/drug master file (APIMF/DMF version number(s) and date(s), if relevant

Name of API	API manufacturer	APIMF/DMF version number(s) and date(s)

B3. API specifications of the FPP manufacturer

Standard (e.g. BP, Ph.Eur., Ph.Int., USP, in-house) ^a		
Specification reference number and version		
Test	Acceptance criteria	Analytical procedure (type/source/version)
Description		
Identification		
Impurities		
Assay		
Others, please specify		

B4. API container closure system and re-test period

Container closure system	Storage statement	Re-test period ^b

^a BP: British Pharmacopoeia; Ph.Eur: European Pharmacopoeia; Ph.Int.: The International Pharmacopoeia; USP: United States Pharmacopoeia.

^b Indicate if a shelf life is proposed in lieu of a retest period (e.g. in the case of labile APIs).

B5. FPP composition (formulation) information

Component and quality standard	Function	Unit composition		Batch composition (largest approved size)	
		Quantity per unit or per mL	%	Theoretical quantity/batch	%

<complete with appropriate title, e.g. core tablet, contents of capsule, powder for injection>

Subtotal 1					

<complete with appropriate title, e.g. film-coating>

Subtotal 2					
Total					

Batch size in number of units, where applicable

Additionally approved batch sizes – in number of units or kg, where applicable (add as many rows as necessary)

Composition of all components purchased as mixtures (e.g. colourants, coatings, capsule shells, imprinting inks):

B6. FPP manufacture			
Master production document reference number and version			
B7. FPP specifications			
Standard (e.g. BP, Ph.Int., USP, in-house) ^a			
Specification reference number and version/effective date			
Test	Acceptance criteria (release)	Acceptance criteria (shelf life)	Analytical procedure (type/source/version)
Description			
Identification			
Impurities			
Assay			
Others, please specify			
B8. Pharmacokinetic/safety/efficacy-related information used for reference SRA approval of multisource products. Indicate:			
Type of study	"X" in appropriate box	Comparator product	
Bioequivalence			
BCS-based biowaiver			
Other (specify)			
No study			
Notes/clarifications			

^a BP: British Pharmacopoeia; Ph.Eur: European Pharmacopoeia; Ph.Int.: The International Pharmacopoeia; USP: United States Pharmacopoeia.

B9. List of variations pending in the reference SRA up to the date of verification

Variation number	Variation	Type of variation according to reference SRA regulations

B10. Discussion of differences between national application and data approved by the reference SRA

Deviation reference no.	Data submitted for national registration which deviates from data approved by the reference SRA presented above. Mention also deviations in content of Product information, especially those related to indications, contraindications and posology.	Explanatory note

C1. Confirmation of content and verification by the reference SRA

Date of completion by the applicant	Name of person representing the applicant who completed the QIS-SRA	Position in the organization
Date of verification by the reference SRA <i>Part B10 is exempted from verification</i>	Person representing the reference SRA who verified the QIS-SRA information	Position in the organization

Change history to QIS-SRA (crp) and Product information

Date of revision (reported variation ^a)	Description of revision/variation

^a Variations approved by the reference SRA **after** national registration of the FPP and affecting **only** the QIS-SRA and/or Product information should be reported in the change history.

Appendix 5

Proposed documentation for collaborative procedure for reference SRA-approved pharmaceutical products and vaccines

Notes:

The format of the documentation corresponds to common technical document (CTD) in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) format/content. For practical reasons nonclinical (Module IV) and clinical data (Module V) are replaced by summaries included in Module II. Should there be a need for more extensive data from Module IV and Module V, these are available on request.

Confidentiality of submitted data and non-disclosure to a third party is – in addition to relevant national legislation and organizational measures applied by national regulatory authorities (NRAs) participating in the Procedure – assured by a commitment on confidentiality that represents an integral part of the Procedure¹ (Appendix 1), is signed by representatives of participating NRAs and archived by WHO.

Adapted Module 1

	Documentation to be provided	Comments
1.0 Letter of application		Cover letter in English, French, or as applicable to the region
Attachments to the letter:		
Appendix 3A of the reference stringent regulatory authority (SRA) Procedure		
Appendix 3B of the reference SRA Procedure		

¹ Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities, facilitated by WHO.

Table *continued*

	Documentation to be provided	Comments
Appendix 4	Includes information as specified in Commitment letter 1 (additional administrative data) and Commitment letter 2 (additional stability data for climatic zones). Any differences in the dossier submitted to the reference SRA should be explained, including differences in product information.	Submitted in English or French as applicable to the region
1.1 Comprehensive table of contents (TOC)	Comprehensive TOC including Module 1 information	
1.2 Quality information summary (QIS-SRA)	This will be included instead of a country-specific application form	Refer to Appendix 9 for the QIS-SRA template To be included in the adapted Module 1
1.3 Product information		
1.3.1 Package insert or summary of product characteristics	Product information as applicable for the region where the application will be submitted	Submitted in English or French as applicable to the region
1.3.2 Patient information leaflet or package leaflet	Mock-ups	Submitted in English or French as applicable to the region
1.3.3 Labelling	Mock-ups	Language and information to reflect national requirements

Table continued

	Documentation to be provided	Comments
1.4 Marketing authorization from reference SRA		
1.4.1 Marketing authorization from reference SRA	Yes	
1.4.2 Assessment report from reference SRA (Access to the full assessment report from the reference SRA, if available)	Agreement from the manufacturer to allow reference SRA to share the report with WHO and national regulatory authorities (NRAs). Prior to sharing, the reference SRA and manufacturer should agree on the content of the document that is shared. If fully justified, sentences referring to highly confidential information and/or highly sensitive data and/or not related to the product assessment data could be masked.	Note that this type of document is available only for products registered in Europe, via the Centralized Procedure. Public reports are preferred as they already contain all useful information, except those considered to give a competitive advantage. The sharing process is facilitated by WHO, between reference SRA and NRAs.
1.5 Good manufacturing practices (GMP) certification		
1.5.1 Copy of the GMP certificate of the active pharmaceutical ingredient (API) supplier, if available	Yes If not available, statement signed by qualified person (QP) from the finished pharmaceutical product manufacturing site to be provided	Currently, this is not always available. No legalization is required.
1.5.2 Copy of the GMP certificate of the finished pharmaceutical product (FPP) manufacturer(s)	Yes	No legalization is required.

Table continued

	Documentation to be provided	Comments
1.5.3 GMP inspection report of the manufacturing site(s) (FPP) from any reference SRA	Agreement from the manufacturer to allow the reference SRA to share the report with WHO and NRAs. Prior to sharing, the reference SRA and manufacturer should agree on the content of the document that is shared. If fully justified, sentences referring to highly confidential information and/or highly sensitive data and/or not related to the product assessment data could be masked.	Public reports are preferred as they already contain all useful information, except those considered to give a competitive advantage. The sharing process is facilitated by WHO, between the reference SRA and NRAs.
1.6 Other documentation		
If generic dossier: – full GCP inspection report of the bioequivalence study from any reference SRA, if any; – bridging report (where applicable) especially for innovative medicines (Appendix 6); – information on local representatives or distributor.	Agreement from the manufacturer to allow reference SRA to share the report with WHO and NRAs. Prior to sharing, the reference SRA and manufacturer should agree on the content of the document that is shared. If fully justified, sentences referring to highly confidential information and/or highly sensitive data and/or not related to the product assessment data could be masked.	Public reports are preferred as they already contain all useful information, except those considered to give a competitive advantage. The sharing process is facilitated by WHO, between the reference SRA and NRAs.

Module 2 summaries

Module 2 should be complete as submitted to the reference SRA.

Note: In the case of generic medicines for which a Clinical summary is not available, the Clinical overview (Module 2.5) should be included.

Module 3 Quality documentation

Complete Module 3 as submitted to the reference SRA, except corresponding open part of the active pharmaceutical ingredient master file (APIMF) is submitted, unless indicated otherwise according to the requirements of the participating NRA. If climatic zone III–IV stability data are not available, the commitment and protocol should be provided for stability studies under the appropriate climatic conditions for the receiving country. Any preliminary data under the required climatic conditions for the participating NRA should be provided. The stability data should be assessed by the reference SRA, where applicable or possible.

Additional region-specific information for Module 3 should be provided, where applicable.

Module 4 non-clinical documentation

Data to be provided only if required by the participating NRAs according to their national requirements, otherwise, these data are on request.

Module 5 clinical documentation

For innovative medicines, data to be provided only if required by the participating NRAs according to their national requirements, otherwise, these data are available on request. For generic products, complete documentation on bioequivalence studies should be provided in the submission in-line with WHO Guidelines on registration requirements to establish interchangeability² and applicable national regulatory requirements for participating NRAs.

² WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. Geneva: World Health Organization; 2017: (WHO Technical Report Series, No. 1003, Annex 6), 181–236.

Appendix 6

Requirements for provision of a bridging report for reference SRA-approved pharmaceutical product and vaccines for consideration of registration in participating countries

It is expected and is general practice that medicines authorized for use by reference SRAs are approved for the conditions of use relevant for the respective reference SRA territory. When a reference SRA-approved product is submitted for the regulatory approval in a country where conditions of use or the benefit–risk profile of the medicine may differ, it is assumed that the applicant for registration (marketing authorization) is able to support the application by providing evidence of a positive benefit–risk profile for the proposed conditions of use for the country concerned. Since reference SRA assessments may not always account for specific circumstances that can significantly affected the benefit-risk of a medicine in countries/regions outside the SRA's region, , the reference SRA assessment reports can be considered incomplete to enable appropriate benefit-risk evaluation in those settings. Currently only the European Medicines Agency (EMA)'s scientific opinion according to Article 58 of Regulation (EC) No. 726/2004, in the EU, may be considered to extensively address these questions.

Differences in target population, epidemiology and other features of the disease, concomitantly used medicines and hence the interaction potential, local treatment and diagnostic modalities and other factors can substantially affect the benefit–risk profile of a medicine. There can also be issues related to certain quality parameters, especially in relation to the stability under different climatic conditions. Therefore, to provide regulators in target countries with information relevant to the use of the product in their countries it is proposed to develop a bridging report supplementing the reference SRA assessment report (quality, safety) and the quality and clinical overviews provided in Module 2 of the common technical document (CTD).

Such a bridging report should, in particular, provide the applicants with the justification of the:

- comparability of the studied population to the target population (e.g. ethnicity, gender representation, age groups) as regards demonstration of safety and efficacy;
- relevance of reference SRA-approved conditions of use as regards epidemiology and disease pattern in the target countries as well as other implications for efficacy and safety, e.g. feasibility of monitoring and precautionary measures (e.g. resistance testing or therapeutic drug monitoring);

- interactions with food and with other medications relevant in the target countries that are not discussed in the reference SRA's assessment report;
- therapeutic role of a product and its recommended use according to relevant national and international treatment guidelines;
- other related quality issues, including but not limited to, storage conditions and conditions of administration and use.

Such a report is justified where the reference SRA assessment report does not sufficiently cover these elements of assessment. Provision of a bridging report should not be mandatory, but can substantially facilitate conduct of the regulatory assessment, reduce the number of potential regulatory questions and shorten the duration of the regulatory approval process. Such a report can be valid for more than one country, where conditions of use of the medicine are considered, in principle, to be similar. Similarly to the the case of overviews submitted in Module 2, the bridging report may be prepared by the applicant, or by expert(s) contracted by an applicant, who will attach their professional CV(s).

Appendix 7

Expression of interest to national regulatory authority

Date: _____ dd/mm/yyyy _____

To: _____

RE: declaration to the <national regulatory authority (NRA)> to initiate and proceed with registration of <Product> in line with the Procedure

Dear [<SRA>],

On behalf of <manufacturer>, the <marketing authorization holder (MAH)> in <stringent regulatory authority (reference SRA) country/region> of the <Product> that is registered with the <reference SRA> under the <reference number>, and solely for the purpose of the “*Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities*” (The Procedure – <date; version>) organized by WHO.

I, <manufacturer representative name> certify that:

1. The product submitted for registration is identical in all aspects of manufacturing and quality to that currently approved by the <reference SRA> under the <reference number>, including formulation, method and site(s) of manufacture, sources of active and excipient starting materials, quality specifications and control methods of the product and starting material, packaging, shelf life and product information.

If applicable:

The only exception(s) to the conditions approved by the <reference SRA> are: <Deviations from current reference SRA approval, explanations and related commitments>.

2. Submitted assessment and inspection reports are complete reports as issued by the <reference SRA>. The <reference SRA> has been authorized by the <manufacturer> to share with <NRA focal point> all <Product> related regulatory information, including information of a confidential nature. A copy of the authorization letter to the <reference SRA> is attached as <Appendix No. 1>.

If applicable:

The only data hidden in the assessment and/or inspection report of the <reference SRA> concern <nature and scope of missing data> and are hidden because of <reason>.

3. Information included in the registration dossier is identical with data currently approved by the <reference SRA>. As for the purpose of the Procedure, Module IV of the registration dossier in CTD format containing nonclinical data and Module V containing clinical data are replaced by respective summaries included in Module II, the <manufacturer> commits to submit without delay the non-submitted data on request of the <NRA>.
4. On behalf of <manufacturer>, the <MAH> in <SRA country/region> of the above-mentioned SRA regulated product, I hereby commit to
 - a. Supplying any additional information in accordance with local regulations or upon request from the <NRA> as soon as possible during the process.
 - b. Should the registration be granted, submitting in accordance with local regulations without delay all relevant variations as approved by the <SRA country/region>.
 - c. Supplying in accordance with local regulations any information about <SRA> regulatory actions relevant to the <Product>, including suspension or termination of registration, should it happen for whichever reason.

Signature

<Appendix No. 1>: Copy of the authorization letter to the <SRA (reference SRA)>

If appropriate:

- Current storage conditions approved by the <SRA country/region> are <storage conditions approved by reference SRA>. On behalf of <manufacturer>, the <MAH> in <SRA country/region> of the above-referenced regulated product, I hereby commit to supplying within <time period> results of stability data applicable to Zones III–IVa or IVb should any of these stability zones be applicable to your country. In addition, <NRA> will be informed of any out-of-specification (OOS) results during the study and protocol for the relevant applicable zones.
- The WHO focal person (s) <name/s> has/have been provided with the <Product> dossier to facilitate the Procedure and is/are authorized by the <manufacturer> to communicate on the Product-related issues with <NRA representatives>. By this letter the <NRA> is authorized to share with WHO all <Product> related regulatory information and communicate for the purpose of the Procedure on the <Product> related regulatory issues, including exchange of confidential information.

- Should the local applicant be a different legal entity from a holder of reference SRA marketing authorization or from a holder of scientific opinion in the case of European Union Article 58 procedures, the relationship should be clarified and agreements assuring information flow should be adjusted to this situation.

Appendix 8

Confidential disclosure agreement

This Agreement, effective as from the last date of signature, is between: _____, of the one part,

and

WORLD HEALTH ORGANIZATION (“WHO”), 20 Avenue Appia, 1211 Geneva 27, Switzerland, of the other part.

WHEREAS, _____ has developed certain information and data relating to _____ which it considers to be confidential and its proprietary property (such confidential information and data being hereinafter collectively referred to as the “Information”).

WHEREAS, _____ is willing to release the Information to WHO, to enable WHO to assess such Information and conduct activities relating to the Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities, including but not limited to collaboration with _____ (the “Purpose”), provided that WHO undertakes to regard the Information as confidential and the property of _____, and release it only to persons who are bound by like obligations of confidentiality and non-use, as are contained in this Agreement.

NOW IT IS HEREBY AGREED as follows:

1. The Parties hereto agree that any disclosure of Information by _____ to WHO will be subject to the following terms and conditions.
2. Any Information which is supplied directly by _____ in written or other tangible form shall be marked by _____ as “confidential”. Any Information which is supplied indirectly by _____, such as from a Stringent Regulatory Authority with _____’s consent, need not be marked “confidential”. Any Information which is disclosed by _____ in oral form shall be confirmed by it in written summary form within 30 days from the date of oral disclosure.
3. In accepting the Information, WHO agrees with _____ as follows:

- a) WHO shall regard the Information disclosed by _____ as confidential and the property of _____. In this regard, WHO agrees to use such Information only for the Purpose (as defined above) and to make no other use thereof, unless and until a further agreement is executed with _____ governing the use thereof;
 - b) nothing in this Agreement shall prevent _____ from disclosing the Information to any third party; and
 - c) WHO has no right in or to the Information of _____.
- 4. WHO undertakes to maintain the Information received from _____ in confidence. In connection with the foregoing, WHO shall take all reasonable measures to ensure that the Information received from _____ shall not be used for any purpose other than the Purpose (as defined above) and shall not be disclosed to any person who does not have a need to know for the aforesaid Purpose and is not bound by similar obligations of confidentiality and restrictions on use as contained in this Agreement.

For the avoidance of doubt, WHO shall be entitled to disclose the Information to third parties collaborating with WHO in connection with the Purpose (including, without limitation, with the relevant regulatory and other authorities of WHO Member States), provided that such third parties are bound by similar obligations of confidentiality and restrictions on use as contained herein.

The obligations of confidentiality and restrictions on use contained in this Agreement shall continue for a period of five (5) years from the date of disclosure by _____ to WHO.
- 5. The obligations of confidentiality and restrictions on use contained in this Agreement shall not apply to any part of the Information which WHO is clearly able to demonstrate:
 - a) was lawfully in its possession and known to it prior to disclosure by _____ hereunder, as evidenced by documents antedating the date of disclosure; or
 - b) was in the public domain or the subject of public knowledge at the time of disclosure by _____ hereunder; or
 - c) becomes part of the public domain or the subject of public knowledge through no fault of WHO; or
 - d) becomes available to WHO from a third party not in breach of a legal obligation of confidentiality to _____ in respect thereof; or
 - e) was subsequently and independently developed by or on behalf of WHO, as shown by written records, by persons who had no knowledge of such Information; or

- f) is required to be disclosed by law, provided that WHO shall in such case immediately notify _____ in writing of such obligation and shall provide adequate opportunity to _____ to object to such disclosure or request confidential treatment thereof (provided always, however, that nothing contained herein shall be construed as a waiver of the privileges and immunities enjoyed by WHO and/or to submit WHO to any national court jurisdiction).
6. WHO undertakes that it will disclose the Information only to those persons who need to receive the Information of _____ for the Purpose (as defined above).
7. WHO undertakes to ensure that all persons who receive the Information disclosed to WHO hereunder shall be bound by similar obligations of confidentiality and restrictions on use as contained in this Agreement.
8. Nothing contained in this Agreement shall be construed, by implication or otherwise, as an obligation to enter into any further agreement relating to any of the Information or as the grant of a licence to WHO to use the Information other than for the Purpose (as defined above).
9. Upon completion of the aforesaid Purpose and in the absence of any further written agreement between the Parties, WHO shall cease all use, shall make no further use of the Information disclosed to it hereunder, and shall, upon written request from _____, promptly return to _____ all of the Information received which is in tangible form, except that WHO may retain one copy of the Information in its files to determine any continuing obligations hereunder.
10. This Agreement constitutes the entire understanding of the Parties hereto with respect to the subject matter hereof and shall not be modified except by mutual agreement in writing.
11. Without the prior written consent of the other Party, neither Party shall, in any statement or material of an advertising or promotional nature, refer to the relationship of the Parties under this Agreement, or to the relationship of the other Party to the Information and/or the Purpose.
12. Any matter relating to the interpretation or the execution of this Agreement which is not covered by its terms shall be resolved by reference to the laws of Switzerland. Any dispute relating to the interpretation or application of this Agreement shall, unless amicably settled, be subject to conciliation. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the Parties or, in absence of

agreement, with the rules of arbitration of the International Chamber of Commerce. The Parties shall accept the arbitral award as final. It is agreed furthermore that nothing contained in this Agreement shall be construed as a waiver of any of the privileges and immunities enjoyed by WHO under national and international law, and/or as submitting WHO to any national court jurisdiction.

Made in two (2) original copies,

_____ **World Health Organization**

By: _____ By: _____

Title: _____ Title: _____

Date: _____ Date: _____

Appendix 9

Notification of an outcome of the national registration provided by the participating manufacturer to the World Health Organization

Details of pharmaceutical manufacturer using the Procedure¹

Manufacturer: Click here to enter text. _____

Country: Click here to enter text. _____

Address: Click here to enter text. _____

Focal point: Click here to enter text. _____

Telephone number (please include codes): Click here to enter text. _____

Email: Click here to enter text. _____

Details of pharmaceutical product or vaccine (the Product) subject to the Procedure

Name of the Product: Click here to enter text. _____

Active pharmaceutical ingredient (s): Click here to enter text. _____

Strength: Click here to enter text. _____

Dosage form: Click here to enter text. _____

Course of the Procedure

Country: Click here to enter text. _____

Regulatory authority: Click here to enter text. _____

Date of submission of the application: Click here to enter text. _____

Date of acceptance of the application (if different from submission date): Click here to enter text. _____

Date of issuance of a decision: Click here to enter text. _____

Length of process interruption/clock-stop (if applicable):² Click here to enter text. _____

¹ Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities – facilitated by WHO.

² Time provided by NRA to the applicant to complete data or respond to regulatory questions.

Decision on registration

Granted, rejected, withdrawn: [Click here to enter text.](#) _____

Registration number (if applicable): [Click here to enter text.](#) _____

Registration granted in line with the reference SRA decision or with deviations, please comment: [Click here to enter text.](#) _____

Compliance with the Procedure, other observations and recommendations

In the course of the Procedure the following deviations were observed and recorded:
[Click here to enter text.](#) _____

Any other observations and recommendations: [Click here to enter text.](#) _____

For the manufacturer

Signature:

Name: [Click here to enter text.](#) _____

Title: [Click here to enter text.](#) _____

Place and date: [Click here to enter text.](#) _____

7.5 Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions

Annex 9, WHO Technical Report Series, 1010, 2018

Background	1084
1. Introduction	1084
2. Aim and objectives of the guidance	1086
3. Scope of the guidance	1087
4. Glossary	1087
5. Essential elements of desk assessment	1090
5.1 High-level support and cooperation	1090
5.2 Commonality of quality management systems in inspectorates	1090
5.3 Convergent standards of good practices	1091
5.4 Reliability and accuracy of information	1091
5.5 Management tools to support consistent and objective assessment	1091
5.6 Risk-based assessment of available information	1091
5.7 Mutual trust and confidence among inspectorates	1092
5.8 Quality assurance of the desk assessment process	1092
5.9 Communication of assessment outcomes	1093
6. Sources of good information and related challenges	1093
6.1 Official websites with databases	1093
6.2 Authenticity of documents	1093
6.3 Failure to submit documentary evidence	1094
7. Submission and assessment of documentary evidence and information	1094
7.1 Submission of application for desk assessment and documentary evidence	1094
7.2 Assessment of documentary evidence and information	1094
7.3 General requirements for documents	1101
8. Regulatory actions and reporting of serious instances of noncompliance	1102
8.1 Communication and information exchange	1103

9. Responsibilities of the applicant	1103
References and further reading	1104
Appendix 1 Model report format for desk assessment for finished pharmaceutical products and active pharmaceutical ingredient manufacturers	1106
Appendix 2 Model report format for desk assessment of quality control laboratories	1110
Appendix 3 Model report format for desk assessment for contract research organizations and clinical trial sites	1113

Background

In recent years both formal and informal collaboration among national regulatory authorities (NRAs) has significantly improved. This, in turn, has strengthened medicines regulatory systems, thereby improving the availability of good quality, safe and effective medical products for patients. A number of regional and supraregional groupings of NRAs are developing, which will facilitate collaboration.

During a World Health Organization (WHO) training symposium on the subject of collaborative registration procedures for national medicines regulatory authorities held in Kenya in September 2016, delegates recommended that the gap in common guidance on best practice for performing desk assessment should be filled. It was proposed that WHO, in collaboration with regulators from Member States, develop guidance that NRAs might leverage in their national regulatory practice and decision-making.

Up to now, there has been no general guidance on approaches and best practices for desk assessment. Desk assessments are conducted in order to verify and confirm compliance with good manufacturing practices (GMP), good laboratory practices (GLP) and good clinical practices (GCP) of foreign facilities for manufacture of finished pharmaceutical products (FPPs) and active pharmaceutical ingredients (APIs), quality control laboratories (QCLs), contract research organizations (CROs) and clinical trial sites.

1. Introduction

NRAs worldwide use systems for the authorization and post-marketing surveillance of medical products that depend upon the assessment of submitted dossiers, variations files and the inspection of FPP and API manufacturers, QCLs and CROs involved in the development, manufacture and distribution of a medical product. Inspections are performed to verify dossier data and to provide evidence that the FPP and API manufacturers, QCLs, CROs and clinical trial sites comply with the relevant good practice (GxP) guidelines and requirements. Thereafter, routine inspections may be conducted depending on the risk rating of the facility.

The performance of on-site inspection of manufacturing, testing and clinical trials as well as the supply and distribution chain outside the NRA's domestic territory is a resource-intensive activity and one that often lies on the critical path to regulatory decision-making. Furthermore, the hosting of multiple regulatory inspections and audits is also a significant overhead for the sites inspected, which adds to the cost of producing the products. Even the best-resourced NRAs face certain limitations and therefore it is regulatory best practice to use quality risk management when prioritizing inspection activities. To make the best use of the limited inspection resources and minimize the need for repeated inspections, it is good practice for national authorities to leverage available and reliable evidence of compliance and noncompliance with good practice

requirements as part of their risk-based inspection planning process, such that there is no on-site inspection without good cause.

Verification and confirmation of compliance with GMP by a manufacturer of an FPP or API in a foreign country may be based on the assessment of evidence that includes the report of a recent inspection of the manufacturer by a competent regulatory authority or another internationally recognized organization.

One element of this risk-based approach is the desk assessment of inspection information from reliable and trusted sources by national or regional authorities in order to decide whether to perform a further inspection before reaching a final decision on marketing authorization, renewal of marketing authorization or another regulatory action. Whereas a desk assessment for GMP and GCP verification and confirmation has been a method used by some organizations and agencies like the WHO Prequalification Team (1), European Member States Agencies (coordinated by the European Medicines Agency (EMA) for centralized marketing authorizations) (2) and the Australian Therapeutic Goods Administration (TGA) (3) for some years, for others it is emerging as an option to be considered.

Such agencies have relied on regulatory decisions made by other agencies, based on bilateral or multilateral agreements depending on the decisions made independently by each individual authority. While not a prerequisite, a range of international and regional formal agreements may be utilized to facilitate the effective management of regulatory decisions in order to increase access to good quality, safe and effective products on the market. These include mutual recognition agreements (MRAs), cooperation agreements (CAs) and memoranda of understanding (MoUs).

Mutual recognition works well if there are common technical standards (including documentation), good regulatory practices; clear procedural legislation in the form of agreement-tracking tools to support the process, trust and political will, with no interference in technical decisions. On the other hand, CAs or MoUs are an option where there is minimal legal obligation. It is also possible to perform desk assessments without a formal agreement.

A desk assessment may be used by an NRA to assess compliance with GMP, GLP and GCP by facilities that manufacture FPPs and APIs. It can also be used to assess CROs, clinical trial sites and outsourced QCLs, where there is an established MRA, CA or MoU, or recognition of a decision made by a competent regulatory authority; Pharmaceutical Inspection Co-operation Scheme (PIC/S) member; or through a WHO prequalification process.

The procedure for the desk assessment will depend on whether the facility was previously inspected by a competent regulatory authority, PIC/S member or under the WHO prequalification scheme, or if an MRA, CA or MoU exists.

The desk assessment process involves submission of documentary evidence by the applicant, usually a manufacturer or representative, to the NRA to demonstrate the conformity of all sites involved in FPP or API manufacturing, or of an outsourced

QCL, CRO or clinical trial site to GMP (the reference is added in the relevant citation), GLP or GCP, respectively. The evidence provided is assessed to determine the level of compliance based on the accepted standards and the scope of the application. The outcome of the assessment process is used as the basis for a regulatory decision that serves as a prerequisite for granting the marketing authorization for a medical product.

Acceptance of data from clinical trial(s) to support a marketing authorization application will rely upon conformance with GCP, including review and approval by an institutional ethics committee where the study was conducted and on obtaining and documenting informed consent of the study subjects if applicable (4).

The option to undertake a desk assessment does not preclude an on-site inspection if the outcome of the assessment does not confirm compliance with the stipulated practices. The confirmation may be granted for a specified period and the process may be subject to recovery of costs. It is important to determine the number of times a desk assessment may be performed before it becomes necessary to conduct a physical inspection, taking into consideration the outcome of the desk assessment, i.e. the number, nature and impact of observations and the integrity of the data provided.

2. Aim and objectives of the guidance

This guidance aims at providing an approach for use by NRAs for assessing compliance with GMP, GLP or GCP using documentation issued by other NRAs in lieu of conducting an inspection of a specific site.

The use of the desk assessment as described in this guidance is intended to provide a way to reduce the necessity for duplication and the frequency of inspections while relying on authentic and reliable documentary evidence from other regulatory authorities. Desk assessment should also reduce the inspection resources needed by both the manufacturing site and the NRAs and result in broader availability of high-quality medicinal products to patients globally. It may also be used by NRAs for continuous evidence-based regulatory decisions and follow-up on quality assurance issues that go beyond marketing authorization.

The guidance also lists the key documents to be submitted by other regulatory authorities and/or manufacturers that provide reliable information about the status of compliance with good practices in manufacturing, quality control and clinical trials of a specified medical product. The essential information and documents that need to be available to conduct the desk assessment in relation to the most relevant GxPs, in this context GMP, GLP and GCP, are described.

The objective of this guidance is to:

- ensure that a standardized procedure is followed for desk assessment of inspection documentation and reports issued by trusted, competent regulatory authorities and of records of corrective actions from inspected sites;

- facilitate a convergent approach and model for exchange and use of inspection information in national and regional decision-making concerning the necessity to perform preapproval and surveillance inspections.

3. Scope of the guidance

This guidance applies to all FPP and API manufacturers (including biologicals and vaccines manufacturers, all sites where APIs are being imported, repackaged or relabelled, and investigational medical product manufacturers), outsourced QCLs, CROs and clinical trial sites that are subjected to GxP inspections in foreign countries. However, the NRA may use desk assessments to set up risk-based inspection plans without loss of regulatory oversight through physical inspections.

The guidance has general geographical applicability for regulatory authorities and United Nations agencies in order to support ongoing harmonization initiatives and optimum use of limited resources. It covers the information and evidence required to undertake a desk assessment process, but not the procedure for on-site inspection, except the process of tracking and review of completion of corrective and preventive action (CAPA). On-site inspection is covered in a separate WHO guidance document (5, 6).

Desk assessment procedures can be used for preapproval, renewal and surveillance inspections. Caution is needed when assessing sites that have failed to meet the specified standard after GxP inspections. However, desk assessments may be appropriate for a site that has failed an inspection, in order to confirm the failure and thus avoid the need for a physical inspection. The NRA takes the ultimate decision on whether it is appropriate to perform a desk review or whether an on-site inspection would be needed.

4. Glossary

The definitions given below apply to the terms used in this guidance. They may have different meanings in other contexts.

active pharmaceutical ingredient. Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

agent or local technical representative. Every applicant who is not resident in the country of the national regulatory authority (NRA) should appoint a person in that country to be an agent (local technical representative). The appointment should be notified to the NRA by submitting a letter of appointment supported by powers of

attorney duly notarized in the country of origin, and registered with the registrar of companies in the country of the NRA.

applicant. A person who applies for marketing authorization of a medical product to the national regulatory authority, who must be the owner of the product. The applicant may be a manufacturer or the party applying for a product certificate. After the product is registered, the applicant becomes the marketing authorization holder.

bioequivalence. Two medical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailability, in terms of rate ($C_{\max}$ and $t_{\max}$) and extent of absorption (area under the curve), after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.

clinical trial (or clinical study). Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamics effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

competent regulatory authority. Any organization that has a legal authority or power to perform a designated regulatory function for authorization of a medical product: the national regulatory authority in the Member State.

cooperation agreement. A formal business document outlining the basic terms of an agreement with another individual, group or entity. It is one of the first steps towards a more detailed contract. Alternative names include, but are not limited to, memorandum of understanding, cooperation contract or collaboration agreement.

desk assessment. The evaluation of documentary evidence by a competent regulatory authority recognized by the national regulatory authority, for compliance with the required good practices (good manufacturing practices (GMP), good laboratory practices and good clinical practices) in support of marketing authorization and other regulatory decisions. Desk assessment may be performed in support of a new marketing authorization, or for routine GMP inspection (including in the frame of specified product(s) life-cycle management as required).

finished pharmaceutical product. A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling.

good clinical practices. In this context the term means a standard for design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials in a way that provides assurance that the data and reported results are credible, accurate and that the rights, safety and well-being of trial subjects are protected.

good laboratory practices. A quality system concerned with the organizational process and the conditions under which nonclinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

good manufacturing practices (GMP). That part of quality management which ensures that products are consistently produced and controlled according to the quality standards appropriate to their intended use and as required by the marketing authorization, clinical trial authorization or product specification. GMP are concerned with both production and quality control. GMP are aimed primarily at managing and minimizing the risks inherent in pharmaceutical manufacture to ensure the quality, safety and efficacy of products.

information sharing. An exchange of data between individuals or entities outside the traditional organizational boundaries, to achieve a common goal in terms of better policies and to deliver better services. This may mean that one party is disclosing information while the other is collecting the information or both parties are mutually disclosing and collecting information.

manufacture. All operations of purchase of materials and products, production, quality control, release, storage, distribution of medical products and the related controls.

manufacturer. A manufacturer is a natural or legal person who holds a manufacturing authorization and has responsibility for manufacturing of a medical product or active pharmaceutical ingredient.

marketing authorization (product licence, registration certificate). A legal document issued by the competent regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself and includes details of packaging, labelling and shelf life.

medical product. A term that includes medicines, vaccines, diagnostics and medical devices.

memorandum of understanding (MoU). A formal agreement between two or more parties. Companies and organizations can use MoUs to establish official partnerships. MoUs are not legally binding but they carry a degree of seriousness and mutual respect, stronger than a gentlemen's agreement.

mutual recognition agreement. This is defined as the reciprocal adoption or acceptance of regulatory decisions or outcomes in other partner states in form of a legal agreement. It is stronger than a gentlemen's agreement and is usually binding.

Pharmaceutical Inspection Co-operation Scheme (PIC/S). This is a non-binding, informal cooperative arrangement between regulatory authorities in the field of good manufacturing practices of medical products for human or veterinary use.

pharmaceutical product. Any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in human beings, or with a view to making a medical diagnosis in human beings, or to restoring, correcting or modifying physiological functions in human beings.

quality control. All measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics

quality management system. An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

quality system. The sum of all features that are necessary to implement an organization's quality policy and meet quality objectives. It includes organizational structure, responsibilities, procedures, systems, processes and resources. Typically these features will be addressed in different kinds of documents, such as the quality manual and documented procedures.

5. Essential elements of desk assessment

5.1 High-level support and cooperation

Interagency communication can facilitate greater regulatory convergence. This in turn can increase the efficiency and quality of medical product development and the NRA review processes as well as improving patients' access to quality medical products. This not only entails accessing information from the public websites of other NRAs, such as guidelines, decisions and product recalls, but also actively sharing information between NRAs, in particular with respect to inspection findings during application review and for decision-making.

The legal framework and governance structure of the NRA should include provisions on support and collaboration with other agencies in making regulatory decisions. Legal provisions (laws and regulations) that allow reliance on foreign NRA inspections and enforcement actions based on well-defined criteria should be established and implemented. Such recognition can take the form of MRAs, CAs or MoUs between collaborating inspectorates and could entail agreements that would enable bilateral or multilateral commitment and exchange of information on specified sites.

MRAs are usually binding and may require inspectorates at the same level of development with the appropriate organization and funding to fulfil the responsibility of protecting and promoting public health. Where such recognition exists, fewer requirements are needed to determine compliance with GMP, GLP and GCP of foreign manufacturing sites, CROs and outsourced QCLs, given the level of cooperation and trust established.

5.2 Commonality of quality management systems in inspectorates

There should be a quality system in place based on recognized international standards, namely the WHO quality management system (QMS) or International Organization for Standardization (ISO) QMS standards. The QMS should be established, implemented and maintained throughout the period of recognition or reliance. The primary purpose of a QMS is to ensure that adequate quality standards are maintained.

Adopting common standards for quality system requirements (within GMP, GLP or GCP of the NRA) helps to achieve consistency in inspection standards between inspectorates and thus facilitates mutual recognition and reliance.

5.3 Convergent standards of good practices

WHO has published standard requirements for compliance with GMP (7) and other good practices including *Good practices for pharmaceutical quality control laboratories* (8) and GCP (4, 9). These serve as a measure of the standards established by the manufacturers in order to deliver and supply a good quality and safe product. The NRA should have similar standards of GxP in order to facilitate uniform desk assessment.

5.4 Reliability and accuracy of information

Applicants are responsible for ensuring that information provided for desk assessment is reliable and not false or misleading.

Mechanisms and controls should be established to ensure that the information provided by the applicant is authentic, legible, current and accurate. There should be strong confidence that the information provided relates to the same strength and specifications of the product and to the same site, workshop or production line (use of unique facility identifiers should be considered); and should accurately relate to the product under assessment, without any false information.

Controls should be established and documented by the NRA to ensure that the information provided by the applicant is secured and remains confidential.

5.5 Management tools to support consistent and objective assessment

Well-structured and up-to-date assessment tools and procedures should be adopted to enable uniform and consistently objective assessment of the documents provided. Personnel involved in the assessment process should have an acceptable level of training and experience with GMP, GLP or GCP. They should also be trained to use the assessment tools and procedures consistently without bias, and to be able to detect inconsistent and inaccurate information regarding the product under assessment. Validated electronic assessment tools (software applications) may be used to perform the desk assessments. Although paper-based systems may also be used, electronic tools are preferred.

5.6 Risk-based assessment of available information

Even the best-resourced NRAs are subject to limitations in terms of time, funding and personnel, and therefore it is regulatory best practice to apply quality risk management as defined and outlined in ICH Q9: Quality risk management, in prioritizing inspection activities (10, 11). The aim of the desk assessment process should be to provide to the

NRA, in a timely manner, the required assurance that the site in question demonstrates an acceptable level of GxP for the FPP, API or trial under assessment.

The assessment should take into consideration and focus on the critical products and critical processes in the manufacture of a specified product in relation to patient risk, based on the knowledge that other competent and trusted inspectorates have inspected and approved the site of manufacture.

Key factors to consider include the origin of the information and its authenticity, the location of the site of manufacture, complexity and type of the product (whether sterile or biological) and the risk to the patient (12).

5.7 Mutual trust and confidence among inspectorates

Joint inspections may be conducted by countries within the same region or countries that are party to a relevant agreement. Through such interactions, regulators may be able to build confidence, share information and experiences in order to be able to rely on others' inspection outcomes and regulatory decisions. Joint inspections also serve as a basis for desk assessments through building mutual trust and identifying barriers to reliance on other regulators' inspection outcomes and devising solutions to overcome them. Building mutual trust and confidence involves exchange of information, identifying areas of collaboration, work sharing and eventually binding through a legal agreement between collaborating NRAs.

Some competent NRAs are already using these models successfully. Examples include the United States Food and Drug Administration's MRA with the European Union, Health Canada's MRA with the European Union, and the TGA's risk-based desktop assessment process. The TGA's process comprises MRA and compliance verification pathways, which are essentially desk reviews. Those two pathways can result in cost savings for both the manufacturer, who does not have to bear the cost of hosting another inspection, and the regulator, who saves on personnel time and other resources.

5.8 Quality assurance of the desk assessment process

Quality assurance of the desk assessment process involves inspiring confidence that the requirements of the assessment process will be fulfilled. This would require documented evidence of compliance of the inspectorate function with a QMS¹ over a period of three to five years.

NRAs should create a cycle for the process of reviewing desk assessments, including timelines for applicants' responses.

¹ For example, ISO/International Electrotechnical Commission (IEC) 17020 *Conformity assessment – requirements for the operation of various types of bodies performing inspection*, PIC/S *Quality management system for inspectorates* or ICH Q9 *Quality risk management*.

5.9 Communication of assessment outcomes

Communication of the outcome of the desk assessment process should be transparent and timely. Communication should focus on the quality of the product and the regulatory decisions between the authorities in the importing country and exporting country, the manufacturers and any other relevant third party, such as procurement agencies. The outcome of the desk assessment should be communicated to the applicant whether the result is an approval, a deferment or a rejection of an application for GxP assessment, and to the responsible NRA.

If a rejection leads to a regulatory decision to conduct an on-site inspection, a statement of the reasons should be provided, with details of the documents, information and regulatory requirements taken into account in reaching the decision. An appeal mechanism, including a time frame within which applicants may lodge an appeal, should also be in place. The NRA should reserve the right to conduct an inspection of any site.

6. Sources of good information and related challenges

Trusted sources of information are available either in the public domain or from the NRAs. The amount of detail provided in the information may vary depending on applicable restrictions and rights of the owners. Websites of NRAs may provide information on non-compliant facilities, market complaints and product recalls, among others.

Certificates, reports or other documents issued by competent regulatory authorities also provide information about a specified manufacturer, outsourced QCL, CRO or clinical trial site.

6.1 Official websites with databases

NRAs and organizations such as WHO and EMA have websites where information on facilities' compliance and noncompliance with GxP is available. Some websites provide GMP certificates and inspection reports together with other information about medicines, pharmaceutical manufacturing facilities, QCLs and clinical trials. Information may also be obtained on medicine sampling and results of the testing, including samples that failed analysis, product recalls and rapid alerts. The website consulted should be current and regularly updated. Certificates presented by applicants for marketing authorization should be verified using the information available on the websites of NRAs or by contacting the relevant NRA directly. The NRA is responsible for checking that information is current and complete.

6.2 Authenticity of documents

It is important that documentary evidence provided by the applicant as the basis for granting approval for GMP, GLP or GCP be current, accurate and authentic. It is the

responsibility of the applicant to ensure this. The applicant should include a cover letter with the application stating that all the documents submitted are authentic and correct. NRAs may request that information such as inspection reports and certificates granted by NRAs be notarized or certified.

Submission of inaccurate or false information may result in declaration of the manufacturer, QCL or CRO as noncompliant.

6.3 Failure to submit documentary evidence

If the applicant is unable to provide adequate documentary evidence, including information on current compliance, or to submit the documents before a specified deadline, or fails to submit documents as required, the application for desk assessment may be rejected, leading to a decision to conduct an on-site inspection. In such circumstances, approval of GMP, GLP or GCP should only be granted after the on-site inspection has been conducted, and the manufacturer, CRO, clinical trial site or outsourced QCL has been found compliant.

7. Submission and assessment of documentary evidence and information

7.1 Submission of application for desk assessment and documentary evidence

Prior to assessment, an application for desk assessment for each site should be submitted by the applicant to the NRA. Applications may be required for preapproval, renewals and surveillance inspections, as specified by the NRAs in the respective inspection guidelines and procedures.

7.2 Assessment of documentary evidence and information

Desk assessment involves a detailed evaluation of the specified documentary evidence supplied by the applicant. It will include an assessment of reports of recent inspections of the relevant manufacturing site undertaken by a competent regulatory authority, together with other available regulatory information. Desk assessment for compliance of facilities manufacturing FPPs and APIs with GMP, GLP or GCP can be used where the NRA has an agreement or understanding on exchange of information, such as an MRA, CA or MoU.

In accordance with international agreements with certain countries, the NRA may accept compliance of a foreign site with GMP, GLP or GCP requirements based on a current certificate or approval letter issued by the regulatory agency of the other party to the MRA.

Marketing authorization may be granted by the NRA on the basis of a current certificate or approval letter issued within the scope of an MRA. The scope of the

manufacturing activities indicated in the application should be within the scope of the activities covered by the certificate or approval letter.

Generally, where an MRA has been established:

- a. a copy of the manufacturing authorization granted by national authorities together with a certified translation, where this is not in English, may suffice.

Where a CA or other bilateral or multilateral arrangement has been established, the document specified in a. above should be provided in addition to the following essential documents:

- b. a site master file (13) whose approval date was not more than one year ago, and any forecast modifications, together with legible colour printouts of water treatment and air-handling systems, including pipeline and instrumentation drawings in A3 or A2 format;
- c. a list of all the products and dosage forms manufactured on-site. The list should include proprietary names and International Nonproprietary Names (INN);
- d. a copy of the last inspection report issued by the NRA with a certified translated copy where this is not in English, and GMP, GLP or GCP certificates or an approval letter with a certified translated copy where this is not in English (production-line specific);
- e. current full inspection report(s) for inspections performed by a competent regulatory authority in the past three to five years, with a certified translated copy where this is not in English;
- f. proof of CAPA implementation and final decision by the NRA related to observations or deficiencies noted in the latest inspection report or any warning letter or equivalent regulatory action (production-line specific);
- g. the most recent product quality review(s) (PQR)(s) of the concerned product(s); PQR(s) (4) or equivalent documentation covering all required subsections and trend results should be presented; proprietary information for vaccines is not required;
- h. the completed batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant product(s);
- i. a list of any recalls in the past three years related to products with quality defects.

The following documents may be evaluated while performing desk assessments:

- a confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the product(s) has been performed and all matters dealt with;

- master batch manufacturing and packaging record(s) of the product(s) of interest;
- a copy of any warning letter, or equivalent regulatory action, issued by any authority to which the site provides or has applied to provide the product;
- out-of-stock situations.

The evidence lists required for desk assessment of compliance with GMP, GLP or GCP for each type of facility and collaborative arrangement are listed in Table A9.1 and the specific documentary evidence required is presented in Table A9.2.

Table A9.1

Type of facility and evidence documents required for desk assessment^a

Type of facility	Where an MRA exists	Where a CA or MoU exists; or member of PIC/S; or competent NRA regulator; or WHO prequalification scheme	Where no MRA, CA or MoU exists; or non-member of PIC/S; or WHO prequalification scheme
Nonsterile products facilities • FPP • API	Evidence list A	Evidence list B	On-site GMP inspection
Sterile products facilities • FPP • API	Evidence list A and certification to relevant ISO standards for sterilization facility ^b	Evidence lists B and C	On-site GMP inspection
Outsourced (contract) testing laboratory; and outsourced sterilization	Evidence list A	Evidence list D	On-site laboratory inspection On-site GMP inspection

Table A9.1 *continued*

Type of facility	Where an MRA exists	Where a CA or MoU exists; or member of PIC/S; or competent NRA regulator; or WHO prequalification scheme	Where no MRA, CA or MoU exists; or non-member of PIC/S; or WHO prequalification scheme
CRO or clinical trial site	Evidence list E	Evidence lists E and F	On-site GLP or GCP inspection
• clinical facility • clinical laboratory • bioanalytical laboratory • company performing pharmacokinetics statistical analysis			

API: active pharmaceutical ingredient; CA: cooperation agreement; CRO: contract research organization; FPP: finished pharmaceutical product; GCP: good clinical practices; GLP: good laboratory practices; GMP: good manufacturing practices; ISO: International Organization for Standardization; MoU: memorandum of understanding; MRA: mutual recognition agreement; NRA: national regulatory authority; PIC/S: Pharmaceutical Inspection Co-operation Scheme.

^a Explanations of the evidence lists are provided in Table A9.2.

^b If applicable to the manufacturing facility or activity.

A list of the documents that should be provided for desk assessment is given in Table A9.2. The documents required for desk assessment of manufacturing sites are indicated in evidence lists A, B, C and D; for outsourced QCL, they are indicated in evidence lists A and D and for CROs and clinical trial sites, they are indicated in evidence lists E and F.

Table A9.2

Documentary evidence requirements for desk assessment

	Required evidence	Comments and exceptions
Evidence list A	Current GMP certificate or approval letter GLP or ISO/IEC 17025 certification for outsourced laboratory	Certificates must be sufficient to cover the scope of the GMP compliance application

Table A9.2 *continued*

	Required evidence	Comments and exceptions
Evidence list B	Current GMP certificate or approval letter	GMP agreements may be requested if the foreign manufacturer performs the release for supply function
	Current manufacturing licence	The manufacturing licence should show the scope of products and activities approved by the NRA
	Regulatory inspections conducted within the past three years and a copy of the most recent inspection report issued by the competent regulatory authorities as stated in Table A9.1	A list of all inspection reports applicable to the scope of the application is required. These may be sent to the NRA directly from the manufacturer CAPA evaluation for the recent inspection report should be provided
	Market complaints register	For the previous three years, including one investigation report for one of the complaints classified as high risk to public health The complaint register should be applicable to the products named in the application
	Details of any regulatory actions in the past three years	For example, product alerts, warning letters, import alerts, recalls due to defects
	Site master file, quality manual or equivalent	Site master file ^a Site master file is not required if the scope of the application is only for the step of release for supply
	List of products intended for supply in the recipient country	

Table A9.2 *continued*

	Required evidence	Comments and exceptions
	• PQR report; • process validation report; and • batch records (batch manufacturing, packaging and testing) for each product for which marketing authorization is being applied	The PQR reports should be provided for each product. If there are multiple products, one PQR report is required for each FPP dosage form for which an application is being made The batch records of a product for each FPP dosage form manufactured in the past 6 to 12 months; and the corresponding process validation reports and annual product quality review reports
	List of reprocessed or reworked product batches in last year (or last two years)	
Evidence list C	Validation master plan	Not required if the scope of the application is only for the step of release for supply
	Aseptic processing and filling validation reports if applicable	Required if the application concerns products that are not terminally sterilized
Evidence list D	Current GMP certificate, or ISO/IEC accreditation certificate or WHO prequalification	For outsourced testing laboratories, a GLP certificate issued by a recognized regulatory authority or a current ISO/IEC 17025 accreditation certificate or prequalification of the laboratory by WHO is required For outsourced sterilization facilities, certification to applicable ISO sterilization standards (e.g. ISO 11137, ISO 11135) is necessary
	Quality manual, laboratory manual or equivalent	The quality manual or laboratory manual should be written in accordance with the principles of <i>WHO good practices for pharmaceutical quality control laboratories</i> (8), or as per the <i>ISO/IEC 17025 General requirements for the competence of testing and calibration laboratories</i> (14).

Table A9.2 *continued*

	Required evidence	Comments and exceptions
	Contract or agreement between the FPP or API manufacturer and the outsourced testing laboratory or sterilization institution	A copy of the contract or agreement clearly describing the roles and responsibilities of the manufacturer and the testing laboratory or sterilization institution should be submitted
	A list of tests a laboratory is authorized to perform as per the scope of its accreditation according to the ISO/IEC 17025 or WHO prequalification For botanical ingredients, evidence that authenticated standard reference materials are used	The scope of activities of the outsourced laboratory should include the type, range and volume of testing and/or calibration, validation and verification activities it undertakes
	Out-of-specifications (OOS) procedure	Records of three OOS including at least one assigned to a laboratory error
Evidence list E	Current GCP or GLP certificate or approval letter	GCP/GLP certificate or approval letter issued by the NRA; non-use of disbarred investigators or firms
Evidence list F	Clinical trial approval by the NRA	Provide a list summarizing the approved trials and their outcome Provide complete study report if no application has been submitted for marketing authorization of a product Where applicable, reports from a data safety monitoring board or independent safety monitors should be provided
	Copy of IRB/IEC clinical trial approval	Provide approved protocol, amended protocol and consent form Provide a list of committee members of the IRB/IEC

Table A9.2 *continued*

Required evidence	Comments and exceptions
Clinical trial master file	Responsibilities of the sponsor and clinical investigator should be reported Records of management and assessment of subcontracted vendors should be provided Deviation management and procedures for handling the investigational product should be made available
Inspections conducted within the past three years and a copy of the most recent inspection report issued by the competent regulatory authority as stated in Table A9.1	A list of all inspection reports applicable to the scope of the application is required. These may be sent to the NRA directly from the manufacturer or CRO Provide the following reports: • reports by the NRA; • clinical monitoring reports by the sponsor or the CRO (if monitoring tasks were outsourced to a CRO)
Concerns or alerts raised by the NRA and any other responsible authority	Provide details of investigation of any instances of noncompliance and how they were addressed

API: active pharmaceutical ingredient; CAPA: corrective and preventive action; CRO: contract research organization; FPP: finished pharmaceutical product; GLP: good laboratory practices; GMP: good manufacturing practices; IEC: independent ethics committee; IRB: institutional review board; ISO: International Organization for Standardization; NRA: national regulatory authority; PQR: product quality review.

^a Refer to WHO Technical Report Series, No. 961, Annex 14, for guidelines on compiling a site master file (13).

7.3 General requirements for documents

Documents to be submitted to NRAs as evidence of compliance should adhere to the following general requirements.

- All certificates and other supporting documents should be in English or in a nationally accepted language.
- Where the document is not in English or a nationally accepted language, it should be submitted with a certified translation.
- Translated documents must be accompanied by a signed and dated statement by the certified translator, stating that each is a true and accurate translation of the original document.

- Submitted documents should be the most recent and reflect current activities and practices, and dated (expired or superseded documentation cannot be used).
- Documents must provide sufficient information to cover the scope of activities for which confirmation of GxP compliance is sought.

All documents, whether the original format is paper or electronic, are to be submitted electronically (for example as DVDs CDs, etc.) and are not required to be certified as original copies unless requested by the NRA. Certification of a document may be requested if, for example, there is concern over the validity of the supplied documents. The NRA can request certified copies of original documents at any time. Certified copies must be legible and authenticated as true copies by either:

- an official of the regulatory agency of a country that is a party to an MRA, or a partner to an MoU or a CA, WHO prequalification, stringent regulatory authority, regulator; or
- a public notary (who must include details of the relevant practice certificate or licence number).

Figure A9.1

Model declaration form for the front page of a certified document

Declaration of authenticity

I, the undersigned, as a _____ for the state of _____, country _____ declare that the attached copy of the document issued by _____ and certified by me, is a true and accurate copy of an original document presented to me for certification.

_____, Date: ____/____/____
Full names [signature] day/month/year

8. Regulatory actions and reporting of serious instances of noncompliance

Regulatory actions should be taken by NRAs in response to the reporting of serious instances of noncompliance, such as a variation from the registered product that has a direct impact on the safety of a patient or subject, and follow applicable procedures for appropriate investigations.

The impact of the noncompliance should be assessed by the NRA to ascertain the potential risk to public health, supply and availability of affected medicines. This

assessment should take into consideration the risk of exposure to national shortages having undesirable safety and financial implications.

The following are some of the actions that can be taken by the NRA in response to confirmed reports of serious noncompliance:

- issuance of a rapid public alert to collaborating partners;
- issuance of a noncompliance letter;
- suspension, revocation, withdrawal or cancellation of GMP, GLP or GCP certificate;
- suspension of certificate of suitability;
- institution of a recall;
- suspension of supply or importation;
- prosecution.

8.1 Communication and information exchange

There should be a mechanism for exchange of information among inspectorates, for example, a shared web-based portal for communication of serious instances of noncompliance in a timely and secure manner. The NRA should have a process for information exchange and use of identifiers for tracking enquiries and applicants' responses.

If facilities are found to have serious issues of noncompliance with GMP, GLP or GCP guidelines, this should be communicated to stakeholders and partners. The regulatory decision and action taken should be explained to the stakeholders, including the analysis of the risk and threats to the patient.

9. Responsibilities of the applicant

The main responsibilities of an applicant for GMP, GLP or GCP desk assessment are summarized below.

- Ensuring that all required evidence documents are submitted with applications for GMP, GLP or GCP desk assessment. Incomplete applications may be rejected.
- Remitting all application fees at the time of lodging an application for GMP, GLP or GCP desk assessment.
- Submitting applications for renewal of a GMP, GLP or GCP certificate prior to the expiry of the current certificate, according to a deadline specified by the NRA.
- Promptly submitting any additional information that may be requested by the NRA during an assessment. Failure to provide required documents in time may result in the application being rejected.

References and further reading

References

1. Essential medicines and health products: prequalification of medicines. Inspections. Geneva: World Health Organization (<https://extranet.who.int/prequal/inspection-services>, accessed 1 February 2017).
2. Compilation of community procedures on inspections and exchange of information EMA/572454/2014 Rev 17 compliance and inspection. London: European Medicines Agency; 2014.
3. Australian regulatory guidelines good manufacturing practice (GMP) – Clearance for overseas manufacturers, seventeenth edition, version 1.0 May 2011. Woden (ACT): Therapeutic Goods Administration; 2011.
4. Guidelines for good clinical practice for trials on pharmaceutical products. In: WHO Expert Committee on the Selection and Use of Essential Medicines: sixth report. Geneva: World Health Organization; 1995: Annex 3 (WHO Technical Report Series, No. 850; https://iris.who.int/bitstream/handle/10665/37340/WHO_TRS_850.pdf?sequence=1&isAllowed=y).
5. Guidelines on pre-approval inspections. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-fourth report. Geneva: World Health Organization; 2002: Annex 7 (WHO Technical Report Series, No. 902; https://iris.who.int/bitstream/handle/10665/42424/WHO_TRS_902.pdf?sequence=1&isAllowed=y).
6. Provisional guidelines on the inspection of pharmaceutical manufacturers. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-second report. Geneva: World Health Organization; 1992: Annex 2 (WHO Technical Report Series, No. 823; https://iris.who.int/bitstream/handle/10665/39645/WHO_TRS_823.pdf?sequence=1&isAllowed=y).
7. WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986; https://iris.who.int/bitstream/handle/10665/112733/WHO_TRS_986_eng.pdf?sequence=1&isAllowed=y).
8. WHO good practices for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 1 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y).
9. Guidance for organizations performing in vivo bioequivalence studies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 9 (WHO Technical Report Series, No. 996; <https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>).
10. ICH Q9 quality risk management. Geneva: The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (<https://www.ich.org/page/quality-guidelines>).
11. Guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 981; https://iris.who.int/bitstream/handle/10665/81144/WHO_TRS_981_eng.pdf?sequence=1&isAllowed=y).
12. Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 5 (WHO Technical Report Series, No. 986; https://iris.who.int/bitstream/handle/10665/112733/WHO_TRS_986_eng.pdf?sequence=1&isAllowed=y).

13. Guidance for site master file. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 14 (WHO Technical Report Series, No. 961; https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1).
14. ISO/IEC 17025:2005, General requirements for the competence of testing and calibration laboratories. Geneva: International Organization for Standardization/International Electrotechnical Commission; 2005.

Further reading

- ICH efficacy guidelines (R2). Geneva: The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (<https://www.ich.org/page/efficacy-guidelines>).
- Inspection of pharmaceutical manufacturers, Annex 2, WHO Technical Report Series 823, 1992.
- ISO 11135:2014. Sterilization of healthcare products – ethylene oxide – requirements for the development, validation and routine control of a sterilization process for medical devices. Geneva: International Organization for Standardization; 2014.
- ISO 11137-1:2006. Sterilization of healthcare products – radiation – part 1: Requirements for development, validation and routine control of sterilization process for medical devices. Geneva: International Organization for Standardization; 2006.
- ISO 11137-2:2013, Sterilization of healthcare products – radiation – part 2: Establishing the sterilization dose. Geneva: International Organization for Standardization; 2013.
- ISO 9001:2015. Quality Management Systems – Requirements. Geneva: International Organization for Standardization; 2015.
- ISO/IEC 17020:2012. Conformity assessment – Requirements for the operation of various types of bodies performing inspection. Geneva: International Organization for Standardization/International Electrotechnical Commission; 2012.
- Outline of a procedure for coordinating the verification for the GMP status of manufacturers in third countries. London: European Medicines Agency; 2005.
- PIC/S. Recommendation on quality system requirements for pharmaceutical inspectorates PE 009-13 (Annexes). Geneva: Pharmaceutical Inspection Co-operation Scheme; 2017.
- PIC/S. Recommendation on quality system requirements for pharmaceutical inspectorates, PI 002-3. Geneva: Pharmaceutical Inspection Co-operation Scheme; 2007.
- WHO global model regulatory framework for medical devices including in vitro diagnostic medical devices. (Annex 4, 51st report, 2017).
- WHO good practice for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 1 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y).
- WHO guidance on good manufacturing practices: inspection report. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 4 (WHO Technical Report Series, No. 996; <https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>).
- WHO Guidelines on variations to a prequalified product. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013: Annex 3 (WHO Technical Report Series, No. 981; https://iris.who.int/bitstream/handle/10665/81144/WHO_TRS_981_eng.pdf?sequence=1&isAllowed=y).

Appendix 1

Model report format for desk assessment for finished pharmaceutical products and active pharmaceutical ingredient manufacturers

Part 1. General information	
a) Particulars of the applicant	Name of applicant, physical address, postal address of applicant (if different from physical address), 24-hour telephone numbers, fax, email address
b) Particulars of the manufacturer	Name of manufacturer, physical address of manufacturer including the block and/or unit number, postal address of manufacturer (if different from physical address), 24-hour telephone number(s), fax, email address, contact person
c) Activities performed on the site	For example, manufacture of APIs, manufacture of FPPs, intermediates or bulk packaging, laboratory testing, batch release, warehousing, primary and secondary packaging
d) Date of last inspection by the NRA	Date when the last inspection was carried out, name of the national medicines regulatory authority that carried out the inspection
e) Production and packaging lines applied for	For FPP: dosage form line, category: beta lactam, non-beta lactam, biologicals, vaccines, hormones, cytotoxic products For API: name of API
f) Authorized representative of marketing authorization holder in the recipient country	For example, representative, agent
Part 2. Documentary evidence (comment on adequacy of information provided)	
a) Current site master file	Comment on date, completeness and adequacy in accordance with WHO or PIC/S guidelines for writing site master file
b) List of all regulatory inspections carried out in the past three years	Name of all the regulatory authorities that carried out the inspection, dates when the inspection was carried out, inspection outcome

Table *continued*

Part 2. Documentary evidence (comment on adequacy of information provided)	
c) Copy of valid manufacturing licence granted by the NRA together with a certified translation, if not in English	Number of manufacturing licence, name of regulatory authority that granted the licence, validity of the manufacturing licence and scope
d) Copy of valid GMP certificate granted by the national medicines regulatory authority together with a certified translation, if not in English	Number of GMP certificate, name of NRA that granted the certificate, validity of the GMP certificate and scope
e) List of products manufactured at the site and those to be exported to the country of import	List of products, dosage form (where applicable), list of registered products and those to be registered
f) Notarized copy of inspection report(s) from the national medicines regulatory authority and/or that from WHO prequalification (whichever is applicable) carried out within the past three to five years	- Name of the regulatory authority that carried out the inspection, dates of the inspection, scope of inspection, findings and recommendations, list of findings of noncompliance, conclusion - CAPA reports submitted and found satisfactory for the most recent inspection (adequacy of CAPA, timelines)
g) Performance of the company's products on the market over the past three years	Any product alerts, warning letters, market complaints, product failure, product recall or any unacceptable findings for the product(s) in scope
h) Reports of product quality review	For products for which marketing authorization is being sought or renewed: assess the consistency of the processes, trends, specifications, process changes, recalls, returns, market complaints, deviations from critical parameters, in-process controls, quality control tests, stability study data (select product of interest)
i) Validation master plan	Validation policy, utilities qualification, equipment qualification, procedures, protocols, reports, cleaning, personnel qualification, process validation, analytical method validation, computer validation, revalidation, requalification, validation matrix
j) Process validation for one of the products marketed or to be registered in the country of import	Comment on adequacy

Table *continued*

Part 2. Documentary evidence (comment on adequacy of information provided)	
k) One batch manufacturing record (BMR) for each product together with the master batch record including the packing and analytical part (with a certified translation of the original BMR where applicable); BMR should refer to a product marketed or to be registered in the country of import	Comment on adequacy
l) Out-of-specification (OOS) procedure: records of three OOS including at least one assigned to a laboratory error	
m) List of reprocessed or reworked product batches in the past two years	
Part 3. Recommendation	
1. Recommended for a GMP compliance approval? <i>(Provide recommendation based on the results of the assessment done in Parts 1 and 2)</i>	
2. If Yes, list production lines, product, pharmaceutical active ingredient recommended:	
3. If No, state reasons and the relevant sections of the guideline(s) below:	

Table *continued*

Part 4. Evaluation team	
First assessor	
Signed: _____	Date: _____
Name: _____ (BLOCK CAPITALS)	Position: _____
Second assessor	
Signed: _____	Date: _____
Name: _____ (BLOCK CAPITALS)	Position: _____

API: active pharmaceutical ingredient; CAPA: corrective and preventive action; FPP: finished pharmaceutical product; GMP: good manufacturing practices; NRA: national regulatory authority; PIC/S: Pharmaceutical Inspection Co-operation Scheme.

Appendix 2

Model report format for desk assessment of quality control laboratories

Part 1. General information	
a) Particulars of the applicant	Name of applicant, physical address, postal address of applicant (if different from physical address), 24-hour telephone numbers, email address
b) Particulars of the quality control laboratory (QCL)	Name of QCL, physical address of QCL, postal address of the laboratory (if different from physical address), 24-hour telephone number(s), email address, contact person
c) Date of last inspection by SRA, WHO or accreditation body for ISO/IEC 17025	Name of NRA or accreditation body that carried out the inspection, dates when the inspection was carried out and the inspection outcome
Part 2. Documentary evidence (comment on adequacy of information provided)	
a) Copy of appropriate certificate or approval granted by a recognized regulatory authority or accreditation certificate granted by accreditation body for ISO/IEC 17025 together with a certified translation, if not in English	Number/reference of appropriate certificate or approval or ISO/IEC 17025 certificate, name of regulatory authority that granted the certificate and validity of the certificate
b) Scope of accreditation	Indicate the analytical methods and techniques
c) Current quality manual, laboratory manual or equivalent	Comment on adequacy ^a
d) Contract between the manufacturer and contract laboratory and its subcontractors if applicable (where testing is outsourced)	Comment on adequacy of the agreement stating responsibilities of the parties
e) List of all inspections carried out in the past three years by a regulatory authority or accreditation body	Provide the list of regulatory authority or accreditation body indicating the name, date of inspection and outcome in the inspection

Table *continued*

Part 2. Documentary evidence (comment on adequacy of information provided)	
f) Copy of inspection report(s) from regulatory authority or accreditation body and/or from WHO prequalification (whichever is applicable) carried out within the past three to five years	Name of the regulatory authority or accreditation body that carried out the inspection, dates of the inspection, scope of inspection, findings and recommendations, list of instances of noncompliance, conclusion
g) CAPA reports submitted and found satisfactory for the most recent inspection	Comment on adequacy
h) Register of OOS, OOS procedure and investigation reports of at least three OOS assigned to laboratory error in past one year handled	Comment on adequacy
Part 3. Recommendation	
1. Recommended for a GMP compliance approval? <i>(Provide recommendation based on the results of the assessment done in Parts 1 and 2)</i>	
2. If Yes, state laboratory testing activities/product analysed:	
3. If No, state reasons and the relevant sections of the guideline(s) below:	

Table *continued*

Part 4. Evaluation team

First assessor

Signed: _____ Date: _____

Name: _____ Position: _____
(BLOCK CAPITALS)

Second assessor

Signed: _____ Date: _____

Name: _____ Position: _____
(BLOCK CAPITALS)

CAPA: corrective and preventive action; ISO/IEC: International Organization for Standardization/International Electrotechnical Commission; NRA: national regulatory authority; OOS: out of specification; SRA: stringent regulatory authority.

^a Refer to WHO good practice for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 1 (WHO Technical Report Series, No. 957).

Appendix 3

Model report format for desk assessment for contract research organizations and clinical trial sites

Part 1(i). General information – study	
a) Particulars of the applicant	Name of applicant, physical address, postal address of applicant (if different from physical address), 24-hour telephone numbers, email address
b) Particulars of the organization	Name of research organization, physical address, postal address (if different from physical address), 24-hour telephone number(s), fax, email address
c) Title of the study	
d) Particulars of the bioanalytical laboratory	Name of bioanalytical laboratory, physical address of bioanalytical laboratory, postal address of the laboratory (if different from physical address), 24-hour telephone number(s), fax, email address
e) Particulars of the sponsor	Name of sponsor, 24-hour telephone number(s), fax, email address, contact person
Part 1(ii). General information – site quality management system	
a) Date of last inspection by NRA (if applicable)	Dates when the last inspection was carried out; name of the national medicines regulatory authority that carried out the inspection
b) Particulars of the investigator's current curriculum vitae and/or qualifications	

Table *continued*

Part 2(i). Documentary evidence – study		
a)	Copy of institutional review board (IRB)/independent ethics committee clinical trial/bioequivalence (BE) study approval	For multicentre trials, only the study approval issued by the IRB/IEC of the coordinating investigator of the trial is required
b)	Copy of clinical trial/BE approval granted by a competent national medicines regulatory authority with a certified translation, if not in English	Name of the approving authority, validity of approval (study)
c)	Copy of clinical trial/BE/bioavailability study protocol and any amendments ^b	Comment on the trial design, selection and withdrawal of subjects, treatment of subjects, assessment of efficacy, assessment of safety, statistics, data handling and record-keeping, ethics, financing and insurance, quality control and quality assurance, and publication policy
d)	Copy of investigator's brochure	Confidentiality statement, physical chemical and pharmaceutical properties and formulation, nonclinical studies, effects in humans, summary of data and guidance for the investigator
e)	Copy of current clinical trial/BE reports including safety reports	Comment on adequacy and compliance with the protocol (study)
f)	Copy of clinical trial monitoring report by the sponsor or contract research organization (CRO)	
Part 2 (ii). Documentary evidence – site quality management system		
a)	Copy of current GCP/GLP certificate or regulatory approval	
b)	Number of clinical trials/BE study approvals granted by a national medicines regulatory authority in the past five years, with a certified translation, if not in English	State number of approved clinical trials/BE studies and their outcomes, name of the approving authority, validity of approval

Table *continued*

Part 2 (ii). Documentary evidence – site quality management system		
c)	Copy of current clinical trial master file ^a (make reference to the quality assurance mechanism for CRO) Documentation on the responsibilities of the sponsor and clinical investigator, management and assessment of subcontracted vendors should be provided.	Comment on adequacy of deviation management and procedures for handling the investigational product
d)	List of all inspections carried out in the past three years	Clinical monitoring reports by the sponsor or the CRO (if monitoring tasks were outsourced to a CRO)
e)	Copy of inspection report(s) from national medicines regulatory authority and/or that from WHO prequalification (whichever is applicable) carried out within the past three to five years	Including bioanalytical method validation and compliance with GLP
f)	Provide evidence of NRA oversight including concerns raised and alerts, if any	
g)	Copy of study monitoring report by the sponsor or CRO (where applicable)	
Part 3. Recommendation		
1.	Recommended for a GMP compliance approval? <i>(Provide recommendation based on the results of the assessment done in Parts 1 and 2)</i>	
2.	If Yes, study/clinical trial site recommended:	
3.	If No, state reasons and the relevant sections of the guideline(s) below:	

Table *continued*

Part 4. Evaluation team

First assessor

Signed: _____ Date: _____

Name: _____ Position: _____
(BLOCK CAPITALS)

Second assessor

Signed: _____ Date: _____

Name: _____ Position: _____
(BLOCK CAPITALS)

GCP: good clinical practices; GLP: good laboratory practices; NRA: national regulatory authority.

^a Guidelines for good clinical practice E6 (R1), Current Step 4 Version, 10 June 1996. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (<https://www.ich.org/page/efficacy-guidelines>).

^b Guidance for organizations performing in vivo bioequivalence studies (revision). In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 9 (WHO Technical Report Series, No. 996).

8. Storage, distribution and supply

8.1 Guidelines on import procedures for medical products

Annex 5, WHO Technical Report Series, 1019, 2019

Background

This document is a revision of the 1996 publication:

- Guidelines on import procedures for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, thirty-fourth report. Geneva: World Health Organization; 1996: Annex 12 (WHO Technical Report Series, No. 863; <http://apps.who.int/medicinedocs/documents/s21962en/s21962en.pdf>).

1. Introduction	1118
2. Scope	1119
3. Glossary	1120
4. Legal responsibilities	1121
5. Legal basis of control	1122
6. Required documentation	1123
7. Implementation of controls	1123
8. Procedures applicable to pharmaceutical starting materials	1125
9. Storage facilities	1125
10. Training requirements	1126
References	1126

1. Introduction

- 1.1 Public health considerations demand that medical products should not be treated in the same way as ordinary commodities. Their manufacture and subsequent handling within the distribution chain, both nationally and internationally, must conform to prescribed standards and be rigorously controlled. These precautions serve to assure that patients receive quality-assured medical products, and to prevent the infiltration of substandard and suspected falsified medical products into the supply system.
- 1.2 The availability of medical products is sometimes limited, owing to economic constraints, difficulty in meeting norms and standards in their production, and lack of resources in their supply chain. These conditions lead to market penetration by substandard and suspected falsified medicines, which poses hazards for public health and forces the diversion of public health resources from other uses. In light of this, investments towards strengthening strategies at the customs level are deemed crucial to ensure quality-assured medical products for patients (1, 2).
- 1.3 The global economy of scale and scope that characterizes modern trade requires continuous improvement in border control. This includes a departure from the traditional reactive control system to a risk-based and proactive approach. A country's risk-based surveillance scheme should identify risks and define the controls that will protect patients from substandard, falsified and unregulated medical products. A risk-based approach can improve the cost–benefit ratio with existing or reduced resources, through more effective and efficient controls. These guiding principles were endorsed in 1994 by the World Health Assembly in resolution WHA47.17 as having global relevance (3).
- 1.4 Within the context of its revised medicines strategy adopted in 1986 by the Thirty-ninth World Health Assembly in resolution WHA39.27 (4), the World Health Organization (WHO) developed *National drug regulatory legislation: guiding principles for small drug regulatory authorities* (5), which established a regulatory approach in line with the resources available within a small national regulatory authority (NRA), and were intended to assure not only the quality, but also the safety and efficacy of medical products distributed under its aegis.
- 1.5 The principles emphasize the need for the effective use of the *WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce* (6, 7). This constitutes a formal agreement between participating Member States to provide information on any medical products under consideration for export, notably on its marketing authorization in the country of origin and whether or not the manufacturer complies with the *WHO good manufacturing practices for pharmaceutical products* (8).

- 1.6 To be fully effective, the WHO Certification Scheme needs to be complemented by administrative and other safeguards aimed at ensuring that imported products are in conformity with all particulars with the relevant marketing authorization, or for specific intended use, such as clinical trials, named patient programmes, emergencies or other means, as appropriate, within the importing country and that they remain secure within the distribution chain. Storage and transit facilities must provide protection against tampering and adverse conditions, and relevant controls must be applied at every stage of transportation (9, 10).
- 1.7 Medical products containing substances controlled under international conventions have long been subjected to rigorous border control. Some of these controls, and particularly those designed to prevent the diversion and illicit interchange of products during transit, are relevant to all medical products and are therefore included in these guidelines. Only those medical products falling under the category of narcotic and psychotropic substances that are permitted by the relevant authorities shall be allowed to be imported as foreseen in the national and regional legislations and international treaties signed by the country.

2. Scope

- 2.1 These guidelines, which stem from the above considerations, were first developed in 1996 in consultation with NRAs, the pharmaceutical industry, the World Customs Organization and the United Nations International Drug Control Programme.¹ Following the recommendation of the 52nd Expert Committee on Specifications for Pharmaceutical Preparations (ECSP), these guidelines were reviewed, adding critical and contemporary topics, such as: the e-commerce/internet-mediated distribution and the alert systems mechanism that should be in place between entry ports/NRAs/WHO, in case of unregistered, unlicensed, substandard and falsified medical products. Lastly, the glossary was revised and cross-references were added to other established WHO guidance documents.
- 2.2 These guidelines are directed to all parties involved in the importation of medical products, including NRAs, competent trade ministries, customs authorities, port authorities and importing agents.
- 2.3 They are intended to promote efficiency in applying relevant regulations, to simplify the checking and handling of medical products for import and, inter alia, to provide a basis for collaboration between the various interested parties.

¹ Since 1997, this has been part of the United Nations Office for Drug Control and Crime.

- 2.4 They are applicable to medical products destined for use within the country of import and are intended to be adopted into prevailing national procedures and legal requirements.

3. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

falsified medical products.² Medical products that deliberately or fraudulently misrepresent their identity, composition or source. Any consideration related to intellectual property rights does not fall within this definition. Such deliberate or fraudulent misrepresentation refers to any substitution, adulteration or reproduction of an authorized medical product or the manufacture of a medical product that is not an authorized product.

import authority. The national agency responsible for authorizing imports (e.g. the ministry or department of trade or of imports and exports).

importation. The act of bringing or causing any goods to be brought into a customs territory (national territory, excluding any free zone).

importer. An individual or company or similar legal entity importing or seeking to import a medical product. A “licensed” or “registered” importer is one who has been granted a licence for the purpose.

marketing authorization (product license, registration certificate). A legal document issued by the competent national regulatory authority that authorizes the marketing or free distribution of a medical product in the respective country after evaluation for safety, efficacy and quality. In terms of quality, it establishes, inter alia, the detailed composition and formulation of the medical product and the quality requirements for the product and its ingredients. It also includes details of packaging, labelling, storage conditions, shelf-life and approved conditions of use.

medical product. A term that includes medicines, vaccines, diagnostics and medical devices.

national regulatory authority. The national agency responsible for the marketing authorization of, and other regulatory activities concerning, medical products.

screening technologies. The qualitative and/or semi-quantitative technologies that could rapidly acquire the analytical information or data for preliminary identification of suspect medical products in the field.

standard operating procedure. An authorized written procedure giving instructions for performing standardized operations – both general and specific.

² This definition reflects the ongoing discussion in the Member State mechanism under the auspices of the World Health Assembly; see Appendix 3 in reference (11).

starting material. Any substance of defined quality used in the production of a medical product, but excluding packaging materials.

substandard product. An authorized product that fails to meet either its quality standards or its specifications, or both.³

unregistered product. A medical product that has not undergone evaluation and/or approval by the NRA for the market in which it is marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation. This medical product may or may not have obtained the relevant authorization from the national/regional regulatory authority of its geographical origin.

4. Legal responsibilities

- 4.1 The importation of medical products should be done in accordance with national and regional legislation and should be enforced by the NRA, customs and other relevant authorities.
- 4.2 National and regional guidelines providing recommendations on the implementation of legislation should be drawn up by the NRA or the ministry of health, if a NRA is not formally established, in collaboration with the customs authority and other responsible agencies and organizations.
- 4.3 The import of medical products should be undertaken by an importer or agency authorized by the NRA as per national and regional legislation. This normally does not include medical products in transit.
- 4.4 The import of all medical products should be channelled exclusively through custom posts or ports specifically authorized for this purpose. This is also applicable to medical products moving through the networking global e-commerce (such as the World Wide Web/internet).
- 4.5 All formalities on importation of medical products should be coordinated by the relevant authorities (customs, border control, or other as appropriate), NRA and/or ministry of health, as relevant. When justified by the workload, NRA officials may be stationed in a full-time position at such designated ports of entry. In carrying out the duties and formalities, the impact of possible delays on, for example, access to medicines and storage conditions of medical products, should be considered (for storage facilities, please see Section 9).

³ These standards and specifications are normally reviewed, assessed and approved by the applicable national or regional regulatory authority before the product is authorized for marketing (11).

5. Legal basis of control

- 5.1 Subject to the exemptions specified in the national and regional legislation, and mentioned in paragraph 5.5 below, only medical products approved by appropriate documentation to be duly registered or authorized, as appropriate for marketing, should be cleared by relevant authorities.
- 5.2 The NRA should publish an updated list of authorized medical products and authorized importers permitted to import into the country for marketing. This does not include a list of exempted products and importers as per national or regional legislation. In all cases, close collaboration with the NRA is needed to verify that the product is authorized for importation and that there are no restrictions, temporary suspensions or withdrawals of marketing authorizations.
- 5.3 NRAs should be empowered to take legal actions and should collaborate closely with customs, police, judiciary and others to detect substandard and falsified products and to avoid the import of such products. Efficient and confidential channels for communicating information on these products and other illicit activities should be established between all responsible official bodies.
- 5.4 In countries where no formal system of product marketing authorization has been established, the importation of products is most effectively controlled by issuing permits in the name of the NRA to the authorized importing agency or agent. Within the framework of the WHO Certification Scheme, WHO provides a list with names and full addresses of those government organizations authorized to sign and issue a certificate of a medical product (CPP).⁴ NRAs receiving a CPP can use this list to check and verify whether the certificate they are receiving has been issued by the authorized organization (6, 7). Additional measures that may be taken under these conditions include:
 - provision by the NRA to the customs authorities and to the importing agency and agents of official lists of medical products permitted and/or prohibited to be imported;
 - provision by the importing agent of certified information to establish that the product is authorized by licence for sale in the country of export.
- 5.5 The NRA should reserve discretionary powers to waive product authorization requirements in respect of consignments of medical products imported in response to emergency situations, specific intended use as in clinical trials, donation (13)

⁴ Information on competent authorities of countries participating in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce can be found in reference (12).

and in response to requests from clinicians for limited supplies of an unlicensed product needed for the treatment of a specific named patient.

6. Required documentation

6.1 As a prerequisite to border and customs clearance, the importing agency or agent should be required to furnish the customs authority with the required documentation in respect of each consignment, except in cases of exemptions as per national or regional legislation (see also paragraph 5.5). For example, the following documents can be considered:

- documents issued by the NRA in the importing country, attesting that:
 - the importer is duly authorized to import the medical products;
 - the product is duly authorized to be marketed or permitted to be imported into the importing country;
- a batch-release certificate issued by the manufacturer;
- a safety data sheet, where applicable;
- a relevant invoice, bill or delivery slip for the batch, including the product name, batch number, quantity and expiry date;
- any other documentation required by national or regional legislation for customs clearance, e.g. a certificate in accordance with the WHO Certification Scheme;
- any other document that should be issued by the competent authority of the exporting country, as applicable.

6.2 The NRA may grant exemptions to the above if the distribution is taking place through regional hubs or by international organizations.

7. Implementation of controls

7.1 Visual examination and preliminary screening technologies should be routinely undertaken by the customs authorities. Where possible, this should be done in collaboration with an inspector or enforcement officer of the NRA. The size of the consignment should be checked against invoices, bills or delivery slips, and attention should be given to the nature and conditions of the packaging and labelling. The external package should be compared with a standard when this is possible. (*Note: spelling errors, low-quality printing and other defects may be signs of a substandard or falsified product. The external package should be intact and should not show any signs of damages or infiltrations that may change the inner content (2, 14–16).*)

- 7.2 Arrangements should be made by the NRA and other relevant authorities (i.e. national official control laboratories, ministry of health) for the sampling and subsequent physical and chemical analysis of medical products, based on established procedures following a risk-based approach.
- 7.3 When samples are taken for analysis to a governmental or other accredited quality control laboratory, prior to the release of the consignment as per national and regional legislation, the consignment should be placed in quarantine at approved sites. During this procedure, and throughout the time that the consignment is held legally under customs control, particular care must be taken to ensure that packages do not come into contact with potential contaminants. In addition, the package should be stored under appropriate conditions, as recommended on the label or in the safety data sheet, such as temperature, light and humidity limits (14–16).
- 7.4 A consignment suspected of being substandard, falsified or not authorized should be placed in quarantine pending the analysis of samples and forensic investigation. During this procedure, particular care must be taken to ensure that packages do not come into contact with potential contaminants. In addition, the package should be stored under appropriate conditions as recommended on the label or in the safety data sheet, such as temperature, light, and humidity limits (14–16). Time is often saved if materials and reagents needed to undertake simple analytical tests and screening technologies are available at the customs border. The consignee should immediately be informed of such action; ideally, the authorized manufacturer or importer should also be promptly involved in the investigation.
- 7.5 National or regional regulations should define the responsibilities of the respective parties and the precise procedures to be followed by representatives from the NRA, police, border control, or ministry of health, as appropriate, for the relevant investigation and legal actions.
- 7.6 Falsified medical products and other products that have been imported in contravention of the law must be forfeited and destroyed, or otherwise dealt with in accordance with the procedures established by national and regional legislation, the records of which should be appropriately archived (17). The relevant authorities must be indemnified against any consequent legal actions and proceedings.
- 7.7 NRAs should notify other national or regional authorities and the WHO Global Surveillance and Monitoring System⁵ of confirmed cases of imported substandard or falsified products, without delay, on the appropriate form.

⁵ The WHO Global Surveillance and Monitoring System collects reports from focal points in the NRAs and international procurement agencies, which will forward the report via email to rapidalert@who.int where necessary. Focal points are encouraged to send any photographs, laboratory reports or other relevant documents as attachments. For further information, see reference (18).

- 7.8 The WHO Member State mechanism has prepared an overview on the different field screening devices, authentication and verification technologies, and “track and trace” models that can facilitate responses (11). Overt/covert technologies, forensic chemical markers, bar-coding and other forms of serializations can support the seamless tracking of products through the supply chain. The implementation of these and upcoming new technologies is considered one of the most prominent preventive measures to tackle substandard and falsified medical products.

8. Procedures applicable to pharmaceutical starting materials

- 8.1 When considering finished medical products, the responsibility for the quality assurance of starting materials (active pharmaceutical ingredients [APIs] and excipients) used in that product is vested in the manufacturer of the finished pharmaceutical product. Few NRAs have introduced authorization requirements for APIs and excipients (10).
- 8.2 Some national and regional authorities also exercise documentary and (in some cases) quality control through laboratory testing of APIs as a prerequisite to customs clearance.
- 8.3 Each imported pharmaceutical starting material should be accompanied by a warranty (or batch certificate) prepared by the manufacturer, for example, as recommended by the WHO pharmaceutical starting materials certification scheme (SMACS) (19).
- 8.4 Pharmaceutical starting materials purchased and imported from third-party vendors should be appropriately labelled in accordance with national regulations and accompanied by a certificate of analysis from the original manufacturer.

9. Storage facilities

- 9.1 Many medical products tend to degrade during storage and some need to be stored under specified conditions, such as 2–8 °C. All customs posts designated to handle consignments of medical products should be provided with secure storage facilities, with the required conditions including cold storage areas.
- 9.2 Customs and NRA officials should ensure that the appropriate environmental conditions are maintained for storage, and monitor that the equipment is maintained and in good working order. The facilities should be inspected periodically by the NRA.

- 9.3 The importer should inform the customs authorities in advance of the anticipated arrival of medical products, in order that they may be transferred from the international carrier to the designated storage facility without delay and, in appropriate cases, without breaking the cold chain.
- 9.4 Consignments of medical products and pharmaceutical starting materials, especially those requiring cold chain, should be accorded high priority for clearance through customs, to avoid extended storage.

10. Training requirements

- 10.1 When implementing these guidelines, the performance of the established procedures (including but not limited to personnel, documentation, procedures, and equipment) should be reviewed on an open-ended basis and improved in the light of on-site monitoring and evaluation. Workshops designed to facilitate efficient implementation of the guidelines and established procedures, and to foster collaborative approaches between the various responsible parties, should be organized by the NRA at intervals, in collaboration with the customs authority and other parties.

References

1. Guidelines on the conduct of surveys of the quality of medicines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fiftieth report. Geneva: World Health Organization; 2016: Annex 7 (WHO Technical Report Series, No. 996; <https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>, accessed 14 February 2019).
2. WHO guidance on testing of “suspect” falsified medicines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization; 2018: Annex 5 (WHO Technical Report Series, No. 1010; <https://iris.who.int/bitstream/handle/10665/272452/9789241210195-eng.pdf?sequence=1&isAllowed=y>, accessed 14 February 2019).
3. Resolution WHA47.17. Implementation of WHO’s revised drug strategy. Safety, efficacy and quality of pharmaceuticals. In: Forty-seventh World Health Assembly, Geneva, 2–12 May 1994. Resolutions and decisions, annexes. Geneva: World Health Organization; 1994:18–19 (https://apps.who.int/iris/bitstream/handle/10665/177385/WHA47_R17_eng.pdf?sequence=1&isAllowed=y, accessed 14 February 2019).
4. WHA39.27. The rational use of drugs. In: Thirty-ninth World Health Assembly, Geneva, 5–16 May 1986. Resolutions and decisions, annexes. Geneva: World Health Organization; 1994 (https://apps.who.int/iris/bitstream/handle/10665/163188/WHA39_R27_eng.pdf?sequence=1&isAllowed=y, accessed 14 February 2019).

5. National drug regulatory legislation: guiding principles for small drug regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, thirty-fifth report. Geneva: World Health Organization; 1999: Annex 8 (WHO Technical Report Series, No. 885; https://iris.who.int/bitstream/handle/10665/42145/WHO_TRS_885.pdf?sequence=1&isAllowed=y, accessed 14 February 2019).
6. Resolution WHA50.3. WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. In: Fiftieth World Health Assembly, Geneva, 5–14 May 1997. Resolutions and decisions, annexes. Geneva: World Health Organization; 1997 (https://apps.who.int/iris/bitstream/handle/10665/179726/WHA50_R3_eng.pdf?sequence=1&isAllowed=y, accessed 14 February 2019).
7. World Health Organization. Guidelines on the implementation of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce (<https://iris.who.int/bitstream/handle/10665/340323/9789240020900-eng.pdf?sequence=1>, accessed 13 March 2019); update in progress.
8. WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-eighth report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986; https://iris.who.int/bitstream/handle/10665/112733/WHO_TRS_986_eng.pdf?sequence=1&isAllowed=y, accessed 14 February 2019).
9. WHO good distribution practices for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-fourth report. Geneva: World Health Organization; 2010: Annex 5 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y, accessed 14 February 2019).
10. Good trade and distribution practices for starting materials. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fiftieth report. Geneva: World Health Organization; 2016: Annex 6 (WHO Technical Report Series, No. 996; <https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>, accessed 14 February 2019).
11. Member State mechanism on substandard/spurious/falsely-labelled/falsified/ counterfeit medical products. Report by the Director-General. In: Seventieth World Health Assembly, Geneva, 22–31 May 2017. Provisional agenda item 13.6.
12. World Health Organization. Essential medicines and health products. Contacts list.
13. Guidelines for medicine donations. Revised 2010. Geneva: World Health Organization; 2011 (https://apps.who.int/iris/bitstream/handle/10665/44647/9789241501989_eng.pdf?sequence=1, accessed 14 February 2019).
14. Guide to good storage practices for pharmaceuticals. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, thirty-seventh report. Geneva: World Health Organization; 2003: Annex 9 (WHO Technical Report Series, No. 908; https://iris.who.int/bitstream/handle/10665/42613/WHO_TRS_908.pdf?sequence=1&isAllowed=y, accessed 14 February 2019).
15. Technical supplements to Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-ninth report. Geneva: World Health Organization; 2015: Annex 5 (WHO Technical Report Series, No. 992; https://iris.who.int/bitstream/handle/10665/176954/9789240693968_eng.pdf?sequence=1&isAllowed=y, accessed 14 February 2019). TRS, No. 992, 2015, Annex 5).

16. Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-eighth report. Geneva: World Health Organization; 2011: Annex 9 (WHO Technical Report Series, No. 961; https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1, accessed 14 February 2019).
17. Guidance on good data and record management practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fiftieth report. Geneva: World Health Organization; 2016: Annex 5 (WHO Technical Report Series, No. 996; <https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>, accessed 14 February 2019).
18. World Health Organization. Essential medicines and health products. WHO medical product alerts – background (<https://www.who.int/teams/regulation-prequalification/incidents-and-SF/full-list-of-who-medical-product-alerts>, accessed 14 February 2019).
19. WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, thirty-eighth report. Geneva: World Health Organization; 2003: Annex 3 (WHO Technical Report Series, No. 917; https://iris.who.int/bitstream/handle/10665/42851/WHO_TRS_917.pdf?sequence=1&isAllowed=y, accessed 14 February 2019).

8.2 Points to consider for setting the remaining shelf-life of medical products upon delivery

Annex 8, WHO Technical Report Series, 1044, 2022

Edit and republication of *Points to consider for setting the remaining shelf-life of medical products upon delivery*, WHO Technical Report Series No. 1025, Annex 8, with a new Appendix 2.

Background

Following the publication of *Points to consider for setting the remaining shelf-life of medical products upon delivery* in 2020, a group from international agencies and humanitarian organizations procuring health kits (including the International Committee of the Red Cross, Médecins Sans Frontières, Save the Children, United Nations Children's Fund, United Nations Population Fund and the World Health Organization) submitted a draft proposal for an amendment to include emergency health kits used as part of the humanitarian response as an additional example for consideration. During the fifth-sixth WHO Expert Committee on Specifications for Pharmaceutical Preparations, the *Points to consider for setting the remaining shelf-life of medical products upon delivery* guideline with a new Appendix 2 (*Example of minimum remaining shelf-life of emergency health kits used as part of the humanitarian response*) was adopted.

1. Introduction	1130
2. Scope	1131
3. Glossary	1131
4. The need for recommendations	1133
5. Remaining shelf-life	1133
5.1 Principles	1133
5.2 Expiry date	1135
5.3 Retesting	1135
References	1136
Appendix 1 Example of minimum remaining shelf-life of medical products	1138
Appendix 2 Example of minimum remaining shelf-life for emergency health kits for use as part of humanitarian response	1139

1. Introduction

Following discussions relating to establishing a document for the remaining shelf-life of medical products upon delivery, and considering the discussion between representatives of the Interagency Pharmaceutical Coordination Group, it was decided to initiate a project to prepare a document on remaining shelf-life for procurement and supply of medical products.

The concept and project to prepare such a document was also discussed during the meeting of the fifty-third Expert Committee on Specifications for Pharmaceutical Products in October 2018. It was noted that some guidance documents were available from different procurement agencies. It was agreed that the World Health Organization (WHO) would initiate the discussion and preparation of a document, while following the WHO process for the establishment of such a paper.

Information and policy on remaining shelf-life was collected from different agencies and interested parties and a first draft document was prepared after an informal discussion meeting in Geneva, Switzerland, in January 2019.

It was then agreed that the document should cover not only finished pharmaceutical products but should be extended to cover other products, including medical devices, vaccines and in vitro diagnostics (IVD) products. (These products are collectively referred to as “medical products” hereafter.)

A draft document was prepared and circulated to members of the Interagency Pharmaceutical Coordination Group and other interested parties, inviting comments. The comments received were reviewed during an informal discussion meeting in June 2019 and the draft document was updated.

The aims of this document are:

- to facilitate the national authorization of importation of medical products, where applicable;
- to promote and support the efficient processing of medical products in the supply chain at all levels and thus prevent wastage because of delays;
- to assist in ensuring that there is sufficient stock of medical products, with acceptable remaining shelf-life, in-country;
- to prevent dumping of medical products;
- to ensure that barriers to access and supply of medical products are addressed;
- to prevent out-of-stock situations;
- to prevent receipt of donations of medical products that are not in accordance with this guideline;
- to prevent having expired stock of medical products.

The document is intended to provide guidance on setting the remaining shelf-life of medical products upon delivery and should be considered by all stakeholders in the supply chain of medical products. It is also recommended that the recommendations herein should be considered for inclusion in the national policy of countries.

2. Scope

The principles contained in this document should be applied to medical products in the supply chain. This includes donated products (1).

This document focuses on remaining shelf-life and does not address details contained in other guidelines, guides and agreements between different parties in the supply chain.

While the principles contained in this guideline apply to humanitarian emergency health kits, “kits” are made up of different products, owing to certain specifics related to the shelf-life of kits. These considerations are outlined in Appendix 2.

All stakeholders, including national regulatory authorities, manufacturers, suppliers, donors and recipients, should consider the recommendations on remaining shelf-life contained in this document.

3. Glossary

The definitions given below are taken from existing WHO guidelines, where available, or alternatively from other recognized guidelines.

batch. A defined quantity of starting material, packaging material or product, processed in a single process or series of processes, so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

consignment (or delivery). The quantity of a medical product or products, made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

expiry date (or expiration date). The date placed on the container or labels of a medical product designating the time during which it is expected to remain within established shelf-life specifications if stored under defined conditions, and after which it should not be used.

finished pharmaceutical product. A product that has undergone all stages of production, including packaging in its final container and labelling. A finished pharmaceutical product may contain one or more active pharmaceutical ingredients.

install-by date. The date by which an instrument, device or other has to be installed.

manufacture. All operations of purchase of materials and products, production, quality control, release, storage and distribution of medical products, and the related controls.

manufacturer. A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of medical products.

manufacturer (in vitro diagnostics). Any natural or legal person with responsibility for design and/or manufacture of an IVD product with the intention of making it available for use under their name, whether or not such a product is designed and/or manufactured by that person or on their behalf.

manufacturing date. The date of production of a batch is defined as the date that the first step is performed involving combination of the active ingredient with other ingredients. Where there are no other ingredients than an active ingredient, the date of the start of the processing or filling operation is considered as the date of production.

marketing authorization (product licence, registration certificate). A legal document issued by the competent medicines regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, including details of packaging, labelling and shelf-life.

medical product. Medical products include a wide range of manufactured items, such as finished pharmaceutical products, medical devices, vaccines and IVD products.

pharmaceutical product. Any material or product intended for human or veterinary use presented in its finished dosage form, or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state or the importing state.

production. All operations involved in the preparation of a product, from receipt of materials, through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

remaining shelf-life. The period remaining from the date of delivery to the expiry date, retest date, install-by date or other use-before date established by the manufacturer.

retest date. The date when a material should be re-examined to ensure that it is still suitable for use.

shelf-life. The period of time, from the date of manufacture, that a product is expected to remain within its approved product specification while handled and stored under defined conditions.

upon delivery. The date a medical product is delivered as specified, for example at the port, at the point in-country after customs clearance, or at the end user, and as defined in the agreement between relevant parties.

4. The need for recommendations

As there was no harmonized approach on remaining shelf-life for medical products amongst procurers, donors and recipient countries, it was agreed that it would be beneficial to have a harmonized approach when considering remaining shelf-life. This will assist national regulatory authorities (NRAs), suppliers, donors, procurers, importers and distributors to manage medical products throughout the supply chain, thus ensuring that quality medical products reach the end user within their remaining shelf-life. The authorization of importation of medical products by NRAs sometimes delays access to medical products. A harmonized approach among countries may facilitate authorization and release of medical products in the supply chain in a timely manner.

This is not a stand-alone document. It should be read with other documents, guides and guidelines, including WHO guidelines such as *Guidelines for medicines donations* (1), *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (2), *Good storage and distribution practices for medical products* (3), *Model quality assurance system for procurement agencies* (4), *The International Pharmacopoeia* (5) and guidelines of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

5. Remaining shelf-life

Note: The manufacturing date of a medical product should be defined by the manufacturer and be provided, if requested.

5.1 Principles

Decisions on remaining shelf-life for medical products should be defined realistically, contextualized and adapted to each importer, following a thorough risk assessment taking into account the criteria below (at the end of this subsection). Remaining shelf-life should be defined based on relevant factors, including the category and type of product, inventory level, manufacturing and transit lead time, local release lead time, storage conditions, delivery chain, and resources in the recipient country or region.

There should be agreements between suppliers, purchasers and recipients covering the relevant responsibilities of each party, including remaining shelf-life or expiry date.

Products should be transported, received, stored and distributed in accordance with WHO *Good storage and distribution practices for medical products* (3). Special attention should be given to temperature-, light- and moisture-sensitive products.

Products supplied by the manufacturer or supplier should meet the policy of national government and the recommendations in terms of remaining shelf-life prescribed in this document.

Products should be appropriately labelled. The label should include the expiry, retest or install-by date, as appropriate. Products with an install-by date should be installed prior to the date specified by the supplier.

Products received should be scrutinized in an attempt to identify possible substandard and falsified products. It should be ensured that, for example, the expiry date is not falsified (6).

Where different periods for remaining shelf-life have been defined for products, recipients should ensure that the products meet the remaining shelf-life requirement for the intended destination, such as central warehouse, regional warehouse, testing site or user point.

National authorization for importation, where required, should be obtained based on the available information, including the expiry date of the product, to enable calculation of the remaining shelf-life and to assist in expediting approval.

Where so justified, suppliers, recipients and national authorities may negotiate deviations from the policy for remaining shelf-life, provided that:

- where the remaining shelf-life is shorter than stipulated in the policy, it is ensured that the stock will be consumed prior to expiry;
- the medical product reaches end users with adequate remaining shelf-life to permit confidence that there is time to consume it before expiry.

Risk assessment should be carried out to ensure that the parameters listed above are met, taking into account the following considerations:

- assessment of need;
- type of product: different criticality for the safety of the patient between pharmaceutical products, vaccines, medical devices and IVD products;
- expiry date: with this information, the remaining shelf-life at delivery time can be estimated;
- compliance with WHO guidelines on *Good storage and distribution practices for medical products* (3);
- delivery time to storage facility;

- storage conditions;
- stock rotation;
- delivery time from storage to end user;
- frequency of stock replenishment or order frequency (based on consumption): recipients and end users should regularly verify that medical products in stock are rotated or used within their remaining shelf-life, and adjust the quantities ordered to make sure that the medical products will be used during their remaining shelf-life;
- assessment of real needs, to ensure that the medical products can be used within their shelf-life;
- emergencies: during an emergency situation, the remaining shelf-life policy should be well balanced to ensure that lifesaving medical products will be received on time, and that the needs will be covered if there is an increased demand;
- logistic set-up: the location of the premises, the number of means or types of transportation (for example, the number of vehicles), and its adaptability will have an impact on the speed of delivery and, hence, on the confidence that products will be used before their expiry date;
- activity specificities: similarly, whether the medical products will be used by the national programme, or are managed directly by the importer outside a national programme, will make a difference in terms of speed of delivery to the end user;
- point of delivery: national warehouses or importer or end user facilities will also have an impact on the speed of delivery.

5.2 Expiry date

Products, such as pharmaceutical products, should have an expiry date allocated by the manufacturer. The expiry date should be established based on the results of stability testing obtained in the relevant packaging (primary and secondary packaging, where appropriate) and required stability conditions (2).

5.3 Retesting

Where a manufacturer or supplier has obtained approval from an NRA for a new or extended shelf-life, this may be applied.

Products with an expiry date should not be subjected to retesting by the purchaser or recipient for the purpose of extension of shelf-life. Only in exceptional cases, such as product shortages, should a recipient consider extending the expiry date of received batches, subject to certain conditions, such as availability of scientific data,

the application of risk management principles, and NRA approval. The new expiry date should be reflected on the packaging. Products with a retest date allocated by a manufacturer, such as chemicals and reagents, may be retested and used if the quality parameters are met.

An illustrative example of recommended remaining shelf-life of products is given in Appendix 1 for bulk medical products and Appendix 2 for the emergency health kits used in humanitarian response.

References

1. Interagency guidelines. Guidelines for medicines donations, third edition. Geneva: World Health Organization; 2011.
2. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. WHO Technical Report Series No. 1010, Annex 10. Geneva: World Health Organization; 2018 (<https://iris.who.int/bitstream/handle/10665/272452/9789241210195-eng.pdf?sequence=1&isAllowed=y>).
3. Good storage and distribution practices for medical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. WHO Technical Report Series No. 1025, Annex 7. Geneva: World Health Organization; 2020 (<https://iris.who.int/bitstream/handle/10665/331814/9789240001824-eng.pdf?sequence=1&isAllowed=y>).
4. Model quality assurance system for procurement agencies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. WHO Technical Report Series No. 986, Annex 3. Geneva: World Health Organization; 2014 (https://iris.who.int/bitstream/handle/10665/112733/WHO_TRS_986_eng.pdf?sequence=1&isAllowed=y).
5. The International Pharmacopoeia, ninth edition. Geneva: World Health Organization; 2019.
6. WHO guidance on testing of “suspect” falsified medicines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. WHO Technical Report Series No. 1010, Annex 5. Geneva: World Health Organization; 2018 (<https://iris.who.int/bitstream/handle/10665/272452/9789241210195-eng.pdf?sequence=1&isAllowed=y>).

Further reading

- WHO guidelines for sampling of pharmaceutical products and related materials. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-ninth report. WHO Technical Report Series No. 929, Annex 4. Geneva: World Health Organization; 2005 (https://iris.who.int/bitstream/handle/10665/43157/WHO_TRS_929_eng.pdf?sequence=1&isAllowed=y).
- WHO good practices for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. WHO Technical Report Series No. 957, Annex 1. Geneva: World Health Organization; 2010 (https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y).
- Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. WHO Technical Report Series No. 961, Annex 9. Geneva: World Health Organization; 2011 (https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1).

- WHO guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. WHO Technical Report Series No. 981, Annex 2. Geneva: World Health Organization; 2013 (https://iris.who.int/bitstream/handle/10665/81144/WHO_TRS_981_eng.pdf?sequence=1&isAllowed=y).
- WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eight report. WHO Technical Report Series No. 986, Annex 2. Geneva: World Health Organization; 2014 (https://iris.who.int/bitstream/handle/10665/112733/WHO_TRS_986_eng.pdf?sequence=1&isAllowed=y).
- Technical supplements to model guidance for storage and transport of time- and temperature-sensitive pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. WHO Technical Report Series No. 992, Annex 5. Geneva, World Health Organization; 2015 (https://iris.who.int/bitstream/handle/10665/176954/9789240693968_eng.pdf?sequence=1&isAllowed=y).
- WHO Good manufacturing practices for biological products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. WHO Technical Report Series No. 996, Annex 3. Geneva: World Health Organization; 2016 (<https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>).
- Guidance for procurement of in vitro diagnostics and related laboratory items and equipment. Geneva: World Health Organization; 2017.
- Establishing stability of in vitro diagnostic medical devices. Technical Guidance Series (TGS) for WHO Prequalification: Diagnostic Assessment (TGS2): In: WHO Expert Committee on Biological Standardization: sixty-eighth report. WHO Technical Report Series No. 1011, Annex 5. Geneva: World Health Organization; 2018 (<https://iris.who.int/bitstream/handle/10665/272807/9789241210201-eng.pdf?sequence=1>).
- Establishing component stability for in vitro diagnostic medical devices. Technical Guidance Series (TGS) for WHO Prequalification: Diagnostic Assessment. Annex to TGS2. WHO/MVP/EMP/RHT/PQT/2019.03. Geneva: World Health Organization; 2019.
- ISO 23640:2011. In vitro diagnostic medical devices: evaluation of stability of in vitro diagnostic reagents. International Organization for Standardization.
- EP25-A: Evaluation of stability of in vitro diagnostic reagents: approved guideline. Wayne (PA): Clinical and Laboratory Standards Institute; 2009.

Appendix 1

Example of minimum remaining shelf-life of medical products

Note: The total shelf-life of a product is based on results from testing during stability (and, where relevant, sterility) studies under specified conditions. The storage and transport conditions stipulated by the manufacturer should be followed to ensure that the product quality is maintained.

Table 1
Example of the minimum remaining shelf-life (RSL), at the time of dispatch and upon delivery, of medical products, based on the outcome of risk assessment

Total shelf-life (TSL)	RSL at time of dispatch from manufacturer's premises	RSL at time of delivery at port of entry of country	RSL at time of delivery at end user level
48 months < TSL ≤ 60 months	40 months	30 months	12 months
36 months < TSL ≤ 48 months	30 months	24 months	12 months
24 months < TSL ≤ 36 months	20 months	15 months	6 months
12 < TSL ≤ 24 months	9 months	7 months	3 months
TSL ≤ 12 months	Special arrangements and conditions apply		

Appendix 2

Example of minimum remaining shelf-life for emergency health kits for use as part of humanitarian response

Emergency health kits are designed to facilitate the provision of priority health services in humanitarian emergencies to affected populations without access to medical facilities or where medical facilities are disrupted during a crisis. Depending on the type of emergency health kit, they contain a mix of essential medicines, health supplies and equipment designed to be used for a limited period of time and for a specific number of people.

Many different international and national organizations will be providing these emergency health kits in an acute or post-acute humanitarian response. Some examples of these organizations include:

- International Committee of the Red Cross (ICRC)
- Médecins Sans Frontières (MSF)
- Save the Children
- United Nations Children's Fund (UNICEF)
- United Nations Population Fund (UNFPA)
- World Health Organization (WHO).

Examples of these kits include interagency emergency health kits, interagency emergency reproductive health kits, MSF emergency health kits, cholera kits, and ICRC surgical team kits. "Kits" manufactured and validated as such are not considered in the amendment (such as in vitro diagnostic kits, laboratory reagent kits or polymerase chain reaction (PCR) kits) and are not intended to be covered by this annex.

Background clarifications

Expiry date of an emergency health kit. Each emergency health kit should have a manufacturing date, defined as an "assembly date", and an expiry date, defined as the "first item to be expired in the kit", allocated by the supplier or the manufacturer assembling the kit.

The shelf-life of an emergency health kit is defined by the "first item to be expired in the kit". In other words, the item in the kit with the shortest expiry date will define the expiry date of the entire kit. This implies that all the other items composing the emergency health kit have the same or a longer shelf-life.

The expiry date of the "first item to be expired in the kit" should follow the principles described in the document. Products, such as pharmaceutical products,

should have an expiry date allocated by the manufacturer. The expiry date should be established based on the stability testing results obtained on the relevant packaging (primary and secondary packaging, where appropriate) and the required stability conditions. These are presented in the number of years, based on the calculation from the date of manufacture.

Remaining shelf-life of an emergency health kit. The remaining shelf-life is calculated based on the expiry date, storage conditions and risks. The remaining shelf-life of an emergency health kit should consider the expiry date of the entire kit (see definition of expiry date of an emergency health kit above) as the end date of possible use of the kit.

Criteria that influence the recommended remaining shelf-life are the purpose of the emergency kit (immediate response or prepositioning) and the phase of the emergency – acute or post-acute (protracted or recovery). Emergency health kit prepositioning requires that careful attention be paid to stock rotation in order to ensure that expiry dates do not arrive before use.

Examples of remaining shelf-life (RSL) at the different point of delivery for the shelf-life, up to the total shelf-life (TSL), are laid out in Table 2.

Table 2

Example of the minimum remaining shelf-life (RSL), at the time of dispatch and upon delivery, of emergency health kits, based on the outcome of risk assessment

Expiry date (as defined above)	RSL at time of dispatch from supplier's premises	RSL at time of delivery at port of entry of country	RSL at time of delivery at end user level
Acute emergency response ^a			
Greater than 48 months	24 months	12 months	6 months
36 months < TSL ≤ 48 months	20 months	12 months	6 months
24 months < TSL ≤ 36 months	16 months	12 months	6 months
15 months < TSL ≤ 24 months	12 months	7 months	3 months
15 months or less	Special arrangements and conditions apply ^b		
Prepositioning in preparedness or post-acute emergency response ^c			
Greater than 48 months	40 months	30 months	12 months
36 months < TSL ≤ 48 months	30 months	24 months	12 months

Table 2 *continued*

Expiry date (as defined above)	RSL at time of dispatch from supplier's premises	RSL at time of delivery at port of entry of country	RSL at time of delivery at end user level
24 months < TSL ≤ 36 months	18 months	15 months	6 months
15 months < TSL ≤ 24 months	14 months	12 months	3 months
15 months or less	Special arrangements and conditions apply ^b		

^a An acute emergency refers to a period of time when there are sudden, often unpredicted, humanitarian needs due to a natural or human-induced crisis, where the complexities of the crisis setting lead to added complexities in the delivery of humanitarian response, or where the scale of humanitarian needs exceeds the capacity of local or national actors; this may or may not refer to an official or unofficial scale-up of a coordinated interagency response.

^b There are some items that will never have more than 12 months of total shelf-life.

^c A post-acute emergency refers to a period of time when there are significant humanitarian needs due to a natural or human-induced crisis, where the complexities of the crisis setting have remained stable for a significant period of time (protracted) or where the crisis has begun to subside, with an implied gradual return to stability (recovery).

It should be kept in mind that when an emergency health kit has expired, many of the items in the kit will still be viable for use. The expired items should be disposed of and replaced in a manner that maintains the integrity and quality of the kit. In cases where these cannot be replaced, the remaining items can be used as bulk individual items and integrated into the health system, provided these individual components of the kits have been manufactured for dedicated use as a “single product” and stored and repackaged according to the approved stability and packaging conditions.

8.3 Model quality assurance system for procurement agencies

Annex 3, WHO Technical Report Series, 986, 2014

Background

The Expert Committee on Specifications for Pharmaceutical Preparations of the World Health Organization (WHO) adopted a Model quality assurance system for procurement agencies (MQAS) during a meeting in Geneva, Switzerland in 2005. This was subsequently published as Annex 6 in the Technical Report Series, No. 937 in 2006. Some procurement organizations have implemented the recommendations presented in the MQAS. Some donor organizations (including the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM)) have endorsed the MQAS as part of their quality assurance policy for the procurement of pharmaceutical products with their funds. Several organizations have also prepared a tool to assess procurement agencies to establish the level of implementation and compliance with the MQAS.

Participants at a WHO/GFATM joint stakeholders meeting on Quality Assurance for Essential Medicines held in August 2011 in Geneva agreed that a working group consisting of representatives from the Committee for Medicinal Products for Human Use (CHMP), Crown Agents, Global Drug Facility (GDF), International Committee of the Red Cross (ICRC), International Development Association (IDA), Médecins Sans Frontières (MSF), Management Sciences for Health (MSH), Partnership for Supply Chain Management (PFSCM), Quality Medicines for All (QUAMED), International Union Against Tuberculosis and Lung Disease (The Union), United Nations Children's Fund (UNICEF), United Nations Office for Project Services (UNOPS), and the United States Agency for International Development (USAID), be created to develop a harmonized Assessment Tool that could be used by all with the aim of better use of resources by coordinating procurement agency assessments and working towards mutual recognition of procurement agency assessment findings, and to participate in the revision of the MQAS.

The Global Fund Secretariat contracted a consultant through a competitive process in 2012 to review the existing MQAS and to make recommendations to WHO (in case the need was identified to change or update the MQAS), to review tools used by procurement agencies in the light of the existing MQAS and to prepare a harmonized tool for the assessment of procurement agencies, based on the MQAS, through a consultative process.

Four informal meetings were also held at the Global Fund between 2012 and 2013 to discuss the MQAS, the comments, the draft tool, progress made and the way forward.

Since the first publication of the MQAS and its use by many organizations, it appeared that a revision would be timely and could include current developments.

A first proposal for revision of the MQAS was presented at the forty-seventh meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, in Amsterdam, Netherlands (Kingdom of the). The recommendations included in the report (WHO Technical Report Series, No. 981) of the forty-seventh meeting of the Expert Committee read as follows (excerpt):

8.1 Revision of model quality assurance system for procurement agencies

The model quality assurance system (MQAS) for procurement agencies was adopted by the Expert Committee in October 2005, since when it has been used by many organizations. ... The revised MQAS and the proposed assessment tool were ... circulated for comment in August 2012 by WHO following the usual Expert Committee consultation process. Comments were collated and the draft revised MQAS and the comments were presented to the Expert Committee for consideration.

The Expert Committee considered the comments and proposed a number of amendments to the draft. The Expert Committee endorsed the proposal for a revision of the MQAS, and noted progress made to date.

8.2 Assessment tool based on the model quality assurance system

In August 2011, WHO and GFATM identified the need for a new assessment tool for procurement agencies in conjunction with the revision of the MQAS. The proposed assessment tool was based on the MQAS. A draft of the proposed tool was prepared during 2012 and was circulated for comment. The draft was being tested in a pilot process from August to December 2012, after which it would be further reviewed and revised according to the experience gained.

During 2012 the draft assessment tool was used in a pilot phase (July to December 2012) by different organizations procuring medicines. Comments received on the MQAS as well as additional comments based on the use of the draft assessment tool (to assess procurement agencies) were reviewed during a meeting of the working group arranged through the Global Fund, on 7 and 8 February 2013, at the Global Fund offices in Geneva.

The fourth informal consultation was held in June 2013 to discuss additional comments on the MQAS as well as the newly developed aide-memoire to be used in assessing procurement agencies. The objective of the revised MQAS and use of an aide-memoire is to promote and ensure that all procurement agencies follow the same standard. A model format for an inspection report was prepared. The product questionnaire was reviewed.

During its forty-eighth meeting, the WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted the updated MQAS together with the replacement texts for Appendix 6 Interagency finished pharmaceutical product questionnaire and Appendix 14 Guidance on good manufacturing practices: model inspection report. In addition, the aide-memoire was recommended for use and is published as Annex 4 in the report of the forty-eighth Expert Committee meeting (WHO Technical Report Series, No. 986).

Glossary	1147
Module I	1153
General requirements for procurement agencies	1153
I.1 Introduction	1153
I.2 Physical resources	1153
I.2.1 Premises	1153
I.2.2 Equipment	1154
I.2.3 Vehicles and transport	1155
I.2.4 Financial systems	1155
I.2.5 Human resources	1155
I.3 Documentation of policies and standards	1157
I.3.1 Quality manual	1157
I.3.2 Standard operating procedures	1159
I.3.3 Change control policy and handling of variations	1162
I.3.4 Code of conduct	1162
I.3.5 Guidelines on conflict of interest	1163
I.3.6 List of prequalified products, manufacturers and suppliers	1163
I.3.7 Maintenance of records	1164
I.3.8 Contract arrangements	1164
Module II	1165
Prequalification	1165
II.1 Introduction	1165
II.2 Principles for prequalification	1165
II.2.1 WHO Model List of essential medicines	1166
II.2.2 Standards for prequalification	1166
II.2.3 Key persons and responsibilities	1166
II.2.3.1 Staff responsible for prequalification	1166
II.2.3.2 Staff responsible for evaluation of product information	1167
II.2.3.3 Staff responsible for inspection of manufacturing sites	1167
II.2.4 Key steps in prequalification	1168
II.2.4.1 Step 1: Soliciting information	1168
II.2.4.2 Step 2: Receive product information	1171
II.2.4.3 Step 3: Screen product information	1171
II.2.4.4 Step 4: Evaluate product information	1172
II.2.4.5 Step 5: Plan, prepare and perform inspections	1173
II.2.4.6 Step 6: Finalize assessment process	1177
II.2.5 Requalification and monitoring	1178
II.2.6 Monitoring of complaints	1178
II.2.7 Cost recovery	1178
II.3 List of suggested SOPs	1178
Module III	1180
Purchasing	1180
III.1 Introduction	1180
III.2 Procurement strategies	1180

III.3	Procurement methods	1181
III.3.1	Restricted tender	1181
III.3.2	Competitive negotiation	1182
III.3.3	Direct procurement	1182
III.3.4	Open tender	1182
III.4	Quality assurance in purchasing	1182
III.5	Key activities in purchasing	1182
III.5.1	Develop a list	1182
III.5.2	Quantification	1183
III.5.3	Procurement method	1183
III.6	Organization and responsibilities	1183
III.7	Monitoring of performance of prequalified manufacturers	1184
III.8	Country legislation	1185
III.9	Donations	1185
III.10	List of suggested SOPs	1185
Module IV		1186
Receipt and storage of purchased products		1186
IV.1	Introduction	1186
IV.2	Pre-shipment quality control	1186
IV.3	Receipt of stock	1187
IV.4	Post-procurement quality control	1187
IV.4.1	Sampling	1187
IV.4.2	Rejected materials	1188
IV.5	Storage of materials and products	1188
IV.5.1	Staff	1188
IV.5.2	Storage areas	1188
IV.5.3	Storage conditions	1189
IV.5.4	Repackaging and relabelling	1190
IV.5.5	Miscellaneous and hazardous materials	1190
IV.5.6	Stock control	1190
IV.5.7	Documentation: written instructions and records	1191
IV.6	List of suggested SOPs	1192
Module V		1193
Distribution		1193
V.1	Introduction	1193
V.2	Transport conditions	1193
V.3	Cold chain	1193
V.4	Temperature monitoring and records	1194
V.5	Delivery order	1194
V.6	Dispatch procedures and policies	1194
V.7	Dispatch containers	1194
V.8	Dispatch records	1194
V.9	Traceability	1194
V.10	Port of entry	1195
V.11	List of suggested SOPs	1195

Module VI	1196
Reassessment	1196
VI.1 Introduction	1196
VI.2 Reevaluation of manufacturers	1196
VI.3 Reevaluation of products	1197
VI.4 Monitoring of contracted services	1198
VI.5 List of suggested SOPs	1198
References	1199
Appendix 1 Example of a Code of Conduct	1201
Appendix 2 Example of a guideline on confidentiality	1208
Appendix 3 Example of a guideline on conflict of interest	1209
Appendix 4 Example of a standard operating procedure (SOP) for writing an SOP	1215
Appendix 5 Example of an invitation for expression of interest	1221
Appendix 6 Interagency finished pharmaceutical product questionnaire based on the model quality assurance system for procurement agencies	1226
Appendix 7 Example of a standard operating procedure for screening and assessing product information	1242
Appendix 8 Quality system recommendations for pharmaceutical inspectorates	1257
Appendix 9 Technical questionnaire for pharmaceutical manufacturers	1258
Appendix 10 Example of a standard operating procedure for planning of inspections	1267
Appendix 11 Example of a standard operating procedure for preparing for an inspection	1273
Appendix 12 Example of a standard operating procedure for performing an inspection	1278
Appendix 13 Example of a checklist for good manufacturing practices	1284
Appendix 14 Guidance on good manufacturing practices: model inspection report	1286
Appendix 15 Good storage practices	1291
Appendix 16 Good trade and distribution practices	1292

Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

accountability: The obligation to account for one's conduct and actions, usually to an individual or group, but ultimately to the public. Both individuals and organizations may be accountable. There is some overlap between accountability and *transparency* (see below).

active pharmaceutical ingredient (API): A substance or compound intended to be used in the manufacture of a pharmaceutical product as a therapeutically active compound (ingredient).

affordability: The extent to which pharmaceutical products are available to the people who need them at a price they can pay.

authorized person: A person (among key personnel of a manufacturing establishment) responsible for the release of batches of finished products for sale. In some *good manufacturing practice* (GMP) guides and legal texts, the term *qualified person* is used to describe analogous functions.

bioavailability: The rate and extent to which the active pharmaceutical ingredient or active moiety is absorbed from a pharmaceutical dosage form and becomes available at the site(s) of action.

bioequivalence: Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities, in terms of peak ($C_{\max}$ and $T_{\max}$) and total exposure (area under the curve (AUC)), after administration in the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.

change control: A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure that the system is maintained in a validated state.

competitive tender: A procedure for procuring pharmaceutical products which puts a number of suppliers into competition. Purchasing is done on the basis of quotations submitted by the suppliers in response to a public notice.

effectiveness: An expression of the degree to which activities have produced the effects planned.

efficiency: The relationship between the results of activities and the corresponding effort expended in terms of money, resources and time.

essential pharmaceutical products: Those pharmaceutical products that satisfy the health care needs of the majority of the population. WHO's Expert Committee on the Selection and Use of Essential Medicines updates the *WHO Model List of essential medicines* at two-year intervals. Each country may use this model to generate its own list of essential pharmaceutical products.

generic products: The term generic product has somewhat different meanings in different jurisdictions. The use of this term is therefore avoided as far as possible, and the term *multisource pharmaceutical product* (see below) is used instead. Generic products may be marketed either under the approved nonproprietary name or under a brand (proprietary) name. They may be marketed in dosage forms and/or strengths different from those of the *innovator products* (see below). Where the term *generic product* is used, it means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of the patent or other exclusivity rights. The term should not be confused with generic names for APIs.

generic substitution: The practice of substituting a product, whether marketed under a trade name or generic name, with an equivalent product, usually a cheaper one, containing the same active ingredient(s).

good manufacturing practice (GMP): That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

indicator: Criterion used to measure changes, directly or indirectly, and to assess the extent to which the targets or objectives of a programme or project are being attained. Indicators should meet the criteria of clarity, usefulness, measurability, *reliability*, *validity* (see below) and acceptance by key stakeholders.

innovator pharmaceutical product: Generally the pharmaceutical product which was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality according to requirements at the time of the authorization. When a substance has been available for many years, it may not be possible to identify an innovator pharmaceutical product.

inspection: An official examination, normally conducted on site, of the compliance with WHO good manufacturing practices as referred to in this document. In some cases, an off-site review of documentation may be done in lieu of the on-site examination.

interchangeability: An interchangeable pharmaceutical product is one that is therapeutically equivalent to a comparator (reference) product.

International Nonproprietary Name: The shortened scientific name based on the active ingredient. WHO is responsible for assigning INNs to pharmaceutical substances.

legislation: The first state of the legislative process, in which laws are passed by the legislative body of government with regard to a subject matter, e.g. control of pharmaceuticals. Laws define the roles, rights and obligations of all parties involved in the subject matter in general terms (see also *regulations below*).

licensing system: National legal provisions on who should manufacture, import or supply pharmaceutical products, what qualifications people in the supplying agency should have, and who should dispense and sell pharmaceutical products.

manufacture (manufacturing): All or any operations of purchase of materials and products, production, quality control, release, storage and distribution of finished products and the related controls.

marketing authorization: A legal document issued by the competent medicines regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It must set out, inter alia, the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using INNs or national generic names where they exist), the shelf-life and storage conditions, and packaging characteristics. It specifies the information on which authorization is based (e.g. “The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence.”). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization, and the period of validity of the authorization. Once a product has been given marketing authorization, it is included on a list of authorized products – the register – and is often said to be “registered” or to “have registration”. Market authorization may occasionally also be referred to as a “licence” or “product licence”.

medicine: Any substance or pharmaceutical product for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient. In this document, the terms *medicine* and *pharmaceutical product* (see below) are used interchangeably.

medicines regulatory authority: A national body that administers the full spectrum of medicine regulatory activities, including at least all of the following functions in conformity with national medicine legislation:

- marketing authorization of new products and variations of existing products;
- quality control laboratory testing;
- monitoring of adverse drug reactions;
- provision of information on medicines and promotion of rational use of medicines;
- *good manufacturing practice* (GMP) inspections and licensing of manufacturers, wholesalers and distribution channels;
- enforcement operations;
- monitoring of drug utilization.

medicines legislation: The legal conditions under which pharmaceutical activities should be organized (see also *legislation above*).

multisource (generic) pharmaceutical product: Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically

equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

national list of essential pharmaceutical products: The list of *essential pharmaceutical products* (see above) that has been defined, adopted and published at country level. It is normally used by all health facilities, including the main hospitals.

pharmaceutical product: See *medicine*.

prequalification: The activities undertaken in defining a product or service need, seeking expressions of interest from enterprises to supply the product or service, and examining the product or service offered against the specification and the facility where the product or service is prepared against common standards of *good manufacturing practice* (GMP). The examination of the product or service and of the facility where it is manufactured is performed by trained and qualified inspectors against common standards. Once the product is approved, and the facility is approved for the delivery of the specified product or service, other procurement agencies are informed of the decision. Prequalification is required for all pharmaceutical products regardless of their composition and place of manufacture/registration, but the amount and type of information requested from the supplier for assessment by the procurement agency may differ.

procurement: The process of purchasing or otherwise acquiring any pharmaceutical product, vaccine or nutraceutical for human use. For the purpose of this document, *procurement* means the pre-selection of products and manufacturers through a procedure of qualification, including *prequalification* (see above) and continuous monitoring thereafter, purchase of the prequalified products from prequalified manufacturers (linked to the specific product) through defined purchasing mechanisms, storage and distribution.

procurement agency: A procurement agency in the context of this document is defined as any organization purchasing pharmaceutical products, vaccines, or other health products or otherwise involved in their *prequalification* (see above), purchasing, storage and distribution.

product information: Information on pharmaceutical products submitted by manufacturers or suppliers in any of the formats specified in the procurement agency's guidelines (including product dossiers, product questionnaires or other formats) to obtain prequalification for the products.

qualification: Action of proving and documenting that any premises, systems and equipment are properly installed and/or work correctly and lead to the expected results. Qualification is often a part (the initial stage) of validation, but the individual qualification steps alone do not constitute process validation. It is the work done to prove that the supply system will deliver products of the quality required and specified on a routine basis, meeting all the applicable quality requirements.

quality assurance: Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality

of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use.

quality control: Quality control is concerned with sampling, specifications and testing, and with the procurement agency's documentation and acceptance/rejection procedures which ensure that the necessary and relevant tests are actually carried out and that starting materials, intermediates and finished products are not accepted for use, sale or supply until their quality has been judged to be satisfactory.

regulations: The second stage of the legislative process (the first stage being legislation, see above). Regulations are specifically designed to provide the legal machinery to achieve the administrative and technical goals of legislation.

reliability: An expression of the degree to which a measurement performed by different people at different times and under different circumstances produces the same results (see also *validity*).

reliable quantification of medicines needs: A careful evaluation of the quantities needed of each medicine, based on either adjusted past consumption or anticipated pattern of diseases and standard treatment, which can be expected to match actual needs reasonably well.

stringent regulatory authority (SRA): A regulatory authority which is:

- a. a member of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (as specified on www.ich.org); or
- b. an ICH observer, being the European Free Trade Association (EFTA), as represented by Swissmedic and Health Canada (as may be updated from time to time); or
- c. a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

transparency: The term transparency means:

- defining policies and procedures in writing and publishing the written documentation; and
- giving reasons for decisions to the public (see also *accountability* above).

validation: Action of proving and documenting, in accordance with the principles of good manufacturing practice, that any procedure, process, or method actually and consistently leads to the expected results (see also *qualification* above).

validity: An expression of the degree to which a measurement performed actually measures the characteristic which the investigator wishes to measure (see also *reliability* above).

variation: Variation to an approved product questionnaire or product dossier that includes, for example, changes in formulation, specifications, or manufacturing process.

WHO-type certificate: A certificate of pharmaceutical product of the type defined in the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce.¹

¹ Guidelines on the implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fifth report. WHO Technical Report Series No. 1033, Annex 9. Geneva: World Health Organization; 2021 (<https://iris.who.int/bitstream/handle/10665/340323/9789240020900-eng.pdf?sequence=1>).

Module I

General requirements for procurement agencies

I.1 Introduction

Procurement agencies often have to purchase and supply pharmaceutical and other health products using scarce resources. In many cases, product quality is compromised when products are obtained from unqualified sources. Procurement agencies may deal with various types of organizations, suppliers and customers, including medicines regulatory authorities, manufacturers, quality control laboratories, contract manufacturers, contract laboratories, traders, brokers, distributors and pharmacies. A quality assurance system should be in place to ensure that transactions with these partners ultimately result in procuring pharmaceutical products and other health products (hereafter referred to collectively as products) of the best possible quality.

This module addresses the general requirements for such a system, including physical resources such as premises, equipment and personnel, as well as the documented policies, standards and procedures required to ensure consistency in all the key activities of procurement. The general requirements described in this module are, therefore, applicable to all procurement agencies and general principles may apply to the activities covered in subsequent modules.

I.2 Physical resources

I.2.1 Premises

I.2.1.1 Offices

The procurement agency should have sufficient office space to accommodate the personnel required and the activities to be performed.

I.2.1.2 Storage

The procurement agency should have sufficient space for storage and retention of products, product documentation, product samples, stock, reports, files and other records relating to all key activities of procurement. Samples and products should be stored under suitable conditions which are specified on product labels, e.g. with regard to temperature, humidity or protection from light. Details of storage requirements are given in Module IV. There should be sufficient space for storage of equipment, stationery and materials for proper distribution. Details of distribution requirements are given in Module V.

I.2.2 Equipment

I.2.2.1 Computers

The use of computers can facilitate, but not replace, efficient procedures in pharmaceutical procurement. When implemented appropriately, computerization will speed up complex tasks, increase accuracy and automate repetitive tasks. Staff must be trained adequately in the use of computerized systems.

Many aspects of procurement are suitable for computerization, including planning of requirements, budget management, financial analysis, preparation of documentation, traceability of batches supplied to customers, and reports and inventory control. Hard copies (printouts) should be produced as required to provide documentary evidence of the activities.

I.2.2.2 Software

The software selected should be suitable for the intended use. The programs used should be able to provide the required quality and management information reliably and accurately. They should be user-friendly and staff should be trained adequately in their use. Where possible, different programs used should be compatible so that data can be transferred between them without having to be re-entered. Where information is exchanged between the procurement agency and the manufacturer(s) by electronic means, appropriate programs should be in place. Suitable security systems should be in place to prevent unauthorized access or changes to computer records and reports. Back-up systems must be in place to prevent loss of data. A good-quality virus protection program and firewall must be installed, configured, used and updated regularly to prevent unauthorized access and loss of data.

Technical support should be available to ensure that software and security systems are kept functional and up-to-date.

Standard operating procedures (SOPs) should be implemented to ensure that back up of data is made at defined, regular intervals.

Back-up data should be stored in a secure place with access control, under suitable conditions (e.g. protected from fire hazard).

Systems should be in place to ensure that back-up data are accessible and will be readable in the future, when required.

I.2.2.3 Hardware

The hardware selected should be able to handle the required software efficiently. The system should have sufficient capacity and memory for the intended use, as well as adequate input and output devices, including good-quality printers. Access to the Internet and possibly to an internal network (LAN) should be provided to facilitate exchange of information.

A maintenance plan should be in place to ensure that the system remains functional.

I.2.2.4 Telecommunications

There should be access to telephone and email systems to ensure instant communication.

I.2.2.5 Furniture

Suitable office furniture should be provided, including desks, chairs, shelves, cupboards, filing cabinets and other items as required.

I.2.2.6 Office equipment

Office equipment should be provided and kept in working order.

I.2.2.7 Stationery and consumables

The procurement agency should provide stationery to enable staff to perform the relevant tasks, including paper, letterheads, business cards and pre-printed forms as required. Computer consumables, including printer cartridges and printing paper, as well as any replacement parts not covered by a maintenance contract, should be provided.

I.2.3 Vehicles and transport

As the procurement agency is responsible for transportation and distribution of products, appropriate transport should be provided to ensure that the quality of the products is maintained. (For details see Module V.)

I.2.4 Financial systems

The procurement agency should be able to effect national and international financial transactions as required. Funds must be available to ensure continued operations.

Adequate banking facilities must be available. Signatories of bank accounts should be appointed to ensure control on one hand, and continuity of operations during the absence of key personnel on the other hand.

An accounting system should be in place. Regular financial audits should be performed.

If the procurement agency is part of a larger organization, it should have sufficient autonomy and/or effective systems in place to enable it to conduct all its financial transactions without delay.

I.2.5 Human resources

I.2.5.1 Personnel

There should be a sufficient number of appropriately trained, educated and experienced personnel to perform the key activities. The number of members of staff required in the department responsible for the key activities will depend on the activities and volume of products sourced and to be supplied.

Sufficient support staff for secretarial, organizational and accounting duties as well as legal support should also be available.

Key personnel should include those responsible for quality assurance, prequalification, purchasing, storage and distribution. The person responsible for quality assurance could also be responsible for prequalification. The personnel responsible for quality assurance/prequalification and the personnel responsible for purchasing should be independent of one another. One should not report to the other.

National legislation should be complied with, for example, requirements for a responsible person for purchasing, storage and distribution of pharmaceutical products.

The responsibilities of the staff in charge of the different key activities are described in Modules II–V.

1.2.5.2 Qualifications and experience

Personnel responsible for quality assurance, prequalification, purchasing, storage and distribution should have sufficient qualifications, knowledge and experience in their respective fields (see Modules II–V).

1.2.5.3 Code of conduct

All staff members should comply with a code of conduct which should guide all their professional activities. More detail on codes of conduct is given in section I.2.4. An example of a code of conduct is shown in Appendix 1.

1.2.5.4 Confidentiality

It is essential that all information obtained by any person working for the procurement agency is treated as confidential. Most of the information obtained from companies and manufacturers is product-specific, may be patented and will be commercially sensitive. Personnel must treat all information submitted and observed during the assessment of product dossiers and inspections at manufacturing sites, and otherwise in connection with the discharge of their responsibilities as strictly confidential and proprietary to the party collaborating with the procurement agency.

Confidentiality agreements should be considered where necessary. An example of such an agreement is attached in Appendix 2. Additional information may be found in Appendix 3 (example of a guideline on conflict of interest).

1.2.5.5 Conflict of interest

Before undertaking any work, key personnel in key activities (e.g. quality assurance, prequalification, purchasing, specification setting – including contracted personnel) should sign a declaration of interest. If, based on their declaration of interest, it is deemed appropriate for them to undertake the work specified, they agree to carry out their functions exclusively for the agency.

They should confirm that the information disclosed by them in the declaration of interest is correct, that no situation of real, potential or apparent conflict of interest is known to them and that they have no financial or other interest in, and/or relationship with a party which:

- may have vested commercial interest in obtaining access to any confidential information disclosed to them in the course of the evaluation activities described in the declaration;
- may have a vested interest in the outcome of the evaluation activities including, but not limited to, parties such as the manufacturers whose products are subject to evaluation or manufacturers of competing products.

Personnel should undertake to advise the procurement agency promptly of any change in their circumstances, for instance if an issue arises leading to a conflict of interest during the course of their work for the procurement agency.

1.2.5.6 Job descriptions

There should be written job descriptions, with definitions of responsibilities, for all key personnel. Personnel and their supervisor should sign and date the job description.

1.2.5.7 Organization chart

The procurement agency should have an authorized, current organization chart indicating the positions, names of responsible persons and reporting lines.

The organization chart should reflect the responsibilities and reporting lines in accordance with the job descriptions.

1.3 Documentation of policies and standards

Documentation is an essential part of a quality assurance system. The procurement agency should have a comprehensive documentation infrastructure, which should include policies, guidelines, norms, standards, manuals, procedures, records and related documents.

All activities of each section or department should be performed and documented in a standardized manner, following approved written procedures.

The main elements of the documentation system of this MQAS are described below.

1.3.1 Quality manual

The procurement agency should have a quality manual. The purpose of such a manual is to document the quality policy as defined by management in relation to the various activities undertaken by the procurement agency. There should be policy statements and

a quality policy in terms of the agency's activities and objectives, as well as documents describing the policy of each section or department with regard to all activities in prequalification and subsequent purchasing, storage and distribution.

The quality manual should contain as a minimum:

- (a) a quality policy statement, including at least the following:
 - (i) a statement of the management's intentions with respect to the standard of service it will provide,
 - (ii) a commitment to establishing, implementing and maintaining an effective quality management system,
 - (iii) the management's commitment to good professional practice and quality of activities and services,
 - (iv) the management's commitment to compliance with the content of these guidelines,
 - (v) a requirement that all personnel concerned with the activities within the procurement agency familiarize themselves with the documentation concerning quality and the implementation of the policies and procedures in their work;
- b) the structure of the procurement agency (organization chart);
- c) the operational and functional activities so that the extent and the limits of the responsibilities are clearly defined;
- d) outline of the structure of documentation used in the procurement agency quality management system;
- e) the general internal quality management procedures;
- f) references to specific procedures, conflict of interest and code of conduct;
- g) information on the appropriate qualifications, experience and competencies that personnel are required to possess;
- h) information on initial and in-service training of staff;
- i) a policy for internal and external audit;
- j) a policy for implementing and verifying corrective and preventive actions;
- k) a policy for dealing with complaints;
- l) a policy for performing management reviews of the quality management system;
- m) a policy for the handling of out-of-specification (OOS) results;
- n) policy to select service providers and suppliers including reference to prequalification;
- o) a policy for storage and distribution of products.

Once this quality policy is defined, it should be implemented, maintained, reviewed and amended as necessary at regular intervals by the procurement agency.

I.3.2 Standard operating procedures

The procurement agency should have written, clear and detailed SOPs for all the activities to be performed in the procurement agency. Quality risk management (QRM) principles may be applied in determining the scope and extent of SOPs. The content of each SOP, particularly the step-by-step descriptions of activities and approved recording or reporting formats attached as addenda (see below), should reflect the operations of the particular procurement agency.

SOPs should be drafted by the person responsible for the procedure. An SOP for writing an SOP should be followed to ensure consistency of design, format and layout. An SOP on how to write an SOP is attached as Appendix 4.

SOPs should be reviewed periodically.

I.3.2.1 Style and layout

SOPs should be written in the procurement agency's approved format, and be formally approved (signed and dated) by the authorized person(s). SOPs should be written in clear, unambiguous language. The name and/or logo of the procurement agency should be included on the front page of each SOP.

I.3.2.2 Elements of standard operating procedures

The SOP should contain at least the following elements.

Title and number

Each SOP should have a title. The title should give a clear indication of the activity which it describes. A numbering system is useful to identify to which activity or department the SOP refers.

Objective

This section should describe what is to be accomplished and/or achieved with the SOP.

Scope

This section should describe to what level or depth, or how widely, the SOP is applicable.

Policy (optional section, if not included elsewhere)

This section should reflect the procurement agency's policy regarding this particular activity.

Responsibility

This section should list the person(s) and/or departments responsible for performing the activities listed in the procedure. It may be useful to refer to the position and/or department rather than the name of the person.

Action

This section should describe the sequence of action steps to be followed, from the beginning to the end of the process, to perform the activity. The action steps should be written in the imperative and should be numbered. It is advisable to indicate who is responsible for each step. This could be done by putting the position (job title) of the responsible person in brackets next to each step, or by indicating the numbers of the relevant steps next to the positions listed under the heading “Responsibility”. Where a step leads to another procedure to be followed, the applicable SOP should be referred to in that particular step.

Distribution and retrieval

Documentation should be distributed with care. No superseded or obsolete SOPs should be available at user points. The sections and/or responsible persons (positions) to whom the SOP was distributed should be listed.

Revisions

In a section which could be headed “History”, the date of each change to the SOP, the person responsible for the review, the change itself and the reason for the change should be recorded. This section will provide the procurement agency with the history of the amendments to the SOP.

Addenda

Any records to be completed or maintained as part of the activity should have a standardized format. It is useful to define and approve these formats in advance. The approved standard format should be part of the SOP and can be attached as an addendum to the SOP.

1.3.2.3 Activities to be covered by standard operating procedures

There should be written SOPs that reflect the activities of the procurement agency and ensure consistency in the execution of the operation, task or activity.

The following list gives examples of activities which could be covered by SOPs. A more specific list is provided at the end of each Module of these guidelines:

- how to write an SOP (see Appendix 4),
- handling of complaints,
- document/record control,

- self-inspection,
- handling of recalls,
- monitoring of environmental conditions (e.g. temperature),
- monitoring supplier performance,
- identifying and reporting substandard/spurious/false-labelled/falsified/counterfeit (SSFFC) products,
- evaluating offers received,
- ordering product(s) from supplier or manufacturer,
- retention of products,
- retention of product documentation,
- handling of product samples,
- stock management and inventory control,
- control, monitoring and recording of temperature and relative humidity,
- handling of materials and/or products requiring special storage conditions,
- budget management,
- financial analysis,
- traceability of batches supplied to customers,
- password control for personnel working with computers,
- how to make back-ups, and storage of data,
- ordering, storage and handling of consumables,
- managing signatories of bank accounts,
- management of the accounting system,
- performing financial audits,
- preparation and management of the code of conduct,
- establishment and maintenance of confidentiality agreements,
- preparation and maintenance of conflict of interest declarations,
- preparation of job descriptions,
- preparation of organization charts,
- preparation of the quality manual,
- distribution and retrieval of SOPs,
- change control,
- handling of variations,
- managing records and archives,
- establishing and maintaining contracts.

Each time the SOP is reviewed and amended, superseded versions of the SOPs should be removed from all user points listed and replaced with the updated version. The retrieval should be documented. The section and/or responsible person who receives the SOP should acknowledge the receipt thereof. Personnel should be trained appropriately in using the revised SOP.

I.3.3 Change control policy and handling of variations

I.3.3.1 Change control

The procurement agency should have a policy and procedure for change control. This policy should be designed to manage changes in the agency, e.g. changes to procedures, internal processes, or premises. The procedure should describe the process that will be followed to initiate the change, and the routing of the request for approvals to effect or reject the change. The review of the change request should include an assessment of the risk and impact of the change.

I.3.3.2 Variations

There should also be a procedure for handling variations to a prequalified product. Examples of variations include those that affect active pharmaceutical ingredients (APIs), formulation, manufacturing processes, analytical testing methods or packaging of prequalified products. The procedure should ensure that these variations are reported to the procurement agency before new batches are manufactured or before they are delivered and released for distribution.

Details of managing variations in product information are given in Module VI.

I.3.4 Code of conduct

The procurement agency should design, authorize and implement a written code of conduct.

The code of conduct should describe the policy of the procurement agency regarding the conduct of staff with respect to their activities. It should be followed by all personnel.

The code of conduct should give guidance to staff members on appropriate conduct in various situations. The following topics could be covered in the code:

- introduction and objectives
- key responsibilities
- personal responsibilities
- safety
- professional competence
- qualifications and experience

- conduct
- integrity and attitude
- attire, health and hygiene
- management relationship
- SOPs
- travel and accommodation
- confidentiality and conflict of interest
- documentation and records
- contracts and terms of reference (TOR)
- product files, evaluation and inspection
- samples
- evaluation and inspection reports
- provision of information and advice.

I.3.5 Guidelines on conflict of interest

The procurement agency should have a policy on conflict of interest which all personnel (including external experts, and consultants) should observe. An example of a guideline on conflict of interest is provided in Appendix 3.

The document should address at least the following points:

- introduction and objectives
- definitions and principles
- responsibilities
- confidentiality
- impartiality.

I.3.6 List of prequalified products, manufacturers and suppliers

The procurement agency should have a procedure for preparing and maintaining a list of prequalified products, manufacturers and suppliers, based on the outcome of the evaluation of product data and information and of manufacturing site inspections. The list should be product- and manufacturing site-specific, i.e. sites are prequalified for one or more specified products, and products are prequalified as manufactured at specified sites.

The key person responsible for prequalification should be responsible for additions to and deletions from the list.

Once the evaluation of a product dossier is complete, and the inspection has been performed to assess compliance with GMP, good storage practices (GSP) and GDP

as appropriate, the procurement agency should prepare a list reflecting the status of the prequalified products and manufacturers.

A current, authorized, access-controlled list of prequalified products and suppliers should be available. The list should be maintained by authorized personnel.

The list should contain at least the following information:

- name and physical address of manufacturer, including the approved site(s) of manufacture linked to each product;
- product details, including the brand name, International Nonproprietary Name (INN), dosage form, strength per dose and pack size;
- date of last (pre)qualification.

I.3.7 Maintenance of records

Records of all operations should be maintained and kept in a suitably organized manner.

Sufficient areas for the storage of records, including product information, manufacturers' information and inspection reports, should be available for a defined period of time. Access to these areas should be restricted to authorized personnel, as confidential information may be filed (including records of manufacture, testing and/or storage).

Records pertaining to batches of product procured should be retained for at least one year beyond the expiry date of the product or in accordance with customer requirements and national legislation, whichever is longer.

I.3.8 Contract arrangements

Where any activity is delegated to another organization (e.g. procurement agency, quality control laboratory, or distributor), this should be done by means of a written agreement between the two parties. The contract giver should ensure that the contract acceptor meets the requirements as recommended in these guidelines.

Module II

Prequalification

II.1 Introduction

Prequalification is one of the key elements in ensuring purchase and supply of pharmaceutical products of acceptable quality. The prequalification process can be subdivided into two major parts, i.e. product-related assessment and manufacturer-related inspection.

Product-related assessment should ensure that the correct product is specified by the procurement agency. The procurement agency should then assess whether the manufacturer is offering a product that meets the predetermined norms and standards in terms of safety, quality and efficacy.

Manufacturer-related inspection should ensure that the manufacturer is able to manufacture the product as specified in the product information questionnaire/dossier and in accordance with GMP as recommended by WHO. The manufacturer must be capable of routinely carrying out the activities to the specified standards to ensure batch-to-batch consistency of the product.

Assessment of contracted-out services, e.g. by storage and distribution agents, contract research organizations (CROs) and quality control laboratories for compliance with GMP, good clinical practices (GCP) and good laboratory practices (GLP), are further elements that may supplement the prequalification process.

The procurement agency is responsible for ensuring that all steps in the prequalification process are carried out in accordance with this MQAS. This should ensure that the manufacturers will be providing products as specified that meet all predetermined norms and standards. Full prequalification may not be required when products are already prequalified by the WHO Prequalification Programme, or registered by SRAs. It will assist procurement agencies in maximizing the use of resources and will avoid duplication of prequalification. Prequalification also reduces the risk of procurement agencies purchasing and supplying substandard products.

This module sets out recommendations which procurement agencies should implement when evaluating their product needs and when assessing the products and the manufacturing and supply arrangements offered by the manufacturers.

II.2 Principles for prequalification

Prequalification procedures should be based on the following principles:

- reliance on the information supplied by the national medicines regulatory authorities (NMRAs);
- evaluation of product data and information submitted by manufacturers, including product formulation, manufacture and test data and results;

- a general understanding of the production and quality control activities of the manufacturers and suppliers and of their commitment to the principles of good manufacturing practices (GMP);
- assessment of consistency in production and quality control through compliance with GMP as described in the latest update of the WHO publication *Quality assurance of pharmaceuticals (1)* and supplementary WHO GMP guidelines.

The procurement agency should have a document describing the policy and procedures for prequalification, including the assessment of product information and of manufacturers for compliance with standards.

Where prequalification is delegated to another party, this should be done by means of a written agreement between the two parties. The contract giver should ensure that the contract acceptor meets the requirements as recommended in this module.

II.2.1 WHO Model List of essential medicines

Procurement agencies may find that many of the products they require are on WHO's Model List of essential medicines, which is updated periodically (2). They will find this list a useful reference for establishing specifications for the medicines needed for their purposes.

II.2.2 Standards for prequalification

Current standards for prequalification can be found at: <http://apps.who.int/prequal/default.htm>

In principle, products should meet the recommendations made by WHO in *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products – a manual for medicines regulatory authorities* (3). Manufacturing sites should comply with WHO GMP.

II.2.3 Key persons and responsibilities

All key personnel responsible for prequalification should have appropriate training.

II.2.3.1 Staff responsible for prequalification

The person responsible for prequalification should be independent from the person responsible for purchasing.

The key responsibilities of the unit responsible for prequalification activities should include the following:

- establishing specifications for products;
- publication of invitations for expressions of interest (EOI) (if this mechanism is used). An example of an EOI is provided in Appendix 5;

- preparation of a questionnaire for collecting product data and information and/or guidelines for the compilation of product information;
- assessment of product data and information for compliance with norms and standards;
- assessment of manufacturing sites, for compliance with WHO GMP;
- the list of prequalified products and manufacturers.

II.2.3.2 Staff responsible for evaluation of product information

Where possible, the person responsible for the evaluation of the product information should be independent from the person evaluating the manufacturing site.

The key responsibilities of the unit or appointed individual responsible for evaluating product information should include:

- preparing and implementing SOPs and guidelines for evaluation of product information;
- receipt of product information;
- screening of product information (for completeness on initial receipt);
- evaluation of product information (full evaluation to assess compliance with standards);
- informing manufacturers of the outcome of the evaluation of the product information;
- communicating with the person responsible for inspections of manufacturing sites.

The people assigned to evaluate product information should have relevant qualifications and experience, which may include a background in pharmaceuticals, pharmaceutical chemistry and pharmacology. Ideally they should be from a regulatory background, or have regulatory experience.

II.2.3.3 Staff responsible for inspection of manufacturing sites

The key responsibilities of the unit or appointed person responsible for inspection of manufacturing sites should include the following:

- preparation and implementation of guidelines and SOPs;
- coordination of inspections to be performed;
- recruiting or appointing inspectors with appropriate qualifications and experience, when necessary;
- conducting inspections;
- preparation of inspection report;

- follow-up of CAPA after inspections;
- finalizing inspection reports;
- informing manufacturers of the outcome of the inspection.

As a minimum, the personnel/appointed person responsible for inspecting manufacturing sites should have relevant qualifications and experience in pharmaceutical manufacturing, quality assurance, GMP and good distribution practices (GDP), performing inspections and audits, chemistry and quality control. Ideally they should have an inspection background from working with a regulatory authority or experience in managing manufacturing sites.

Although decision-making should be independent, there should be communication between the person responsible for evaluation of product information and the person responsible for inspection of manufacturing sites, as some information on the product may have to be verified during the site inspection.

II.2.4 Key steps in prequalification

The key steps in prequalification include soliciting and receiving product data and information, screening and assessment of the data and information, and assessment for compliance with standards for manufacture such as GMP.

The preparatory steps of drafting a documentation system, including confidentiality agreements, declaration of conflict of interest, SOPs and guidelines, are described in Module I.

II.2.4.1 Step 1: Soliciting information

Prepare product specifications for prequalification

Specifications for the product(s) to be prequalified should be prepared.

The specifications should be detailed, clear and unambiguous to avoid unnecessary submission and processing of documentation not relevant to the product to be sourced.

The specification should state at least:

- the name of the API(s)/INN;
- strength per dose;
- dosage form (route of administration).

Other aspects to consider include pack size, primary packaging materials and labelling requirements.

Once the specification is finalized, the information can be published widely to all manufacturers, or targeted to prequalified manufacturers according to the internal rules of the procurement agency. The information communicated should include at least:

- the purpose of the invitation;
- the list of products, including specifications for each product;
- information on quantities required (if available);
- details of the information to be submitted;
- procedure for submission, including information on details to be submitted, on the focal point for the submission and on the format for the submission;
- contact details (name, address, telephone number, fax, email and postal address) for submission;
- the closing date for receipt of the information by the procurement agency.

Procedure for submitting product information

The procedure for submitting product information should be publicly available and accessible. In cases where this is not the case, reasons for the decision should be given and documented.

The procedure should be written in clear, unambiguous language and should contain information detailing at least:

- the content and format of submission, including the type and format of information required (e.g. the procedure for submission of information for a product registered in a country recognized as having an effective medicines regulatory agency, and instructions for cross-referencing an existing dossier with the prescribed submission format);
- the process of submission, including the address to which the documentation should be sent and a statement of any fees payable for cost recovery.

Content and format of submission

For each product to be prequalified, interested manufacturers should be asked to submit product information, together with a sample of sufficient quantity to allow analyses of the product against its finished product specification as stated in the product information. A covering letter and a checklist for the product information may be added (optional).

Depending on the active ingredients, country of manufacture and registration of products to be prequalified, different formats for submission will be required.

Detailed information should be submitted for products for which bioavailability may be altered by chirality, isomerism, controlled release formulation, polymorphism or other properties which may affect the therapeutic outcome.

In this document, the term “product information” refers to any of the following three formats in which submissions should be made:

1. For products manufactured and registered in countries where regulatory requirements are in line with international regulations for assessment of safety, efficacy and quality, the following information should be submitted:
 - a WHO-type certificate of a pharmaceutical product (CPP) (4) issued by a stringent regulatory authority, together with a summary of product characteristics (SmPC), or proof of the official registration of the product;
 - if the product is different to the one registered by the SRA, arguments and/or data to support the application should be submitted. This may include differences in formulation, strength or other specifications including packaging.

Products registered for export purposes only, should be fully assessed unless these were approved or subject to a positive opinion under the Canada S.C. 2004, c. 23 (Bill C-9) procedure, or Article 58 of European Union Regulation (EC) No. 726/2004 or United States Food and Drug Administration (US FDA) tentative approval.

2. A standard product dossier as prepared for a national medicine regulatory authority should be submitted, provided it contains the appropriate information as required in the WHO guidelines, e.g. common technical document (CTD). In such cases, the supplier should provide a covering letter which indicates where the required information can be found in the standard product dossier.
3. A completed questionnaire with information on the product should be submitted. An example of a pharmaceutical product questionnaire is shown in Appendix 6.

Process of submission

Suppliers should be allowed at least 60 days for the compilation and submission of product information.

Manufacturers should be requested to state that the information submitted is true and correct.

The procurement agency should reserve the right to terminate the prequalification procedure of a product and manufacturer if the manufacturer fails to provide the required information within a specified time period, or if the information supplied is inadequate to complete the prequalification effectively.

II.2.4.2 Step 2: Receive product information

Receipt of information

The procurement agency should have the necessary infrastructure to receive and process the product information submitted by manufacturers. It will require personnel for processing the documentation; written procedures for receiving, identification and marking of files, containers and samples, and sufficient space for unpacking and storage.

Containers with product information should be received at the specified address before a specified date as determined by the procurement agency.

The procurement agency should have a clear policy regarding the acceptance of information after the specified closing date. Processing of late submissions should not normally be allowed. Only in exceptional instances should late information be considered, e.g. when a manufacturer is the only one to express an interest in supplying a specific product. It would be appropriate to express concern at the late arrival of the information, and manufacturers should give reasons for late submission.

Each product should be allocated a unique reference number to ensure traceability of the product information.

A record of all the information received from each manufacturer should be maintained.

II.2.4.3 Step 3: Screen product information

Each product information package submitted by the manufacturer should be screened for completeness. The screening should be done in accordance with a written procedure. If the product information submitted fails to meet the requirements, it should be excluded from the evaluation procedure and inspection process.

A screening form should be used to ensure consistency of screening. There should be a written record of the screening of each product information package.

Information to be recorded should include:

- date of receipt
- name of the interested manufacturer(s)
- address of the manufacturer
- name of the product
- country of manufacture
- product number
- outcome of the screening.

An example of an SOP for screening and assessing product information, including a sample screening form, is shown in Appendix 7.

Incomplete information should not be kept for evaluation purposes. The manufacturer should be informed that an incomplete information package was

received, and be requested to supply the missing information within a specified period. If this request is not complied with, the application should be rejected on grounds of incompleteness.

Product information packages which meet the requirements of the screening procedure should be retained for full evaluation.

A summary should be made of each product information package received, stating any reference number allocated to the product by the procurement agency, the INN, strength, dosage form and pack size of the product, the name of the supplier, the name and address of the manufacturing site(s), whether a sample has been submitted, and if so, the sample size.

II.2.4.4 Step 4: Evaluate product information

Evaluators

Evaluators with suitable qualifications and experience in the evaluation of product data and information should be available to conduct the assessment. Suitably qualified external evaluators may be appointed. Appointment of external evaluators should be subject to compliance with the policy of the procurement agency regarding aspects such as confidentiality, conflicts of interest and financial resources. Examination of potential conflicts of interest and confidentiality must go beyond the potential evaluator signing a declaration. Checks on references should also be made.

A formal agreement for the performance of work and terms of reference for contracted evaluators should be in place before commencement of work.

A summary list of names, addresses, dates of appointment, qualifications and experience of evaluators should be maintained. Copies of signed agreements should be kept in a central file.

Evaluation

Time frames should be set for evaluation of product information. Product information should be evaluated within a reasonable period after the closing date for submission.

A written procedure for evaluation should be followed. An example of an SOP for screening and assessing product information is attached as Appendix 7.

The person responsible for evaluation should monitor the process to ensure that each product information package is evaluated in compliance with these requirements.

Evaluation reports

Each evaluator should prepare a formal evaluation report for each product, including a recommendation for acceptance or rejection. The evaluation report should be communicated to the manufacturer.

A response should be invited from the manufacturer in cases where data and information are found to be incomplete or do not meet the guidelines.

A reasonable period should be allowed for submission of additional data and information.

This additional information should be assessed and the final outcome of the evaluation should be communicated to the manufacturer.

The evaluation report should be filed with the product evaluation documentation for reference purposes and follow-up where relevant.

Analysis of samples

Samples submitted together with product information packages should be analysed – if deemed necessary based on risk assessment – in accordance with the finished product specification. Certificates of analysis of product samples should be made available to the procurement agency.

The procurement agency should have access to a quality control laboratory to perform the analyses. The WHO *Guide for a quality systems manual in a control laboratory* (5) seeks to establish a practical basis for the quality systems manual of a control laboratory which each country can adopt and adapt when preparing its own more detailed manual to meet the required level of specificity and complexity.

A laboratory may be contracted to perform the analyses. In that case, the procurement agency should ensure that the laboratory complies with GMP and good practices for control laboratories (6). The use of a WHO-prequalified quality control laboratory or an accredited laboratory is, therefore, recommended. The procurement agency should verify the accreditation. There should be a written contract or agreement between the procurement agency and the contract laboratory. The wording of the contract should be clear and it should specify the responsibilities of the contract giver and the contract acceptor.

The procurement agency is responsible for ensuring access to raw data.

The procurement agency should have a procedure for investigating, handling and reporting out-of-specification results when these are obtained from laboratories. If a sample fails to meet the specifications, the procurement agency should investigate the problem and communicate the outcome to the manufacturer.

II.2.4.5 Step 5: Plan, prepare and perform inspections

Each batch of every product procured by a procurement agency should be manufactured in compliance with WHO GMP to ensure batch-to-batch consistency.

The actual site of manufacture of the product should be known and specified.

In some cases, a contract manufacturer may manufacture the product on behalf of the supplier or agent. Each manufacturing site specified in the product information should be inspected to assess compliance with WHO GMP.

Manufacturers of the APIs may be inspected, based on risk assessment, as part of the assessment procedure to ensure that the APIs were manufactured in accordance with WHO GMP.

Existing certificates

ISO certification is not an assurance of compliance with WHO GMP and is not a replacement or substitute for verification of compliance with WHO GMP.

Similarly, a CPP is not a guarantee of compliance with GMP. Participation in the WHO Certification Scheme (7) is a voluntary process, and there is no formal assessment or evaluation of medicines regulatory authorities entering the scheme. In some cases, reliance on the CPP alone is therefore not recommended.

The certification scheme is an administrative tool and is reliable only where the relevant national medicines regulatory authority has an established system which is known to comply with acceptable standards for evaluation and registration or licensing of products and manufacturers, including products for export markets. Information in addition to the CPP, e.g. a copy of the inspection report and corrective action plan from the manufacturer, may be requested. These documents, in addition to other documentation, may be considered useful in the prequalification process and in follow-up assessment or evaluation at a later stage.

The procurement agency should still verify compliance with WHO GMP as part of the prequalification procedure, and an inspection of the manufacturing site must be considered in every case. An example of requirements applicable to quality systems for the operation of inspection services can be found in Appendix 8.

Inspectors

Inspections should be performed by a suitably qualified, experienced inspector or team of inspectors with relevant qualifications, training and experience in performing inspections in foreign countries. Inspectors should have sound knowledge of quality assurance and GMP in production and quality control of pharmaceutical products. A sufficient number of inspectors should be appointed to carry out inspections within predetermined time frames.

Where possible, a representative from the procurement agency (the person responsible for prequalification with knowledge of GMP) should be part of the inspection team.

In exceptional cases, consultants from the private sector may be appointed to perform inspections, provided that there is no conflict of interests and that all confidentiality undertakings are agreed upon and maintained. For these reasons, persons working in a manufacturing company may not be considered suitable. Interested external inspectors should submit their letters of interest and curricula vitae to the procurement agency. The agency should review the documentation before deciding to appoint any inspectors. A formal agreement for the performance of work and terms of reference should be in place before commencement of work by contracted inspectors.

A summary list of names, addresses, dates of appointment, qualifications and experience of inspectors should be maintained.

Planning and preparation of inspections

In preparation for the inspection, the procurement agency should ensure that the manufacturers who have submitted EOIs to supply products are listed in a recording system for inspection planning purposes.

To facilitate planning and to save costs, manufacturers should be grouped together by country. In some countries, one manufacturer may have different manufacturing sites in addition to the submitted address of the headquarters.

Manufacturers should be informed of tentative inspection dates, and should be requested to submit information about each manufacturing site to be inspected.

This information should normally be provided in a site master file (SMF). An example of a technical questionnaire for pharmaceutical manufacturers is attached as Appendix 9.

This information will be used during the preparation for the inspection and during the inspection itself to verify information supplied by the manufacturer to the procurement agency.

An example of an SOP for planning an inspection is shown in Appendix 10.

As the manufacturer will be inspected as part of the process of prequalification for the supply of specific products to the procurement agency, inspectors should prepare for inspections by studying the product information submitted by the manufacturer.

Appendix 11 contains an example of an SOP for preparing for an inspection.

A site visit before deciding whether a GMP inspection should be performed may in some cases be appropriate. This visit is optional and does not lead to the requirement for the performance of the inspection being waived.

Performing inspections

Inspections should be performed in accordance with a written procedure.

The inspection should cover all aspects of WHO GMP. An example of an SOP for performing an inspection is shown in Appendix 12.

Information submitted in relation to the supply of the API, formulation of the product, manufacturing method and stability data should also be verified during the inspection.

The inspection should cover the evaluation and assessment of the documentation, premises, equipment, utilities and materials. It should also cover verification of data and documentation such as results, batch records, compliance with an SOP and information submitted on the manufacturing method, equipment and aspects including (but not limited to) validation of the manufacturing process, validation of utilities and support systems, and validation of equipment.

If checklists are used, these should be drawn up and agreed upon for use by collaborating procurement agencies implementing this MQAS. An example of a GMP checklist is shown in Appendix 13.

Waiving of inspections

The need for an inspection may be waived where there is evidence that the site was inspected and approved by an inspection authority which is a member of PIC/S; an ICH member or its associated country; or from the WHO Prequalification Programme for the manufacturing site under consideration, covering activities for the product(s) being prequalified, provided that:

- all aspects of GMP for the relevant product(s) have been covered;
- the approval was within the last 36 months;
- there is a statement from the manufacturer that no major changes have been made to premises, equipment and key personnel since the inspection by the medicines regulatory authority.

Inspection report

Each inspector or inspection team (where inspection teams are performing inspections) should prepare a formal inspection report for each manufacturing site inspected.

The inspector or inspection team should make a recommendation on the status of the manufacturer in relation to compliance with WHO GMP. According to the findings, the recommendation following the inspection may for example be one of the following.

- The manufacturer is considered not to be operating at an acceptable level of compliance with WHO GMP and a follow-up inspection is recommended to verify implementation and acceptability of corrective actions.
- The manufacturer is considered not to be operating at an acceptable level of compliance with WHO GMP and a compliance report is needed to verify implementation and acceptability of corrective actions.
- The manufacturer is considered to be operating at an acceptable level of compliance with WHO GMP.
- The manufacturer is considered not to be operating at an acceptable level of compliance with WHO GMP.

The inspector or inspection team(s) will finalize a report according to the recommended format published in WHO *Guidance on good manufacturing practices (GMP): inspection report* (8) (see Appendix 14 for a model inspection report).

A copy of the inspection report should be filed in a central manufacturer's file that is unique to that manufacturer.

The inspection report should be communicated to the manufacturer. Where noncompliance was observed, corrective actions and timelines for completing them

should be suggested. A response with supporting documentation should be invited from the manufacturer.

If any additional information is required, or if corrective action has to be taken, a final recommendation as to the acceptability of the product and manufacturer should be made only after such information has been evaluated, or the corrective action has been verified. In the event of any dispute, a standard procedure should be followed for discussing and resolving the issue.

The ownership of the report should be with the procurement agency, as it is responsible for the prequalification.

II.2.4.6 Step 6: Finalize assessment process

Decision-making process for acceptance or rejection of a manufacturer

The procurement agency should follow a written procedure to collate the outcomes of the evaluation of product information, laboratory results for samples analysed and inspection reports.

This SOP should also identify the people responsible for taking the decision to accept or reject a product and/or manufacturer, including the grounds for the decision. It may be helpful to refer to the responsible person by position, rather than by name.

The procurement agency should inform the manufacturer in writing of the outcome of the prequalification of each product manufactured at each specified site.

Recording of outcomes

The person responsible for prequalification should record the outcome of the prequalification process in a list of prequalified products and manufacturers.

The list should include only those products evaluated as indicated by the manufacturer. It should be product- and manufacturing-site-specific.

The list may be published in the public domain.

Information on prequalified sources should be transparent and made available to customers when required.

The procurement agency should have an agreement with the supplier to ensure compliance with the prequalification principles and that the products supplied are the same products as were prequalified (e.g. they are manufactured at the same site and the same processes are adhered to).

The list should be reviewed and updated at regular intervals. Newly prequalified manufacturers should be added to the list as they become qualified, and non-compliant manufacturers should be removed from the list as soon as they are recognized as such.

Where possible, more than one supplier of a product should be included on the list to ensure open and transparent procurement through competitive procurement procedures (see Module III).

II.2.5 Requalification and monitoring

Requalification should occur at regular intervals. Routine re-inspection of manufacturers should take place as required based on risk assessment but at least every five years. Routine reevaluation of product information or questionnaires should be done every five years. Non-routine reevaluation and/or inspection should be done when necessary, e.g. when the manufacturer implements any change to the formula, manufacturing method or manufacturing site; if any product supplied is considered not to be in compliance with the agreed specification of the product; or if a serious complaint has been received. For more details on reassessment see Module VI.

II.2.6 Monitoring of complaints

Complaints should be handled in accordance with a written procedure.

A written report of the complaint, investigation, effective implementation of corrective and preventive action (CAPA) and outcome should be available.

Any complaint concerning a pharmaceutical product or batch of products supplied should be thoroughly investigated and include a root cause analysis, risk assessment and effective CAPA to avoid recurrence. The nature of the complaint should be communicated to the manufacturer.

The outcome of the investigation should be communicated to the complainant.

II.2.7 Cost recovery

It is recommended that the costs of prequalification should be covered by the procurement agency. If costs are to be recovered, defined transparent procedures should be established and manufacturers should be notified of these procedures in advance.

Cost recovery should be based on a fee-for-services structure.

II.3 List of suggested SOPs

- communication between the procurement agency and national medicines regulatory authority
- assessment of product data and information for compliance with norms and standards
- assessment of manufacturing sites for compliance with WHO GMP
- assessment of product data and information submitted by manufacturers
- assessment report writing
- planning of inspection
- inspection report writing
- procedure for prequalification

- delegation of prequalification to another procurement agency
- establishing specifications for products
- publication of invitations for expressions of interest (EOI)
- preparation and maintenance of the guidelines for the compilation of product information
- preparation and maintenance of the list of prequalified products and manufacturers
- receipt of product information
- screening of product information (for completeness on initial receipt)
- informing manufacturers of the outcome of the evaluation of the product information
- communicating with the person responsible for inspections of manufacturing sites
- recruiting or appointing inspectors with appropriate qualifications and experience when necessary
- follow-up of CAPA after inspections
- training of inspectors when necessary
- informing manufacturers of the outcome of the inspection
- preparation of product specifications for prequalification
- publication of product specifications for prequalification
- receipt of information (including late arrivals) and record-keeping
- contracting of a quality control laboratory
- submission of samples to a contract laboratory
- investigating, handling and reporting out-of-specification results
- waiving of inspections
- decision-making process for acceptance or rejection of a manufacturer
- requalification
- handling of complaints
- cost recovery on a fee-for-services basis.

Module III

Purchasing

III.1 Introduction

Procurement should be done with the aim of purchasing effective, quality assured products, and should not be focused on price alone.

Prequalification of products and manufacturers as described in Module II contributes to ensuring in advance that manufacturers and suppliers can deliver quality products on a sustained basis.

This Module gives an overview of the strategies and methods used in pharmaceutical procurement. The term “procurement” in this Module relates specifically to the purchase of health sector goods from manufacturers or suppliers. The Module goes on to describe the key activities in purchasing pharmaceutical products, as well as the recommended organizational structure of the procurement agencies which carry out these key activities.

See also *Operational principles for good pharmaceutical procurement* as recommended by the Interagency Pharmaceutical Coordination Group (IPC) (9).

III.2 Procurement strategies

Strategic objectives for good pharmaceutical procurement include:

- selection of reliable suppliers of quality products;
- procurement of the most cost-effective pharmaceutical products in the right quantities and meeting the quality standards;
- mitigating possible risks;
- timely delivery;
- achievement of the lowest possible total cost (which includes but is not limited to the price, cost of analysis, and transportation).

Where the supplier is an entity other than the manufacturer, such a supplier should meet the standards recommended in this MQAS.

These objectives should be achieved through efficient and transparent management reflected in an appropriate division of the different activities and responsibilities; appropriate standardization, selection, specification and quantification of pharmaceutical products; the use of good financial management procedures and competitive procurement methods; and a quality system that involves the selection and monitoring of qualified suppliers and their products.

It is recommended that a standard procedure be prepared to assist in the calculation of the lowest possible total cost. This approach aims to ensure that costs are

calculated in a consistent manner, with a consistent weight given to each of the factors taken into account.

- To be effective, a procurement agency should ensure that the following principles are applied:
- prequalified products are purchased from approved manufacturers or suppliers;
- procurement and purchasing procedures are transparent;
- activities follow formal written procedures throughout the process, including explicit criteria for awarding contracts;
- independent contract review;
- purchasing is based on the defined procurement policy of the procurement agency;
- purchasing and tender documents list all pharmaceutical products by their INN or national generic names;
- suppliers are selected and monitored through a process that takes into account product quality, service reliability and performance, delivery time, ethics, legal status, financial viability and minimum order quantities;
- intellectual property rights are respected in accordance with best practice and national law.

III.3 Procurement methods

Although there are different methods of procurement, they all involve a number of common activities that must take place beforehand. These activities are the establishment of technical specifications, quantification of requirements, and selection of product(s) and manufacturer(s) preferably based on prequalification.

Whatever the procurement method, responses should be examined to ensure that offers have been received from invited suppliers and that the offers are substantially responsive to the defined terms and conditions. Awards should be made to the maker of the lowest acceptable offer for the prequalified product that meets the terms and conditions. The companies should be informed of the outcome.

A brief description of different procurement methods is given below. (See also *Operational principles for good pharmaceutical procurement* (IPC) (9); and *Managing drug supply* (MSH)) (10).

III.3.1 Restricted tender

In a restricted tender, also called a “closed bid” or “selective tender”, interested suppliers are approved in advance through a prequalification process. This type of procurement is often referred to as “limited international bidding” (LIB) which is an “invitation

to competitive bids” conducted by direct invitation to all prequalified suppliers. Procurement agencies should use restricted tenders to invite bids from prequalified suppliers for all health products and services whenever possible.

III.3.2 Competitive negotiation

This method is also referred to as “international/national shopping”. The basis of this method is the comparison of price quotations obtained from several local or foreign suppliers. Usually, quotations are solicited from a minimum of three suppliers to ensure competitive prices.

This method is appropriate for procuring small amounts of readily available products. However, its use should be explicitly justified, and approval should be obtained from senior management. Only prequalified products and suppliers should be used.

III.3.3 Direct procurement

In direct procurement, products are obtained directly from a single source without applying the requirements of a tender process or comparing price quotations.

Normally direct procurement is not recommended, but it may be used when there is only one prequalified source for the product to be procured. A history of “reasonable” prices for the product in question should be assessed to negotiate the price with the supplier.

III.3.4 Open tender

Open tender is the formal procedure by which all manufacturers, national and international, are invited to bid for the sale of goods. The term “international competitive bidding” (ICB), which is an open tender to all manufacturers, is often used.

Open tendering is not appropriate for health products, because it may be difficult to establish, before a contract is awarded, whether unknown bidders will be able to supply products of the required quality in the required quantities on a sustained basis.

III.4 Quality assurance in purchasing

The procurement agency should have a documented infrastructure for purchase and procurement of health products and services, which should aim to ensure that products are of the quality required for their intended use.

III.5 Key activities in purchasing

III.5.1 Develop a list

The procurement agency should develop a list or catalogue of products, listed by INN, that are identified for purchasing based on need, the national list of essential medicines, and the WHO Model List of essential medicines (2).

The procurement agency should develop specifications for the products in accordance with what has been prequalified and the terms and conditions for procurement. These may include pack size, remaining shelf-life, and lead time, among others.

III.5.2 Quantification

All requests for products should include quantities. Accurate quantification of needs is essential to avoid shortages or excess stocks. Quantities purchased should be based on a reliable estimate of actual need.

The possible methods of product quantification include the consumption method, the morbidity method and the adjusted or extrapolated consumption method.

III.5.3 Procurement method

The procurement agency should apply the procurement method according to their policy and procedures (see also section III.3 above).

III.6 Organization and responsibilities

Purchasing should be done by personnel with appropriate qualifications and training, following established procedures.

Each staff member who undertakes purchasing or provides support to purchasing should have a job description which clearly describes his or her tasks and responsibilities.

The personnel responsible for purchasing should be independent from those responsible for prequalification and quality assurance.

Key responsibilities may include:

- preparing requests for quotations or tender documents
- publishing and handling tenders (when applicable) according to best practices
- handling contracts
- price negotiations
- placing orders
- market research
- monitoring suppliers' performance.

The personnel should follow transparent, written procedures throughout the process of purchasing and should use explicit criteria for deciding to whom to award contracts.

All staff in the purchasing group must sign confidentiality agreements and declarations of conflict of interest.

There should be mechanisms in place to ensure reliable financing for procurement. Good financial management procedures should be followed to ensure that financial resources are used with maximum efficiency. Funds should be allocated before the tender is issued, and should be released in accordance with the purchase contract.

Procurement should be planned properly, and procurement performance should be monitored regularly.

III.7 Monitoring of performance of prequalified manufacturers

There should be a procedure for continuous monitoring of the performance of the manufacturers and suppliers. This may be a joint responsibility of different sections/units and include quality assurance and purchasing, among others. If a decision is taken to remove a product, manufacturer or supplier from the list, the supplier or manufacturer should be notified and a mechanism should be in place to prevent purchasing from this supplier or manufacturer.

Monitoring may include:

- review of quality control results;
- verification that the product batches supplied have been manufactured in compliance with standards and specifications accepted in the product dossier through inspection;
- pharmacovigilance (e.g. management of adverse event reporting);
- monitoring of complaints;
- outcome of inspection of manufacturing sites;
- outcome of reassessment of product information;
- monitoring of direct and indirect product costs;
- monitoring of adherence to delivery schedules.

Random samples of batches of pharmaceutical product(s) supplied by prequalified manufacturers, taken in accordance with a predefined sampling procedure (based on risk assessment), should be sent for independent testing at a reliable quality control laboratory (e.g. a WHO-prequalified laboratory) for compliance with final product specifications as part of the continuous monitoring programme.

The monitoring process should include continuous commercial monitoring that includes tracking of lead-time and monitoring for compliance with all of the contract terms and conditions.

There should be an information system that keeps track of the value of contracts awarded, the value of total purchases from each supplier per year and the performance for each tender (e.g. speed of delivery and compliance with specifications).

III.8 Country legislation

Customers requesting products from procurement agencies should be responsible for ensuring that the products supplied comply with the destination country's legislation on registration and licensing status and intellectual property rights.

III.9 Donations

Any procurement agency receiving donations should handle donated medicines in accordance with a written procedure to ensure that patients receive products of known, appropriate quality. The WHO *Guidelines for drug donations* (11) outline the key issues. The principles established in these guidelines should be followed.

III.10 List of suggested SOPs

- selection of suppliers and products
- quantification of products
- calculation of the lowest possible total cost
- ensuring that prequalified products are purchased from approved manufacturers
- awarding contracts
- independent contract review
- purchasing of products
- considering intellectual property rights
- preparation of requests for quotations or tender documents
- publishing and handling tenders
- handling contracts
- price negotiations
- market research
- monitoring suppliers' performance
- pharmacovigilance
- monitoring of direct and indirect product costs
- monitoring of adherence to delivery schedules
- donations.

Module IV

Receipt and storage of purchased products

IV.1 Introduction

The procurement agency should ensure that the pharmaceutical products purchased are received and stored correctly and in compliance with applicable legislation and regulations. Products should be received and stored in such a way that their quality and integrity is preserved, batch traceability is maintained and stock can be rotated.

It is recommended that premises are designed in such a manner that products will follow a unidirectional flow from receiving to dispatch, to avoid any possible mix ups.

Effective measures should be in place to ensure the security of materials and products.

This Module focuses on quality assurance and quality control during receipt and storage of products.

Quality control is concerned with sampling, specifications and testing as well as with the organization, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials or products are not released for use until their quality has been judged satisfactory for their intended purpose.

Each procurement agency should have access to a quality control laboratory, which should meet the general requirements for facilities, policies and procedures, staff expertise, experience and training as specified in Module I, as well as the requirements outlined in Module II under “Analysis of samples”.

The quality control laboratory must be capable of undertaking the full range of tests required. Any subcontracting of such work to third parties should be managed correctly and the responsibility for the quality of the work done should be clearly defined.

The principles established in the WHO guide to good storage practices for pharmaceuticals (12) (see Appendix 15) should be followed throughout the steps described in this module.

IV.2 Pre-shipment quality control

Note: Pre-shipment is considered at manufacturer level prior to sending the product(s) to the procurement agency or customer.

Each batch of finished product should be tested by the manufacturer to determine that it conforms satisfactorily to its finished product specification, prior to supply.

The procurement agency may decide, using a risk-based approach, to test selected batches.

Products failing to meet the established specifications or any other relevant quality criteria should be rejected.

IV.3 Receipt of stock

Receiving and dispatch bays should protect materials and products from the weather. Receiving areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.

All incoming materials and finished products should be quarantined immediately after receipt until they are released for use or distribution.

Products should be quarantined until test results confirm that the products meet all of the requirements, specifications, terms and conditions of the purchase order. It is strongly recommended that a review of certificates of analysis be made to confirm that what has been delivered is what was ordered and is certified by the manufacturer to meet specifications.

Upon receipt, each incoming delivery should be checked for correspondence between the order, the delivery note, the supplier's labels and transport conditions (e.g. temperature and relative humidity as appropriate). The consignment should be examined for integrity of packages and seals, and for uniformity of the containers. Should the delivery comprise more than one batch, it should be subdivided according to the supplier's batch number.

Containers should be cleaned where necessary and labelled, if required, with the prescribed data, e.g. label description, batch number, type and quantity.

Containers and products should be visually inspected for possible contamination, tampering and damage, expiry date, compliance with labelling and packaging instructions, and any suspect containers, or the entire delivery, should be quarantined. Damage to containers and any other problem that might adversely affect the quality of the material should be recorded and investigated.

The person responsible for receiving the goods should be independent of the person responsible for purchasing the goods.

IV.4 Post-procurement quality control

Note: Post-procurement is considered at procurement agency level or at the level of the customer.

IV.4.1 Sampling

The procedures for receipt of supplies should include random sampling for independent laboratory analysis by the procurement agency to ensure that pharmaceutical products meet the required standards. Sampling should be performed in accordance with a written procedure and with national legislation. Products may also be randomly sampled at the end of the distribution chain and sent for independent analysis. Representative samples

should be taken from containers in the consignment. The samples should be analysed for compliance with the product specification.

Samples should be taken only by appropriately trained and qualified personnel and strictly in accordance with written sampling plans and sampling instructions that are based on risk assessment. (See also WHO guidelines on sampling and International Organization for Standardization (ISO)/American National Standards Institute (ANSI) guidelines on sampling (13–15).) Containers from which samples have been taken should be labelled accordingly.

Following sampling, goods should be quarantined. Batch segregation should be maintained during quarantine and all subsequent storage. Materials and pharmaceutical products should remain in quarantine until an authorized written release or rejection is obtained.

IV.4.2 Rejected materials

Stringent precautions should be taken to ensure that rejected materials and pharmaceutical products cannot be used. This can be achieved through separate storage or by means of a validated computerized system. Rejected materials may await destruction or return to the supplier. Whatever action is taken should be approved by authorized personnel and recorded. Rejected materials should be handled in accordance with a written procedure.

IV.5 Storage of materials and products

IV.5.1 Staff

All members of staff should be trained to observe high levels of personal hygiene and sanitation. The duties and responsibilities of all members of staff should be available in the form of a written job description.

Personnel employed in storage areas should wear protective or working garments appropriate for the activities they perform.

IV.5.2 Storage areas

Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products, including space for segregation of rejected, expired, recalled or returned stock. This includes appropriate measures for narcotics and psychotropic medicines which should be kept locked up and controlled under specific procedures as required by national legislation.

Adequate ventilation should be in place to control temperature and relative humidity. Where special storage conditions are required (e.g. for temperature and humidity) these should be provided, checked, monitored and records maintained.

Precautions should be taken to prevent unauthorized entry into the storage areas. A security system sufficient to safeguard all areas of the warehouse and offices should be in place.

A written procedure for fire control measures should be in place, including prevention of fire, fire detection and fire drills. Fire detection and fire-fighting equipment should be serviced regularly.

Smoking and eating should not be permitted in the storage areas.

Toilet and washing facilities should be sufficiently separated from storage areas.

IV.5.3 Storage conditions

All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation according to the first-expiry, first-out (FEFO) rule.

Stock should be stored off the floor and suitably spaced to permit cleaning and inspection. Pallets should be kept in a good state of cleanliness and repair and contents on pallets should be stacked in a manner that ensures that there is no damage to containers on the lower level.

Storage areas should be kept clean and free of vermin and accumulated waste. A written sanitation programme should be available indicating the cleaning and pest-control methods used, and their frequency of use. Safe pest-control agents should be used which will not contaminate materials and pharmaceutical products. There should be appropriate procedures for the cleaning up of any spillage to eliminate any risk of contamination.

Storage conditions used for pharmaceutical products and materials should comply with the instructions on the label, which are based on the results of stability testing.

In general, the instructions on the label have the meanings given in WHO GSP (<https://iris.who.int/bitstream/handle/10665/331814/9789240001824-eng.pdf?sequence=1>).

Cold rooms should be provided for storage of materials and products requiring storage under specified conditions between 2 and 8 °C. Cold rooms should be qualified, which includes temperature mapping. The temperature should be controlled, monitored and recorded with results reviewed for compliance with the specified limits. Where electronic systems are used for data collection, provision should be made for back-up of data at regular and defined intervals. Cold rooms should be fitted with alarm systems that will alert personnel out of limit conditions.

In certain cases, e.g. with freeze-sensitive vaccines, products that have been stored below the temperature specified on the label should be destroyed.

Freeze-sensitive products should be equipped with an appropriate monitoring device.

IV.5.3.1 Monitoring of storage conditions

Temperature mapping of the facility should be well designed to support assurance of uniformity of the temperature across the storage facility. It is recommended that temperature monitors should be placed in the worst-case areas of the facility. Recorded temperature monitoring data should be available for review.

The equipment used for continuous monitoring should be calibrated at suitable predetermined intervals and the results should be recorded, reviewed and retained. Out of limit and out of trend results should be investigated in accordance with an SOP and appropriate action should be taken. All monitoring records should be kept for at least one year after the end of the shelf-life of the stored material or product, or as long as required by national legislation.

IV.5.4 Repackaging and relabelling

Where repackaging or relabelling is done, compliance with the requirements of national legislation and WHO GMP will be considered mandatory.

IV.5.5 Miscellaneous and hazardous materials

Materials which may affect other materials stored in their vicinity should be handled in accordance with a written procedure. Rodenticides, insecticides, fumigating agents and sanitizing materials should not be permitted to contaminate equipment, materials, or products. Toxic substances and flammable materials should be clearly marked as such and should be stored in suitably designed, separate, enclosed areas as required by national legislation. Flammable substances should be kept away from corrosive or oxidant substances at all times.

IV.5.6 Stock control

Stock rotation and control is best maintained by the use of a validated stock control system. Care must be taken to select a system that can manage the rigid requirements for batch number control and expiry dating, which are essential for handling pharmaceutical products.

Periodic stock reconciliation should be performed comparing actual and recorded stock levels.

All significant stock discrepancies should be subjected to investigation as a check against inadvertent mix ups and/or incorrect issue. Records should be maintained.

Damaged containers should not be issued unless it is certain that the quality of the material inside is unaffected. Any damaged containers should be reported without delay to the person responsible for quality assurance. Any action taken should be in accordance with an SOP and documented.

IV.5.6.1 Control of obsolete and outdated materials and products

All stock should be checked regularly for obsolete and outdated materials and pharmaceutical products. All due precautions should be observed to prevent issue of outdated materials and pharmaceutical products. The handling of such materials should be subject to a written procedure.

IV.5.6.2 Recalled materials and products

Recalled products should be identified, recorded, reconciled, and stored separately in a secure area until a decision has been taken on their fate. The decision should be made as soon as possible in coordination with the manufacturer. An assessment should be made by an appropriately qualified and experienced member of staff.

IV.5.6.3 Returned goods

Returned goods should be handled in accordance with a written procedure.

They should be placed in quarantine until a decision has been taken on their fate. Products returned from the customer should be destroyed in compliance with national requirements unless it is certain that their quality is satisfactory. In that case, they may be considered for resale. The nature of the product, any special storage requirements, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue. Any action taken should be recorded.

IV.5.6.4 Waste materials

Waste materials should be handled in accordance with a written procedure. Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.

Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals in accordance with national regulations.

IV.5.7 Documentation: written instructions and records

Written instructions and records should be kept which describe the storage procedures and define the routes of materials, pharmaceutical products and information through the procurement agency, including handling of expired stock. Batch traceability is essential in the event of a product recall.

Permanent information, written or electronic, should exist for each stored material or product to indicate recommended storage conditions, any precautions to be observed and retest/expiry dates. National regulations concerning labels and containers should be respected at all times.

Records should be retained for each delivery. They should include the description of the goods, quality, quantity, supplier, supplier's batch number, the date of receipt, assigned batch number and the expiry date. National regulations which state a period for retention of records must be observed.

Where no such regulations exist, records should be retained for one year after the end of the shelf-life of incoming products. Comprehensive records should be maintained of all receipts and issues of materials and pharmaceutical products according to a specified system, e.g. by batch number.

IV.6 List of suggested SOPs

- receipt of products
- storage of products
- access control to areas
- handling of damaged containers
- preshipment sampling and testing
- postshipment sampling and testing
- handling of rejected products
- handling of returned products
- procedure for gowning
- fire control
- environmental monitoring
- cleaning of storage areas
- FEFO
- rodent and pest control
- packaging of freeze-sensitive materials
- temperature mapping studies
- handling of toxic and flammable goods
- handling of spillages
- stock reconciliation
- control of obsolete materials and products
- handling of waste materials.

Module V

Distribution

V.1 Introduction

A well-managed distribution system should achieve the following objectives:

- maintain a constant supply of medicines;
- keep medicines in good condition throughout the distribution process;
- ensure controlled transport conditions;
- minimize losses of medicines due to spoilage and expiry;
- maintain accurate inventory records;
- rationalize medicine storage points;
- use available transportation resources as efficiently as possible;
- reduce theft and fraud;
- provide information for forecasting medicine needs.

This Module focuses on measures to be taken to ensure product integrity and quality during distribution, and outlines the main points. The principles established in the WHO *Guidelines for good trade and distribution practices for pharmaceutical starting materials* (16) (see Appendix 16) should be followed.

V.2 Transport conditions

Materials and pharmaceutical products should be transported in such a way that the integrity of the material or pharmaceutical product is not adversely affected and that appropriate storage conditions are maintained.

Where temperature excursions occur during transport, risk assessment should be done to ensure that an informed decision is taken as to the fate of the products.

Every precaution should be taken to minimize the risk of theft and fraud.

V.3 Cold chain

Special care should be exercised when using a cold chain. If goods are distributed under controlled cool or cold conditions, appropriate containers should be used. Containers should be packed following established standard procedures to ensure that products are not negatively affected.

When a cooling agent, such as dry ice, is used in cold chains, it is necessary to ensure that the material or product does not come in contact with the cooling agent as this may adversely affect the quality of the product, e.g. as a result of freezing.

The process should be validated to cover the expected transport time, taking into account expected environmental conditions.

V.4 Temperature monitoring and records

Calibrated devices should be used to monitor conditions such as temperature during transportation. Records should be available for review.

V.5 Delivery order

The dispatch and transport of materials and pharmaceutical products should be carried out only after receipt of a delivery order, which has to be documented. There should be a procedure to ensure that products are supplied to authorized recipients only.

V.6 Dispatch procedures and policies

Rules for dispatch procedures should be established according to the nature of the materials and pharmaceutical products being dispatched and after taking into account any special precautions to be observed. Any special packaging requirements for movement of goods must be met. Some goods may require special protection before they can be shipped by sea or by air.

All legislation that may affect these requirements must be complied with.

V.7 Dispatch containers

The outside container should offer adequate protection from all external influences and should be indelibly and clearly labelled.

Products should be packed in such a way as to minimize the risk of theft, e.g. by using locked containers or by shrink-wrapping entire pallets in plastic.

V.8 Dispatch records

Records for dispatch should be retained, stating at least the following:

- date of dispatch;
- customer's name and address;
- product description, e.g. name, dosage form and strength (if appropriate), batch number and quantity;
- transport and storage conditions.

V.9 Traceability

Records of distribution should contain sufficient information to enable traceability of the product from the point of supply to the point of delivery.

Traceability of goods is crucial in case of the need for product recalls. It will also help to detect theft and fraud. Any discrepancies should be investigated and followed up by appropriate measures to tackle possible security breaches.

V.9.1 Recalled materials and products

When required, materials and products should be recalled following a written procedure. Written records of all major actions signed by the person responsible for carrying out each action should be maintained.

Recalled products should be identified, recorded, and reconciled.

The effectiveness of the arrangements for recalls should be evaluated at regular intervals.

V.10 Port of entry

All conditions required for storage should be achievable at the port of entry of goods. This is particularly important for all temperature-sensitive products shipped to ports where temperatures may be less well controlled. Specific arrangements may need to be made with local handling agents and customs to ensure speedy handling and clearance.

Security measures to prevent theft, fraud and bribery should be in place during storage at the port of entry.

V.11 List of suggested SOPs

- packaging of products in containers
- maintaining appropriate storage conditions during transport
- maintaining the cold chain
- calibration of temperature sensors and devices
- verification of authorized recipients
- labelling of outer containers
- maintaining dispatch records.

Module VI

Reassessment

VI.1 Introduction

The quality of all products and services procured in accordance with this MQAS should be continuously monitored. Reassessment will be required to ensure that the products procured continue to meet the norms and standards defined. This module briefly outlines the principles of routine and non-routine assessment of manufacturers, products and contracted-out services.

II.2.5 Requalification and monitoring

Requalification should occur at regular intervals. Routine reinspection of manufacturers should take place as required based on risk assessment but at least every five years. Routine reevaluation of product information or questionnaires should be done every five years. Non-routine reevaluation and/or inspection should be done when necessary, e.g. when the manufacturer implements any change to the formula, manufacturing method or manufacturing site; if any product supplied is considered not to be in compliance with the agreed specification of the product; or if a serious complaint has been received. For more details on reassessment see Module VI.

Random samples of batches of pharmaceutical product(s) supplied by prequalified manufacturers, taken in accordance with a predefined sampling procedure (based on risk assessment), should be sent for independent testing at a reliable quality control laboratory (e.g. a WHO-prequalified laboratory) for compliance with final product specifications as part of the continuous monitoring programme.

VI.2 Reevaluation of manufacturers

Reinspection of manufacturers should take place at regular intervals based on risk assessment, but no less often than every five years.

Procurement agencies should have a mechanism in place that ensures that manufacturers inform them immediately of any changes to the manufacturing site, manufacturing process or equipment that may have an impact on its prequalification. Non-routine requalification may be required in the following situations:

- in case of any omission of information in the initial assessment;
- if false or misleading information is suspected during the follow-up assessment;
- if changes are implemented that may have an impact on the prequalification of the manufacturing site, such as changes to key personnel or organizational structure, changes to equipment, apparatus or

the manufacturing process, or the renovation or addition of facilities that need validation, commissioning or reinspection; or

- if a complaint considered to be serious in nature has been received.

The procurement agency should suspend or withdraw a prequalified facility from the prequalification list if there is evidence of noncompliance with the requirements for prequalification.

VI.3 Reevaluation of products

Product information should be reviewed every five years or sooner if major changes occur in the meantime.

Procurement agencies should have a mechanism in place that ensures that manufacturers inform them of any contemplated changes to the product that may affect its safety, efficacy or quality. With regard to the product, manufacturers should, for instance, report the following:

- change of manufacturing process, site or equipment relating to the product;
- change of contract manufacturers;
- change of pharmaceutical product release control laboratories;
- change of suppliers of starting materials or container or closure;
- changes to the formulation or composition of the product;
- new analytical method in the testing of starting material, intermediate or final product;
- change of specifications;
- change in shelf-life.

Based on the information submitted, the person responsible for prequalification should decide whether to approve the changes or whether to request additional data.

The section or department responsible for prequalification of products and manufacturers should inform the purchasing office about the changes and the result of the evaluation of such changes.

Non-routine reevaluation of products should be done in the following cases:

- if any omission by the manufacturer in the initial evaluation procedure, or during the follow-up activities, is evident in relation to the requirements, including compliance with quality system standards and failure to notify complaints;
- if any batch or batches of supplied product(s) are documented by the procurement agency as not being in compliance with the agreed specifications of the product or as revealing failure(s) regarding safety, performance or quality of the product;

- if the investigation of a complaint considered leads to the conclusion that the quality and/or safety of the product is in question;
- if any fraud or misconduct by the manufacturer is evident;
- if any batch or batches of product(s) was supplied and is considered not to be in compliance with the agreed specification of the product;
- if a complaint considered to be serious in nature had been received by the organization;
- in cases of changes or variations to products, the WHO publication *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for medicines regulatory authorities* (3) gives guidance on when to proceed with which type of reevaluation;
- if, in the opinion of the organization, changes made in the sourcing of the API, formulation, manufacturing method, facility or other production aspects require that a reassessment be made;
- if supply has been suspended for one year or longer.

VI.4 Monitoring of contracted services

Monitoring of the performance of contractors (e.g. prequalification, quality control, storage, transport and distribution) and follow-up of noncompliance should be carried out according to a written procedure. It should include continuous monitoring, as well as periodic review and renewal of the contract.

The procurement agency should document any reported problems with service and inform the contractor of each problem. Continuous monitoring should also cover compliance of the contract-giver with contract conditions, and correction of any factors that prevent the contract-acceptor from fulfilling the specified duties.

Periodic review of the contract should be based on an assessment of the contractor's overall performance. The criteria outlined for monitoring of prequalified products and manufacturers (see section III.6) also apply to monitoring of contract acceptors who store and distribute pharmaceutical products.

Contracted laboratories should comply with the principles of GLP (17). The accreditation status alone does not guarantee compliance with GLP. The performance of contracted laboratories should be continuously monitored.

VI.5 List of suggested SOPs

- reassessment of product data and information
- reinspection of suppliers and manufacturers
- handling variations
- monitoring of the performance of contractors
- review of agreements.

References

1. *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials*. Updated, comprehensive edition. Geneva, World Health Organization, 2013 (CD-ROM and online).
2. WHO Model Lists of essential medicines (<https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists>).
3. *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for national medicines regulatory authorities (NMRA)s* 2nd ed. Geneva, World Health Organization, 2011 (<https://iris.who.int/rest/bitstreams/53072/retrieve>).
4. World Health Assembly Resolution WHA50.3, 1997. WHO-type certificate of a pharmaceutical product (CPP) issued by one of the regulatory authorities of an International Conference on Harmonisation (ICH) region (European Union, Japan or the USA), together with a summary of product characteristics (SmPC).
5. *WHO guide for a quality systems manual in a control laboratory*. Geneva, World Health Organization, 1988 (WHO/VSQ/98.04).
6. WHO good practices for pharmaceutical control laboratories. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-fourth report*. Geneva, World Health Organization, 2010, Annex 1 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y).
7. WHO Certification scheme on the quality of pharmaceutical products moving in international commerce (<https://iris.who.int/bitstream/handle/10665/340323/9789240020900-eng.pdf?sequence=1>).
8. WHO Guidance on good manufacturing practices: inspection report. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, thirty-seventh report*. Geneva, World Health Organization, 2003, Annex 6 (WHO Technical Report Series, No. 908; https://iris.who.int/bitstream/handle/10665/42613/WHO_TRS_908.pdf?sequence=1&isAllowed=y).
9. *Operational principles for good pharmaceutical procurement*. Geneva, World Health Organization, 1999 (WHO/EDM/PAR/99.5).
10. *Managing drug supply*, 3rd edn. Medford, MA, Management Sciences for Health (MSH), 2012.
11. WHO guidelines for drug donations (https://iris.who.int/bitstream/handle/10665/44647/9789241501989_eng.pdf?sequence=1).
12. WHO guide to good storage practices for pharmaceuticals. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, thirty-seventh report*. Geneva, World Health Organization, 2003, Annex 9 (WHO Technical Report Series, No. 908; https://iris.who.int/bitstream/handle/10665/42613/WHO_TRS_908.pdf?sequence=1&isAllowed=y).
13. Sampling procedures for inspection by attributes. Sampling schemes indexed by acceptance quality limit for lot-by-lot inspection. British Standard BS 6001-1:1999/ International Organization for Standardization, ISO 2859-1:1999.
14. *Sampling procedures and tables for inspection by attributes*. Washington, DC, American National Standards Institute (ANSI) (ANSI/ASQCZ1.4 and ANSI/ASQCZ1.9).
15. WHO guidelines for sampling of pharmaceutical products and related materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report*. Geneva, World Health Organization, 2005, Annex 4 (WHO Technical Report Series, No. 929; https://iris.who.int/bitstream/handle/10665/43157/WHO_TRS_929_eng.pdf?sequence=1&isAllowed=y).

16. Good trade and distribution practices for pharmaceutical starting materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, thirty-eighth report*. Geneva, World Health Organization, 2004, Annex 2 (WHO Technical Report Series, No. 917; https://iris.who.int/bitstream/handle/10665/42851/WHO_TRS_917.pdf?sequence=1&isAllowed=y).
17. *Good laboratory practice: quality practices for regulated non-clinical research and development*, 2nd ed. Geneva, World Health Organization, 2009.

Further reading

- Guidelines for good clinical practice for trials on pharmaceutical products. In: *WHO Expert Committee on the use of Essential Drugs, sixth report*. Geneva, World Health Organization, 2002, Annex 8 (WHO Technical Report Series, No. 902; https://iris.who.int/bitstream/handle/10665/42424/WHO_TRS_902.pdf?sequence=1&isAllowed=y).
- Model application form for new marketing authorizations, periodic reviews and variations, with notes to the applicant.
- WHO guidelines on quality risk management. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-seventh report*. Geneva, World Health Organization, 2013, Annex 2 (WHO Technical Report Series, No. 981; https://iris.who.int/bitstream/handle/10665/81144/WHO_TRS_981_eng.pdf?sequence=1&isAllowed=y).
- WHO Model Formulary (https://iris.who.int/bitstream/handle/10665/44309/9789241599320_eng.pdf?sequence=1).

Appendix 1

Example of a Code of Conduct

1. Introduction

This Code of Conduct must be followed by appointed staff members as well as all other staff involved.

All members of staff including temporary advisers and experts appointed to carry out evaluations and inspection on behalf of WHO should keep in mind at all times the image of WHO.

(In the context of this Code of Conduct, staff and members of staff include contract appointments, short-term staff, advisers and experts appointed for the performance of work.)

2. Key responsibilities

Each member of staff, expert and temporary adviser has key responsibilities to fulfil. The overall objective is to perform these key responsibilities within the framework of this Code of Conduct.

An internal oversight framework has existed within WHO since the early days of the Organization. It is necessary periodically to ensure that all staff understand this function. The WHO summary statement on WHO's Office of Internal Audit and Oversight (IAO) which describes its purpose, authority and scope of work, should be read by each member of staff. This document summarizes the expectations for IAO and it furnishes direction for internal audit at WHO.

By accepting appointment, staff members pledge themselves to discharge their functions and to regulate their conduct to serve the best interests of WHO.

In the performance of their duties staff members shall neither seek nor accept instructions from any government or from any other authority external to the Organization.

No staff member shall accept, hold or engage in any office or occupation, which is incompatible with the proper discharge of his duties with WHO.

Staff members shall conduct themselves at all times in a manner compatible with their status as international civil servants.

Staff shall avoid any action and in particular any kind of public pronouncement which may adversely reflect on their status. While they are not expected to give up their national sentiments or their political and religious convictions, they shall at all times bear in mind the reserve and tact incumbent upon them by reason of their international status.

Staff members shall exercise the utmost discretion in regard to all matters of official business. They shall not communicate to any person any information known

to them by reason of their official position, which has not been made public, except in the course of their duties or by authorization of the Director-General. At no time shall they in any way use to private advantage information known to them by reason of their official position. These obligations do not cease with separation from service.

Any staff member who becomes a candidate for a public office of a political character shall resign from the Secretariat.

The immunities and privileges attaching to WHO by virtue of Article 67 of the Constitution are conferred in the interests of the Organization. These privileges and immunities furnish no excuse to staff members for nonperformance of their private obligations or failure to observe laws and police regulations. The decision whether to waive any privileges or immunities of the staff in any case that arises shall rest with the Director-General.

All staff members shall subscribe to the oath or declaration as set out in WHO Staff Regulations.

A staff member may not act as a delegate or observer for, or adviser to, his or her government.

A staff member may participate in international or national societies when such participation is not in conflict with the standards referred to in WHO Staff Rules and may represent such societies at an international meeting with the Director-General's authorization.

A staff member shall obtain the Director-General's permission before publishing articles whose contents reflect work performed for the Organization or information obtained arising out of such work.

All rights, including title, copyright and patent rights, in any work or invention produced or developed by a staff member as part of his official duties shall be vested in the Organization.

"Misconduct" means:

- any improper action by a staff member in his official capacity;
- any conduct by a staff member, unconnected with his official duties, tending to bring the Organization into public discredit;
- any improper use or attempt to make use of his or her position as an official for his or her personal advantage.

Any conduct contrary to the terms of his oath or declaration.

2.1 Personal responsibilities

Staff members must be committed to a strong oversight environment and must give IAO their full cooperation.

Staff must observe, implement and maintain the responsibilities in relation to the position in which they have been appointed.

Staff must perform the work they have been allocated to the best of their ability and finalize tasks in accordance with the timeframes set by WHO.

2.2 Safety

Safety is the responsibility of WHO staff, supervisors and WHO management. It includes reporting of possible hazards and suspected hazards and taking the necessary precautions and implementing safeguards to minimize safety problems.

Staff involved in activities where safety problems may arise, e.g. the inspection of a manufacturing site, should observe safety rules and regulations as recommended by WHO, the manufacturer and national legislation.

Staff must wear protective devices such as protective clothing, shields, eye covers (glasses), earplugs, where relevant, to protect the body, organs and extremities from possible harm. Staff must use their professional knowledge to ensure that they take appropriate care of their own safety. This means that should a manufacturer not provide what is deemed to be adequate personal protection, then the inspectors should refuse to enter an area on the grounds of lack of safety.

Staff must observe national regulations when driving vehicles.

Staff must be aware of, and take, the necessary precautions when collecting samples.

Special attention to safety requirements is necessary when performing site inspections. These include aspects in relation to the dosage form and activities observed (e.g. radioactive pharmaceuticals, hazardous materials, laboratory reagents, equipment and apparatus, explosions, personnel lifts, ladders, glassware, freezers, steam, radiation, microbiological hazards, viral and biological products and waste, and other relevant possible hazards).

3. Professional competence

3.1 Qualifications and experience

The staff appointed must have the required qualifications and experience to perform the tasks required. Any person appointed to perform work for or on behalf of WHO must indicate if he/she is not suitably qualified to perform the task, or does not have the relevant experience, before taking on the work or being appointed.

When people are approached to perform work on behalf of WHO, they must be truthful in providing evidence of their qualifications and experience.

Staff must not mislead WHO or procurement agencies in relation to their qualifications and/or experience. Any case of misrepresentation of qualifications or experience will be treated as fraud and may eventually lead to prosecution. No future employment in any capacity by any WHO or United Nations organization will be possible at any time.

4. Conduct

During daily activities, staff must maintain high standards of ethical conduct.

Staff must observe the WHO constitution and are responsible for complying with the WHO regulations and guidelines.

4.1 Integrity and attitude

To ensure that the business of WHO is conducted effectively, and without improper influence, all staff members must be persons of integrity and observe the highest standards of conduct.

- WHO must be able to rely upon staff to do the right things.
- Staff must be honest and dependable.
- Staff must be devoted to accuracy, truthfulness, objectiveness and fairness.
- Staff must not use restricted information not available to the general public for gain or to advance private interests.
- Staff must report findings such as presentation of false, misleading and fraudulent information provided to WHO.
- Staff should maintain a positive attitude towards WHO and its policies and projects.
- Staff must be dignified, diplomatic, tactful and courteous. Strong-arm tactics must be avoided.
- Staff must not act with an air of superiority or special authority.
- Staff must use a firm approach when requesting necessary and authorized information.
- Staff members are the contact persons of WHO and their action will be the basis upon which the public will judge the organization. Staff must exhibit exemplary behaviour at all times.

A staff member who has any financial interest in any business concern with which he may be required, directly or indirectly, to have official dealings on behalf of the procurement agency shall report such interests to the Director-General, who shall decide on the applicability of Staff Regulations. Staff may not have financial interests in companies to be evaluated or inspected. Shareholdings through pension schemes and other such “arm’s length” arrangements will not normally be taken as a financial interest in this context. Any doubts on this matter should be referred to the WHO Internal Audit Office for clarification.

4.2 Attire, health and hygiene

Good public relations require that all members of staff dress appropriately for the activities to be performed. Staff should observe WHO guidelines regarding appropriate dress code.

Staff should normally wear protective clothing for inspections. Inspectors must wear protective clothing at least equivalent to that worn by employees of manufacturing sites (e.g. head covering or masks, when appropriate). Staff should conform to company procedures at all times. However, if company procedures are considered inappropriate then this fact should be recorded.

Staff involved in inspections must inform supervisors or managers of their health status when this could have impact on inspections, as persons with communicable diseases, wounds and open lesions may not be allowed in areas where products and material are exposed.

Staffs are responsible for taking the necessary precautions when travelling (e.g. having the appropriate inoculations).

Staff must practice good hygiene at all times.

4.3 Gifts, meals and favours

No staff member shall accept any honour, decoration, favour, gift or remuneration from any government, or from any other source external to the Organization, if such acceptance is incompatible with his status as an international civil servant.

A staff member who is offered any honour, decoration or gift from sources external to the Organization shall report this offer to the Director-General who shall decide on the applicability of Staff Regulations.

No member of staff shall receive or accept anything of value from any manufacturer for or because of any official act that has been performed or is to be performed.

Staff will not solicit or accept directly or indirectly any gift, gratuity, favour, entertainment loan or any other item of monetary value from members of the public with whom staff members have official relationships.

When performing inspections, staff must pay for their own meals whenever possible and must make an effort to pay for their own meals even when invited by the manufacturer, unless the situation is such that it will provoke a scene or create an embarrassment to WHO.

4.4 Management relationship

Staff must promote a positive relationship with supervisors and managers.

4.5 Standard operating procedures

Staff must follow authorized standard operating procedures (SOPs) for the performance of tasks.

4.6 Travel and accommodation

Staff must observe WHO regulations, guidelines and SOPs when travelling. The relevant procedures shall be followed for planning of visits, meetings, inspections and other activities such as making reservations and paying for accommodation.

4.7 Confidentiality and conflict of interest

Staff must observe the WHO policy, country rules and regulations, and company policy with respect to confidentiality.

Staff must sign and abide by the conflict of interest and confidentiality undertaking.

4.8 Documentation and records

Staff shall follow SOPs and maintain appropriate records as required in the procedures.

All information provided by staff members must be truthful and correct, including reports and related documentation.

4.9 Contracts and terms of reference

Staff shall perform activities as stipulated in the contract or agreement for performance of work (APW) and terms of reference (TOR).

4.10 Product files, evaluation and inspection

Staff shall handle product files with care and treat all information as confidential relating to the task to be performed.

All data submitted initially and as a result of the evaluation, shall be dealt with in accordance with SOPs and be considered as confidential information between WHO and the manufacturer.

All aspects relating to the inspection performed shall be considered as confidential between WHO and the manufacturer.

Staff members shall observe the requirements and undertaking with regard to confidentiality and conflict of interest.

4.11 Samples

Samples taken during inspections shall be in accordance with a WHO SOP, with the approval of the manufacturer.

4.12 Evaluation and inspection reports

There shall be written evaluation and inspection reports for every product evaluated, and every manufacturing site inspected.

The reports shall be a true reflection of the findings of the evaluation and inspection.

4.13 Provision of information and advice

Staff shall not act as consultants to individual companies or manufacturers when appointed for the purposes of evaluation or inspection for a particular project, where the company can in particular benefit from such advice, unless the information is in the public domain or given to all manufacturers.

Appendix 2

Example of a guideline on confidentiality

The evaluators and inspectors will treat all information submitted and observed during the inspections and otherwise in connection with the discharge of their responsibilities with regard to the above-mentioned project, as strictly confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set forth below and those contained in the attached provisions for team members participating in site visits within the scope of the prequalification procedure of pharmaceutical products. An example of a confidentiality undertaking is shown at the end of Appendix 3.

Evaluators and inspectors will take all reasonable measures to ensure:

- that the confidential information is not used for any purpose other than the evaluation activities described in this document;
- that confidential information is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

Evaluators and inspectors will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

- was known to them prior to any disclosure by or on behalf of WHO (including by manufacturers); or
- was in the public domain at the time of disclosure by or on behalf of WHO (including by manufacturers); or
- has become part of the public domain through no fault of theirs; or
- has become available to them from a third party not in breach of any legal obligations of confidentiality.

All personnel involved in prequalification and related matters, having access to confidential information regarding products and manufacturers, should treat all information submitted and observed during the inspections and otherwise in connection with the discharge of their responsibilities with regard to these activities, as strictly confidential and proprietary to the procurement agency or the parties collaborating with the procurement agency.

Appendix 3

Example of a guideline on conflict of interest

Introduction

This document presents policy on “conflict of interest” as it applies to external evaluators and members of advisory committees. These two categories are together referred to as “consultants” for the purposes of these guidelines. An example of a signed statement on conflict of interest is shown at the end of this Appendix.

Definitions and principles

The common meaning of “conflict of interest” is a conflict between an individual’s private or personal interest and his or her duty. However, it may also refer to a situation where an individual has several duties which conflict without involvement of any private or personal interests.

A conflicting private or personal interest may be financial or non-financial as explained below.

When a decision-maker or consultant has a direct financial interest, however slight, in the matter to be decided, there is a conclusive presumption of bias and the decision-maker or consultant will thus be disqualified from acting.

Where a decision-maker or consultant has a *non-financial* interest, which gives rise to a reasonable presumption of bias, the decision-maker or consultant will be disqualified from acting. The test here is whether a reasonable observer would suspect that there is a possibility of bias, not whether that bias actually exists. A relevant non-financial interest may arise, for example, out of personal or family involvement between a decision-maker or consultant and a party whose interests are affected by the decision or recommendations. Such an interest may also arise where a decision-maker or consultant is seen to have prejudged the issues, either through preconceived opinions or prior involvement with the facts of a case on which he or she is required to make a decision on recommendations.

Conflict of interest in relation to consultants

There are a variety of situations in which consultants may find themselves in a situation of conflict of interest between their professional activities (e.g. preparation of objective and independent evaluations or membership of independent committees) and personal and private interest (e.g. private consultancies, grants to cover travel and accommodation at company-sponsored conferences, share holdings, research grants or honoraria). It is recognized that almost all consultants have some *potential* conflict of interest because of their present or past association with the pharmaceutical industry.

Some situations of conflict of interest are clear-cut and some are more difficult to determine. If an individual is an employee of, or a retained consultant to, a pharmaceutical company, there is a clear possibility of conflict of interest. If an individual is an employee of a government organization, does no work on behalf of pharmaceutical companies, and is not in receipt of gratuities or funding, there is a minimal risk. Between these two situations is a spectrum of possibilities where the decision as to whether there is a conflict of interest may be less obvious.

Contracts are unlikely to be offered to consultants in any one of categories 1 to 6 listed below.

1. The consultant works in the pharmaceutical industry, either as an employee or as an owner or part owner (e.g. shareholder in the pharmaceutical company to be assessed).
2. The consultant receives a retainer (fee) from one or more of the pharmaceutical companies whose products she or he has to assess or which the new product is likely to replace.
3. The consultants have a *significant* direct current relationship with one or more companies. This may take the form of (a) financial support for a current research project or projects; (b) sponsorship of graduate or postgraduate students; or (c) company employees who are under the direct responsibility of the consultant.
4. He or she receives *substantial* financial assistance or expensive equipment to conduct research on behalf of the pharmaceutical company.
5. The consultant acts or has acted as a consultant for a pharmaceutical company *on the product she or he has agreed to assess*. Such a consultancy may include sponsorship as a speaker, or appointment as chairperson at professional meetings concerning the product, or attendance on behalf of the sponsoring company at national or international professional meetings concerning the product.
6. The consultant has provided significant input to the planning or conduct of a clinical trial of the product to be assessed, for example as a principal investigator, signatory to the study report, or author of any published or unpublished paper or other report of the study. Participation limited to the inclusion of patients in a large-scale multicentre study is *not* considered a significant conflict of interest.

A conflict of interest is less likely to be seen in situations 7 to 10 (see below).

7. The consultant has occasional contracts with one or more companies for particular projects, but does not have a significant relationship with any one company. She or he has not been directly involved with the product in question.

8. The consultant owns or works for a consultancy, which does not provide advice to the pharmaceutical industry but may provide advice to other industries, such as the devices, food or paint industries. However it is unlikely that such consultants will have the technical knowledge or experience to qualify as a consultant in the pharmaceuticals field.
9. The consultant occasionally provides advice to one or more companies on the design of clinical trials to be conducted prior to submission of an application for marketing authorization, but does not have a significant current relationship with any one company (e.g. points 1 to 6 above).
10. The consultant has been invited to attend and contribute to national or international meetings organized by professional or academic associations.

The responsibility of consultants

A drug regulatory authority cannot be aware of all of the consultant's involvements and their ramifications when a contract is offered. The onus is therefore on the consultant to declare in writing any potential conflict or what may be seen as a potential conflict to the staff member of the drug regulatory authority who negotiated the contract or committee membership. If there is any doubt, the potential conflict must be declared. The consultant may only proceed with the evaluation of the data or take up committee membership after any potential conflict has been discussed with the drug regulatory authority and found not to be significant.

For this reason, each evaluation contract requires the evaluator to sign a statement to the effect that she or he has no current conflict of interest and that, if the risk of such a conflict arises during the evaluation, the drug regulatory authority will be notified immediately in writing.

The evaluator is expected to cease reading the application *immediately she or he becomes aware of a conflict of interest*, and return it promptly to the drug regulatory authority. This clause applies also to those involved in the inspection of facilities.

Confidentiality

Any data concerning a company's product which are supplied by the drug regulatory authority to a consultant for review are strictly confidential. As stated in the contract, all materials related to or referred to in the contract must be accepted in strict confidence and held in safe and secure custody at all times. An application may be discussed only with the staff members of the drug regulatory authority.

Consultants must be aware of and avoid the possibility of indirect breaches of confidence. There is clearly a potential, consciously or subconsciously, to misuse information gained from a consultancy in other papers or scientific presentations on the

product in question. Such a case would also constitute a conflict of interest. The consultant must not use information gained in this way in future scientific papers or presentations without the agreement of the company or individual that submitted the data.

Impartiality

To protect impartiality, the company concerned is not informed by the drug regulatory authority of the identity of the consultant to whom applications, data or committee papers are forwarded. For this reason, the consultant should have no direct communication with the company concerning the product. The consultant may not disclose his or her role to the company, even after a decision on the application has been completed. This is clearly not possible in the case of an inspector of the manufacturing facility.

Subcontracting the evaluation

A consultant is not allowed to subcontract part or all of an evaluation to any second person without written permission from the drug regulatory authority. If the drug regulatory authority agrees to such an arrangement, the consultant must ensure that the subcontractor is fully aware of the provisions on conflict of interest, confidentiality and impartiality set out in these notes.

If any part of an evaluation is subcontracted, the person who actually undertakes the work must also sign all the reports to which she or he has contributed.

Example of a confidentiality undertaking and declaration of Conflict of Interest



PROVISIONS FOR EVALUATORS OF PRODUCT INFORMATION AND FOR INSPECTORS (TEAM MEMBER PARTICIPATING IN SITE VISITS) WITHIN THE SCOPE OF THE QUALITY ASSESSMENT PROCEDURE OF PHARMACEUTICAL PRODUCTS

In the course of discharging your functions as an expert adviser to WHO under the attached agreement for performance of work (APW), you will gain access to certain information, which is proprietary to WHO or entities collaborating with WHO, including the manufacturers of the product(s) which need to be assessed as part of the quality assessment procedure by WHO. You undertake to treat such information (hereinafter referred to as “the Information”) as confidential and proprietary to WHO or the aforesaid parties collaborating with WHO. In this connection, you agree:

- (a) not to use the Information for any other purpose than discharging your obligations under the above-mentioned APW; and*
- (b) not to disclose or provide the Information to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.*

However, you will not be bound by any obligations of confidentiality and non-use to the extent that you are clearly able to demonstrate that any part of the Information:

- (i) was known to you prior to any disclosure by or on behalf of WHO (including by the manufacturer(s)); or*
- (ii) was in the public domain at the time of disclosure by or on behalf of WHO (including the manufacturer(s)); or*
- (iii) becomes part of the public domain through no fault of your own; or*
- (iv) becomes available to you from a third party not in breach of any legal obligations of confidentiality.*

You also undertake not to communicate your deliberations and findings and/or those of the team(s) of experts in which you will participate, as well as any resulting recommendations to, and/or decisions of, WHO to any third party, except as explicitly agreed by WHO.

You will discharge your responsibilities under the above-mentioned APW exclusively in your capacity as an expert adviser to WHO. In this connection, you confirm that the information disclosed by you in the declaration of interest is correct and that no situation of real, potential or apparent conflict of interest is known to you, including that you have no financial or other interest in, and/or other relationship with, a party, which:

- (i) may have a vested commercial interest in obtaining access to any part of the Information referred to above; and/or*
- (ii) may have a vested interest in the outcome of the evaluation of the product(s), in which you will participate (such as the manufacturers of those products or of competing products).*

You undertake to promptly advise WHO of any change in the above circumstances, including if an issue arises during the course of your work for WHO.

I hereby accept and agree with the conditions and provisions contained in this document.

Signed _____

Name (typewritten) _____

Organization _____

Place _____ Date _____

Appendix 4

Example of a standard operating procedure (SOP) for writing an SOP

1. Title

Standard procedure for writing a standard operating procedure (SOP)

	Signature	Date
Prepared by		9 May 2005
Authorized by		

2. Policy and objective

- 2.1 The procurement agency should have an SOP for each activity performed by the procurement agency. All SOPs should be in the required format and distributed with care to a predetermined list of personnel. SOPs should be authorized, implemented and kept up to date.
- 2.2 All SOPs should be written in English if any international use is expected, or in the local language if required only by local staff,
- 2.3 Documentation is a prime necessity in quality assurance. Its purpose is to define the system of control, to reduce the risk of error inherent in oral communication, to ensure that personnel are instructed in the details of, and follow the procedures concerned in a logical, reproducible manner.
- 2.4 There should be a written SOP for every critical or important activity in the procurement agency. SOPs should be written in the standardized format as attached.
- 2.5 A list should be kept of all SOPs required by the procurement agency.
- 2.6 Management should authorize SOPs prior to their distribution and implementation.

3. Responsibility

All members of staff should adhere to the SOP when drawing up the SOP. The project manager should supervise its implementation.

4. Action

4.1 Any person may initiate the first draft of an SOP. The headings (listed below) should conform to the attached format and should be used when writing the relevant sections of the SOP.

4.2 The SOP should include at least the following headings:

- A. Title
- B. Policy and objective
- C. Responsibility
- D. Action
- E. Addenda
- F. Distribution
- G. Review date
- H. Revision history

The following information should appear under each heading.

A. Title

Write in clear language the title of the procedure to ensure understanding of the process that the SOP will be describing. The procedure should also contain a clear indication of who was responsible for the preparation, review and approval of the procedure.

B. Policy and objective

Describe the WHO or procurement agency policy regarding the matter to be dealt with under the SOP. Describe the objective to be reached in following the SOP.

C. Responsibility

Describe and list the people responsible for performing the activities listed in the SOP. Wherever possible, it is preferable to use job descriptions or position names for these people rather than names of individuals. Use of the personal names of staff members means the SOP has to be changed every time personnel changes occur.

D. Action

4.1 Describe the sequence of actions needed to perform the task.

4.2 List the actions in the order in which they need to be performed and number them from 1 to the end.

- 4.3 Explain all the steps in detail in clear, unambiguous, language.
- 4.4 Put the initials of the responsible person in brackets next to the action step if a specific person is responsible for the action step.
- 4.5 Read the completed SOP to determine whether it describes all the action steps to be followed from the start of the process to the end.
- 4.6 If a step leads to another SOP, then refer to the relevant SOP in that step.
- 4.7 If the SOP requires any records to be kept, draft the required format of the document to be completed and attach it to the SOP as an addendum.
- 4.8 Forward the SOP to the supervisor or person responsible for documentation and quality assurance.
- 4.9 Read the SOP and assess its suitability and applicability.
- 4.10 If any changes are to be made, make amendments to the SOP in ink and return it to the person who wrote the SOP for their comments.
- 4.11 Return the SOP to the supervisor.
- 4.12 Sign and date the SOP if satisfied with its contents.
- 4.13 Forward the SOP to the second person who is responsible for approving documentation.
- 4.14 The SOP should be signed and dated by the second person who is responsible for approving the documentation if he or she is in agreement with the contents.
- 4.15 Return the SOP to the person responsible for maintaining the documentation infrastructure.
- 4.16 If applicable, proceed with the steps for distribution and retrieval of the previous version of the SOP.
- 4.17 File the original SOP in the SOP file.

E. Addenda

- 4.18 Draft each addendum in such a manner that it leads the person responsible for completing the addendum to document all the required information.
- 4.19 Each addendum shall form part of the authorized SOP and shall be reviewed when the SOP is reviewed, or when necessary.

F. Distribution

- 4.20 Records shall be maintained of the distribution and retrieval of SOPs to ensure that superseded SOPs are not still in use anywhere.
- 4.21 Complete the table (see Addendum A, point 6) to indicate the name of the person to whom the SOP will be sent.
- 4.22 Make a copy of the original SOP and stamp it in red ink as “official copy”.
- 4.23 Only official copies of SOPs shall be controlled. SOPs not having a red stamp will be considered non-official and uncontrolled SOPs.
- 4.24 The person shall sign and date (in the appropriate space in the table (see Addendum A, point 6) on the original SOP), as proof of receipt of the SOP.
- 4.25 When the SOP is reviewed and amended, copies of the superseded SOP should be retrieved from all those who hold a copy when the new version is distributed.
- 4.26 When replacing the superseded SOP, the persons from whom it has been retrieved should sign (and date) the appropriate space on the distribution table in the original SOP.
- 4.27 Mark the original SOP as “superseded” on each page and file in the “superseded SOP” file.
- 4.28 Destroy all retrieved copies of superseded SOPs.

G. Review date

A date should be assigned on which the SOP will be reviewed to determine whether any changes are required to keep it up to date.

H. Revision history

- 4.29 To maintain a record of the history of the information on the SOP, complete the table regarding the history of the changes to the SOP (see Addendum A, point 7).
- 4.30 Each SOP should have a time limit for validity and should be reviewed before the end of the period of validity. This is an opportunity to consider whether the SOP still meets all its objectives and is appropriate for the work to be done and the methods of working. The updated SOP should go through the same writing and revision process.

5. Addenda

Addendum A contains an outline of the format of an SOP.

6. Distribution and retrieval

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

Date	Reason for change
	New SOP

Addendum A: Format of a standard operating procedure

WHO Logo	Document no.
Review date: 2006	
Standard operating procedure	

1. Title

(indicate title)

	Signature	Date
Prepared by		9 May 2006
Authorized by		

2. Policy and objective

3. Responsibility

4. Action

4.1

4.2

4.3

5. Addenda

6. Distribution and retrieval

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

Date	Reason for change

Appendix 5

Example of an invitation for expression of interest

SIXTH INVITATION FOR EXPRESSION OF INTEREST (EOI)

In the context of dramatically increasing the access to, and affordability of, HIV/AIDS-related care and treatment, WHO, together with UNICEF, UNAIDS and UNFPA are inviting expressions of interest from manufacturers of pharmaceutical products in respect to the provision of drugs for the management of HIV-related diseases. The World Bank is in support of this effort.

This sixth invitation is published in order to increase the range of possible products and sources as a follow up to the interest that was expressed as a result of the first, second, third, fourth and fifth invitations published in 2000, 2001, 2002, 2003 and 2004.

Manufacturers should be committed to providing the above-mentioned products at preferential prices to developing countries. Interested manufacturers are encouraged to submit documentation and samples as specified below for various dosage forms and strengths of the products in the following categories:

I) Antiretrovirals as single-ingredient formulations for use in adults and adolescents:

- **Nucleoside/Nucleotide Reverse Transcriptase Inhibitors, including**
Abacavir
Didanosine
Lamivudine
Stavudine
Tenofovir
Zidovudine
- **Non-Nucleoside Reverse Transcriptase Inhibitors, including**
Efavirenz
Nevirapine
- **Protease Inhibitors, including**
Indinavir
Nelfinavir
Ritonavir
Saquinavir

Applications are also encouraged for single-ingredient formulations suitable **for use in paediatric populations**, that support existing international and or national treatment guidelines for paediatric antiretroviral therapy (ART).

As solid dosage formulations are the preferred formulations for treating children except for in the very young infant, manufacturers should also apply for reduced and/or scored solid dosage formulations of:

Zidovudine
Abacavir
Lamivudine
Nevirapine
Efavirenz

Also sought are syrups, solutions or dissolvable nucleoside/nucleotide and non-nucleoside formulations of the following products:

Zidovudine
Abacavir
Lamivudine
Nevirapine

II) Antiretrovirals as fixed-dose combinations (FDC):

Applications are also encouraged for fixed-dose combinations of any first-line ARV regimens as described in the *WHO Guidelines for Scaling Up Antiretroviral Therapy in Resource Limited Settings – 2003 Revision*.

Fixed-dose combinations listed below:

For use in adults and adolescents:

- **Reverse Transcriptase Inhibitors**
 - Lamivudine + Stavudine
 - Lamivudine + Zidovudine
 - Lamivudine + Stavudine + Efavirenz
 - Lamivudine + Stavudine + Nevirapine
 - Lamivudine + Zidovudine + Efavirenz
 - Lamivudine + Zidovudine + Nevirapine
 - Lamivudine + Zidovudine + Abacavir
 - Tenofovir + Emtricitabine
- **Protease Inhibitors**
 - Lopinavir + Ritonavir

For paediatric use, reduced and/or scored solid dosage formulations of:

- **Reverse Transcriptase Inhibitors**
 - Lamivudine + Stavudine
 - Lamivudine + Zidovudine
 - Lamivudine + Stavudine + Nevirapine
 - Lamivudine + Zidovudine + Nevirapine
 - Lamivudine + Zidovudine + Abacavir
- **Protease Inhibitors**
 - Lopinavir + Ritonavir

Co-packaged preparations of the standard ARV combinations, for adult, adolescent and paediatric use are also sought.

- **Anti-infective drugs listed below:**

Antibacterial and antimycobacterial agents (other than MTB)

Azithromycin
 Ceftriaxone
 Cefixime
 Ciprofloxacin
 Clarithromycin
 Clindamycin
 Rifabutin
 Spectinomycin

Antiprotozoal and Antifungal agents

Amphotericin B
 Dapsone
 Folinic acid
 Fluconazole
 Itraconazole
 Pentamidine
 Pyrimethamine
 Sulfadiazine
 Trimethoprim/Sulphamethoxazole

Antiviral agents

Acyclovir
 Ganciclovir

- **Anti-cancer drugs**
Bleomycin
Etoposide
Vinblastine
Vincristine
- **Palliative care drugs**
Amitriptyline
Codeine
Chlorpheniramine
Ibuprofen
Loperamide
Morphine (oral formulation)

The medicines listed in this Invitation for Expression of Interest are those for which a need has been identified by the HIV/AIDS department, WHO. The submitted products should be of assured pharmaceutical quality and relevant data to support efficacy should be provided.

Procedure for submission of EOI

1. Submit a covering letter expressing the interest in participating in the project, confirming that the information submitted in the product dossiers is correct.
2. Submit a product dossier in the recommended format* as specified in the Guideline for submission of a product file which can be obtained by electronic mail from oakesl@who.int, also available on the the web page <https://extranet.who.int/prequal/>. The dossier should be accompanied by a sample of the product to enable analyses (e.g. 1 × 100 tablets).

Submitted documentation reaching UNICEF Supply Division will be evaluated during March, May, July, September and November 2005. Documentation should be provided in English.

Interested manufacturers should submit the above-mentioned information to:

UNICEF Supply Division

Reference: Accelerated Access to HIV/AIDS Care

SIXTH EOI

UNICEF Plads - Freeport DK-2100 Copenhagen, Denmark

Email: supply@unicef.org

Tel: (45) 35 27 35 27 Fax: (45) 35 26 50 48

* If the dossier is compiled in a different format (e.g. EU), then such a dossier can be submitted with a covering letter cross-referencing the pages where the relevant data can be found in accordance with the above-mentioned Guideline

3. Submit a site master file for each manufacturing site as listed in the product dossier, in the recommended format, also available by electronic mail and on the web page <https://extranet.who.int/prequal/> to:

**The Secretary
WHO/HTP/PSM/QSM
20 Ave Appia
1211 Geneva 27
Switzerland**

Products and manufacturing sites assessed for acceptability and meeting the specified standards will be added to the list published on the project web page (<https://extranet.who.int/prequal/>). Products and manufacturers included in this list may be invited to bid for the supply of products, individually or collectively, directly by member governments, by the aforesaid United Nations agencies and/or by associated NGOs.

The following criteria will be taken into account in the quality assessment process.

- Valid manufacturer's licence for production.
- Product registered or licensed in accordance with national requirements.
- Products manufactured in compliance with GMP as certified by the national regulatory authority and/or certified GMP inspectors.
- Product certificates exist in accordance with the WHO Certification scheme on the quality of pharmaceutical products moving in international commerce.
- Product dossiers of acceptable quality submitted and outcome of the assessment in respect of the prequalification procedure.
- Outcome of the inspection performed by or on behalf of the above-mentioned agencies.
- Manufacturer demonstrates sound financial standing.

Only manufacturers THAT CAN SUPPLY APPROPRIATE PRODUCTS OF ACCEPTABLE QUALITY COMPLIANT WITH APPLICABLE REGULATORY REQUIREMENTS, WHO GUIDELINES AND LEGISLATION will be considered.

The United Nations procurement agencies reserve the right to determine specific conditions, as for example the exclusion of companies using child labour, or engaged in the manufacture of land mines or parts thereof.

Appendix 6

Interagency finished pharmaceutical product questionnaire based on the model quality assurance system for procurement agencies

Please fill out one separate form for each pharmaceutical product

Section 1: Administrative section

1.1 Product identification

1.1.1 Active pharmaceutical ingredient(s) (use INN if any):

1.1.2 Generic name of the product:

1.1.3 Trade (proprietary) name (if any):

1.1.4 Dosage form:

- ☐ Tablets ☐ Capsules ☐ Injectable ☐ Syrups/oral liquids
☐ Other: (Please specify)

1.1.5 Strength per dosage unit: _____

1.1.6 Route of administration: _____

- ☐ Oral ☐ I.M. ☐ I.V. ☐ S.C.
☐ Other (Please specify)

1.1.7 Please provide the formulation of the product (complete qualitative and quantitative composition including active ingredient(s), overages if any and excipients). Please also indicate the standard for each ingredient (e.g. BP, USP, in-house). Mention specifically if the product is a fixed-dose combination (FDC) or co-packaged: Annex A

- 1.1.8 Please state inactive ingredients (excipients) of medical/pharmaceutical relevance, amount in dosage form or per dosage unit (e.g. contains alcohol 10%, paraben.....)

1.2 Packaging

- 1.2.1 Description and materials used for primary packaging¹ and pack size (quantity of dosage-form units per pack): Annex B
- 1.2.2 Description, pack size and material used for secondary packaging materials: Annex C

Contact details

1.3 Manufacturer identification

Name, address and activities of the manufacturer and manufacturing site(s) (or contract manufacturer(s):

Name of manufacturer, contract manufacturer if any	Reference of manufacturing licence, date and expiry date, if any	Physical address. Please specify units, and block if existing	Telephone number, facsimile number and email contact details	Activity (e.g. packaging)

1.4 Supplier identification

(to be filled in if not identical to that indicated in 1.3)

Name of company: _____

Physical address (complete details required): _____

Telephone number: _____

Fax: _____

Website: _____

Email: _____

¹ For example, HDPE bottle, Alu-Alu strip, neutral glass vial.

Link with the product

- ☐ Marketing licence holder ☐ Manufacturer
☐ Distributor/wholesaler ☐ Other

1.5 Note for the applicant

Please note that the information in this questionnaire can be shared confidentially among ICRC, MSF, WHO procurement centre, UNFPA and UNICEF for procurement purposes. If you have any objection, please indicate this to the relevant agency that you are dealing with.

Has the dossier been submitted to any of the following agencies: ERP, ICRC, MSF, WHO procurement centre, UNFPA, UNICEF?

Please provide the date of the submission: _____

1.6 Regulatory (licencing) status

1.6.1 In the country of manufacture

- ☐ Product registered and currently marketed

Licence no.: _____

Provide a copy in Annex D

- ☐ Product registered for marketing in the country of manufacturing but not currently marketed

Licence no.: _____

- ☐ Product registered for export only

Licence no.: _____

- ☐ Product not registered (*please clarify*):

- Please attach a certificate of pharmaceutical product (CPP) according to the WHO Certification Scheme (WHO Technical Report Series, No. 863) in Annex E. An earlier version is not acceptable).
- If a CPP cannot be obtained from the national medicines regulatory authority (NMRA), please state the reason and send an equivalent document if any.
- Submit recent as well as historical deficiency letters issued by the WHO Prequalification Programme (PQP)/SRA in relation to the specific product dossier in Annex F.

1.6.2 In other countries

List other countries where the product is registered and is currently marketed (*please provide registration number*)

1.6.3 WHO prequalification status, if applicable

This product is prequalified by WHO/PQP.²

☐ Yes ☐ No

If yes, please attach a copy of the relevant WHO/PQP acceptance letter signed by your company (Annex G).

1.6.4 Submitted for prequalification: indicate date of submission, WHO acceptance letter for product dossier review mentioning the WHO reference number assigned by WHO for this specific product (Annex H)

1.7 Samples for technical evaluation**1.7.1 Samples of finished product and insert information**

You are required to please provide a sample of the finished product(s) offered, and relevant inserts/leaflets. (If you cannot submit any of the above with the questionnaire, please state why not and when you will do so.) (Annex I)

1.7.2 Label language (attach a copy): primary packaging

☐ Bilingual English/French ☐ English ☐ French

☐ Other (specify) _____

1.7.3 Label language (attach a copy): secondary packaging

☐ Bilingual English/French ☐ English ☐ French

☐ Other (specify) _____

For oral powder for suspension and powder for injection, in-use periods and storage conditions after reconstitution should be stated on the product label.

1.7.4 Patient information leaflet (Annex J)

☐ Yes (attach a copy) ☐ No

² WHO Prequalification website: <https://extranet.who.int/prequal/>.

Section 2: Active pharmaceutical ingredients

(If there is more than one active ingredient or more than one manufacturer is used, please replicate this section.)

2.1 Details of API used (INN if any):

2.1.1 Manufacturer

Manufacturer (name, physical address and country)/manufacturing site (please list all alternative sources):

GMP certificate from the country of origin: attach a copy of the GMP certificate, if available, in Annex K.

Last inspection of API manufacturing sites performed, when available, (please attach GMP certificate or relevant letter) by:

- ☐ Finished product manufacturer
- ☐ WHO Prequalification Programme, Geneva
- ☐ EDQM
- ☐ US FDA
- ☐ PIC/S members
- ☐ Others (specify)
- ☐ None of above

Outcomes and date:

Is/are the API(s) used to manufacture this product WHO-prequalified?

- ☐ Yes ☐ No

2.1.2 API specifications

➤ API specifications:

- ☐ British Pharmacopoeia (BP) (edition/year):
- ☐ United States Pharmacopeia (USP) (edition/year):

- ☐ *The International Pharmacopoeia* (Ph.Int.) (edition/year)
- ☐ Others (specify):
- ☐ Specifications additional to those in the pharmacopoeia referred to above if available
- ☐ Yes ☐ No

- Attach a copy of the FPP manufacturer internal API(s) specifications in Annex L.
- If analytical methods are in-house, different from BP, USP and Ph.Int., attach a copy of the analytical method and analytical validation data in Annex M.

For sterile API:

Please provide the data on validation of the sterile aspects of the product including recent media fill validation data, as applicable, in Annex N.

Describe the method of sterilization used when applicable:

2.1.3 Certificate of analysis

Please provide a copy of the certificate of analysis of the API from the API manufacturer as well as from the finished pharmaceutical product (FPP) manufacturer in Annex O.

2.1.4 Suitability of monograph for API

Are you in a possession of the following information for APIs?

Certificate of suitability to the monograph of the European Pharmacopoeia (CEP): please attach a copy of the CEP and its annexes (Annex P).

Certificate No.: _____

2.1.5. Open part of drug master file (DMF) registered in (country):

Technical file (please attach):

- ☐ Yes ☐ No

Section 3: Finished pharmaceutical product

3.1 Manufacturing site GMP status

GMP inspections carried out by an NMRA

	NRA of country of origin	Any other inspection of PIC/S member	
GMP certificate no.			
Valid until			
Country			

Please attach the recent/valid GMP certificates/letter (Annex Q)

Other GMP inspections carried out by (include information for all that apply):

Agency	Date of audit	Outcome
WHO Prequalification Programme		
UNICEF Supply Division		
MSF International		
ICRC		
Other (specify)		

3.2 Finished pharmaceutical product specification

Standard	Edition	Year published
BP		
USP		
Ph.Int.		
In-house	Year documented	
Specifications additional to those in the pharmacopoeia referred to above (e.g. dissolution, syringeability) explain:		
Other (specify)		

Please attach copies of release and shelf-life specifications for the FPP in Annex R. If analytical methods are in-house, different from BP, USP and Ph.Int., attach a copy of the analytical method and analytical validation data in the same Annex R.

- Please attach a copy of the certificate of analysis for the three last batches released in Annex S.

3.3 Method of manufacture and process validation:

- Have the manufacturing methods for each standard batch size been validated?
☐ Yes ☐ No

If no, please clarify:

If yes, please provide details of validation status in the table below:

The batch size of the validated batches	
The batch numbers of the validated batches	
Manufacturing dates of the validated batches	
Reference number for the process validation report	
If processes are yet to be validated, the reference number for the process validation protocol should be indicated	

Provide batch formulae for all proposed batch sizes:

- Please provide in Annex T a flow diagram and brief narrative describing the manufacturing and control process of this product with relevant parameters.

3.3.1 Additional information for sterile products

- Provide the data on validation of the sterile aspects of the product including recent media fill validation data as applicable in Annex U.
- Describe the method of sterilization used if applicable:

3.4 Stability of finished product

3.4.1 Is stability testing data available?

☐ Yes ☐ No

Please provide the protocol and the report for accelerated and long-term stability testing, including: type and material of container; conditions (temperature/relative humidity/duration of stability study); number of batches involved in the study (minimum three); batch sizes for each lot tested; date of beginning of the study; and study conclusions. (These can be provided in Annex V.)

3.4.2 Was the stability testing done on a product of the same formula, same API source, manufactured on the same site and packed in the same packaging material as the product that will be supplied?

☐ Yes ☐ No

If no, describe the differences:

3.4.3 Please specify whether stability studies have been done or are ongoing with all declared API sources:

☐ Yes ☐ No

Submit a declaration in Annex W that stability studies have been done or are being done with all declared API sources.

If no, explain why:

3.4.4 Do you have ongoing stability data for this product?

☐ Yes ☐ No

Attach status report of any ongoing stability studies in Annex X.

3.4.5 Shelf-life as it appears on packaging:

☐ 2 years ☐ 3 years ☐ 4 years ☐ 5 years

Other (please specify): _____

3.4.6 Specific storage conditions for this product as they appear on the packaging and based on stability studies (e.g. “Do not store above 30 °C – Protect from light”):

Temperature	
Light	
Humidity	
Other (specify)	

3.4.7 Product suitable for use in:

- ☐ Zone I
☐ Zone II
☐ Zone III
☐ Zone IVa
☐ Zone IVb
☐ Other (please specify): _____

3.4.8 For oral powder for suspension and powder for injection, or injection that may be further diluted, or multidose containers provide in-use stability data and storage conditions after reconstitution and/or dilution in Annex Y.

Indicate the period (hours/days) until which the product is stable after reconstitution and/or dilution based on the available in-use stability data:

Section 4: Safety/efficacy and/or therapeutic equivalence

(WHO Technical Report Series (TRS), No. 902, Annex 11/ TRS No. 937, Annex 7 or later)

4.1 For innovator products

Please attach a summary of pharmacology, toxicology and efficacy of the product in Annex Z.

4.2 For generic products: therapeutic equivalence

- ☐ Demonstrated
☐ Not demonstrated
☐ Not relevant, please explain why: _____

If demonstrated,

4.2.1 By in vivo bioequivalence studies

Study period (dd/mm/yyyy): from to

Reference product

Generic name:	
Dosage form:	
Strength:	
Brand/trade name:	
Manufacturer:	
Manufacture site:	
Batch number:	
Expiry date:	

Study protocol

Contract research organization (CRO) name:	
Country of study:	
Number of volunteers:	
Study design (describe in detail):	

Bio batch size:	
Bio batch number:	
Bio batch API(s) source(s):	
Study conclusion:	

Study results:

Study conclusion:

4.2.2 By comparative in vitro dissolution tests according to conditions described in WHO BCS classification document (WHO Technical Report Series, No. 937, or later)

☐ Yes

☐ No (explain): _____

Reference product

Generic name	
Dosage form	
Strength	
Brand/trade name	
Manufacturer	
Manufacture site	
Batch number	
Expiry date	

Name and contact details of laboratory performing tests:

Study results

F2 (similarity factor) value (standard 50–100%):

F1 (difference factor) value:

Study conclusion:

4.2.3 By another method (please describe study conclusion briefly):

Attach graphic/pictorial representation of summary study results in Annex AA.

4.3 The product used in the therapeutic equivalence study is essentially the same as the one that will be supplied (same materials from the same suppliers, same formula and same manufacturing method):

- ☐ Yes
- ☐ No (explain what the differences are and justify that the differences do not have any impact on the bioavailability): _____
- _____
- _____

- Provide a copy of the report of the proof of therapeutic equivalence (BE study) comparative dissolution profile, dissolution tests, and others, if any, in Annex AB.
- For bioequivalence studies, indicate the stringent regulatory authority (SRA)/WHO/PIC/S inspection status of the CRO (if the CRO has ever undergone inspections in relation to the current or other studies).
- _____
- _____
- _____

- Attach schematic representation of study design (Annex AC)
- Attach study protocol summary (Annex AD)

Section 5: Commitment and authorization

5.1 Commitment

I, the undersigned, _____ (*position in the company, e.g. General Manager, Authorized Person, Responsible Pharmacist*), acting as responsible for the company _____ (*name of the company*), certify that the information provided (above) is correct and true,

(if the product is marketed in the country of origin, select the appropriate box below)

- ☐ and I certify that the product offered is identical in all aspects of manufacturing and quality to that marketed in _____ (*country of origin*), including formulation, method and site of manufacture, sources of active and excipient starting materials, quality control of the product and starting material, packaging, shelf-life and product information.

☐ and I certify that the product offered is identical to that marketed in _____ (*name of country*), except:

(e.g. formulation, method and site of manufacture, sources of active and excipient starting materials, quality control of the finished product and starting material, packaging, shelf-life, indications, product information)

If any changes occur to the information after the submission of this product questionnaire, the manufacturer/supplier undertakes to provide the relevant update as soon as possible.

Date: _____ Signature: _____

5.2 Power of attorney

The manufacturer authorizes a distributor to submit the questionnaire

Date: _____ Signature: _____

Distributor (Signed by Distributor for Manufacturer under power of attorney)

Please provide a copy of the power of attorney (Annex AE).

5.3 Authorization for sharing information with other agency

I, the undersigned confirm that the company has no objection to the information contained herein being shared with the agencies listed on page 2 (1.5) except:

I, the undersigned, certify that the information provided above is accurate, correct, complete, up-to-date and true at the time of submission.

Full name:

Full title/position in company:

Company name:

Signature

Date

Company seal/stamp:



Section 6: Attachments/annexes

Attachments or Annexes to the questionnaire should be in PDF format and should be well indexed to facilitate review

Please ensure that all documents necessary to enable objective evaluation of your product are attached. This checklist may not be exhaustive.

- ☐ A. Formulation of the product (complete qualitative and quantitative composition including active ingredient(s) and excipients (1.1.7)
- ☐ B. Description and composition of primary packaging materials (1.2.1)
- ☐ C. Description and composition of secondary packaging materials (1.2.2)
- ☐ D. Copy of product registered and currently marketed – Licence no. (1.6.1)
- ☐ E. Certificate of pharmaceutical product (CPP) according to the WHO Certification Scheme (WHO Technical Report Series, No. 863). An earlier version is not acceptable) (1.6.1)
- ☐ F. Submit recent as well as historical deficiency/acceptance letters issued by PQP/SRA in relation to the specific product dossier (1.6.1)
- ☐ G. Copy of the relevant WHO Prequalification approval letter signed by your company (1.6.3)
- ☐ H. WHO acceptance letter for product dossier review mentioning the WHO reference number assigned by WHO for this specific product (1.6.4)
- ☐ I. Package insert/leaflet (1.7.1)
- ☐ J. Patient information leaflet (1.7.4)

- ☐ K. GMP certificate from the country of origin (2.1.1)
- ☐ L. Attach a copy of the internal API(s) specifications (2.1.2)
- ☐ M. Validated analytical methods if analytical methods for finished product are in-house analytical method, different from BP, USP and Ph.Int. (2.1.2)
- ☐ N. Please provide the data on validation of the sterile aspects of the product including recent media fill validation data, as applicable (2.1.2)
- ☐ O. Copy of the certificate(s) of analysis of the API from the API manufacturer as well as from the FPP manufacturer (2.1.3)
- ☐ P. Copy of the certificate of suitability to the European Pharmacopoeia (CEP) and its annexes (2.1.4)
- ☐ Q. Recent/valid GMP certificates/letter (3.1)
- ☐ R. If specifications are in-house specifications, different from BP, USP and Ph.Int., attach copy of the in-house finished product specifications and also validated analytical methods (3.2)
- ☐ S. Copy of the certificate of analysis for the three last batches released (3.2)
- ☐ T. Flow diagram and brief narrative describing the manufacturing and control process of this product with relevant parameters (3.3)
- ☐ U. Data on validation of the sterile aspects of the product including recent media fill validation data as applicable (3.3.1)
- ☐ V. Protocol and report for accelerated and long-term stability testing (3.4.1)
- ☐ W. Submit a declaration that stability studies have been done or are being done with all declared API sources (3.4.3)
- ☐ X. Attach status report of any ongoing stability studies (3.4.4)
- ☐ Y. For oral powder for suspension and powder for injection, provide in-use stability data and storage conditions after reconstitution (3.4.8)
- ☐ Z. Please attach a summary of pharmacology, toxicology and efficacy of the product (4.1)
- ☐ AA. Attach graphic/pictorial representation of summary study results (4.2.3)
- ☐ AB. Provide a copy of the report of the proof of therapeutic equivalence (BE study) comparative dissolution profile, dissolution tests, and others if any (4.3)
- ☐ AC. Schematic representation of study design (4.3)
- ☐ AD. Study protocol summary (4.3)
- ☐ AE. Copy of the power of attorney (5.2)

Appendix 7

Example of a standard operating procedure for screening and assessing product information

1. Title

Assessing product files

	Signature	Date
Prepared by		9 May 2005
Authorized by		

2. Policy and objective

- 2.1 Each product file submitted by an interested manufacturer should be assessed as part of the prequalification process.
- 2.2 Each product file should go through a screening procedure.
- 2.3 Product files found to comply with the screening requirements will be retained for assessment.
- 2.4 The objective is to screen product files to determine whether these comply with the requirements. This will prevent loss of valuable assessment time, should the product files be incomplete when received.
- 2.5 The objective of the assessment process is to verify that the required information regarding safety, efficacy and quality of the product is documented and submitted in the required format. Where possible during inspections, and as a part of the verification process, the data and results should be verified to ensure that correct, accurate and reliable data have been submitted to the procurement agency.

3. Responsibility

Project Manager
Evaluators

4. Action

A. Screening

- 4.1 Unpack each product file onto the working surface in the presence of at least two other persons. Sign a sheet indicating the names of the persons responsible for opening the containers on that date.
- 4.2 Complete the relevant details in the “product received register”.
- 4.3 Record details such as the product number, date, product detail (INN), name of supplier, name of manufacturer(s), country of manufacturer(s), screening outcome, date manufacturer informed (Addendum A).
- 4.4 Allocate the product number in numerical order starting from 001.
- 4.5 The number should start with the year, e.g. 01 (for 2001).
- 4.6 Identify the project for which the product was submitted, e.g. HA for HIV/AIDS. The first product for the project would thus be numbered 01HA001.
- 4.7 Open a WHO file for the product. Write the product name, number and the name of the manufacturer on the outer page.
- 4.8 Write the product number on the product file and screening form for the product.
- 4.9 Screen the product file to assess its completeness. Confirm that all the required information, data and forms have been submitted by the manufacturer/supplier.
- 4.10 Use the attached screening form for this purpose (Addendum B).
- 4.11 Enter the relevant information in the appropriate column of the screening form as part of the screening process.
- 4.12 Once the screening is complete, make a copy of the screening form.
- 4.13 File the copy of the screening form in the screening form file.
- 4.14 Place the original of the completed screening form in the front of the product file.
- 4.15 If the product file is complete, place the product file in numerical order in the designated area marked “For evaluation”.
- 4.16 If the product file is incomplete, place the file in the designated area, marked “Incomplete files”.
- 4.17 Enter the outcome in the “product received register”.

- 4.18 For each product file received, send a letter of acknowledgement of receipt to the manufacturer. For an “Incomplete file”, inform the manufacturer in writing that the product file submitted was incomplete and cannot be considered for evaluation or assessment (see Addendum C for a model letter).

B. Assessing product files

Note: Each product file must be assessed by at least three evaluators.

Three evaluators should evaluate Part I (quality aspects) and at least two evaluators should evaluate Part II (bioavailability, safety and efficacy aspects).

Step 1 (Evaluator 1)

- 4.19 Take a product file from the section marked “For evaluation”.
- 4.20 Use the attached product assessment report (Addendum D) for the purpose of evaluating the product information.
- 4.21 Go through each section and assess compliance with the required standards for the submission of the relevant information.
- 4.22 Record your findings in the report form.
- 4.23 On completion of the assessment record your name, signature and the date on the report form.
- 4.24 Record any specific problem associated with the evaluation of the product on a separate report form, entitled “Product-specific problem report” (Addendum E).

If you are evaluating Part 2, “Bioequivalence (safety and efficacy)”, and the efficacy part of the dossier is not included for all oral preparations, except aqueous solutions, at the time of administration, inform the manufacturer in writing that the product file was submitted without bioavailability aspects and cannot be evaluated at present.

- 4.25 Place the report forms in the front of the product file.
- 4.26 Replace the file in the section “For evaluation”.

Step 2 (Evaluator 2)

Perform steps equivalent to steps 4.19 to 4.26 above.

Step 3 (Evaluator 3)

Perform steps equivalent to steps 4.19 to 4.26 above.

Step 4

- 4.27 If a file contains the evaluation reports signed by three evaluators (quality aspects) and two evaluators (bioavailability), place the file in the area marked “Evaluation completed”.
- 4.28 Assess whether the relevant number of evaluators (three for quality aspects, and two for bioavailability) have evaluated each product adequately.
- 4.29 Collate the information in the reports. If additional information is required from the manufacturer or supplier, draft the letter on the basis of the information contained in the reports.
- 4.30 Request the additional information to be submitted within the specified period. Remind the manufacturer that failure to supply the requested information within the timescale requested may lead to exclusion of the product from further consideration.
- 4.31 Record the recommendation of evaluators on the list for the inspection of the manufacturing site.

5. Addenda

- Addendum A: Product details
- Addendum B: Screening form to assess the quality of the submission of EOI
- Addendum C: Product information receipt
- Addendum D: Product assessment report
- Addendum E: Product-specific problem report

6. Distribution and retrieval

The record of distribution and retrieval of the SOP should be entered in a table; see the model below.

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

The history of changes to the SOP should be recorded in a table; see the model below.

Date	Reason for change

Addendum A: Product details

Product Number	Date	Product details (INN)	Name of supplier	Name of manufacturer(s)	Country of manufacture	Screening outcome	Date manufacturer informed	Inspection planned (Y/N)

Addendum B: Screening form to assess the quality of the submission of an expression of interest

Access to drugs and diagnostics of acceptable quality
Pilot procurement quality and sourcing project

Complete the following:

Product submission number:

Product name	
Active pharmaceutical ingredient	
Strength	
Dosage form	
Pack size	
Name of supplier of drug products	
Address of supplier of drug products	
Name and address of manufacturer if different from that of the supplier above	

Table *continued*

Name and address of manufacturer (and if appropriate of supplier) of the active pharmaceutical ingredient			
Date of submission			
Country of origin of the submission	Supplier: _____ Manufacturer: _____		
Is the product licensed in	Japan USA EU*	YES YES YES	NO NO NO
If "Yes", proceed to Appendix 1 If "No", proceed to Appendix 2			

* (EU countries: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands (Kingdom of the), Portugal, Spain, Sweden, United Kingdom)

Appendix 1

The following is included in the submission:

A WHO-type certificate of a pharmaceutical product (CPP) issued by one of the regulatory authorities of ICH regions	YES	NO
The summary of product characteristics (SmPC)		
Assessment report(s) issued by the respective regulatory authority		
WHO-type batch certificate from the manufacturer		
The packaging of the product is the same as that approved by the drug regulatory authorities of the ICH regions		¹
The product information is the same as on the WHO-type CPP for at least:	_____	_____
Formulation		²
Strength		²
Specifications		²

¹ Stability testing data are submitted

² Arguments and/or data to support the applicability of the certificate(s) despite the differences are submitted.

If the answers to 1 and 2 are "no", then the EOI should be rejected.

Appendix 2

	YES	NO
Details of the product (Name of the product; approved generic name(s) (use INN, if any); visual description of the product; visual description of the packaging; strength per unit dosage and dosage form)		
Regulatory situation in other countries (Marketing authorization, withdrawn from the market, application rejected, deferred or withdrawn)		
API		
Properties Chemical structure; solubility in water, other solvents such as ether, ethanol, acetone and buffers of different pH; its isomeric nature including stereochemical configuration; partition coefficient and the existence of polymorphs; copies of infrared, nuclear magnetic resonance (proton and C-13), ultraviolet and mass spectra; information on the chemical and physicochemical stability if relevant (e.g. formation of a hydrate, change of polymorphic form)		
Sites of manufacture Name and street address of each facility of manufacture (synthesis, production), including any alternative manufacturers GMP certificate attached (including for all alternative sites of manufacture being submitted)		
Route(s) of synthesis 1. Including reagents and reaction conditions; specifications for starting materials, reagents, solvents, catalysts and intermediates in the synthesis; synthetic by-products and degradation products 2. If a European certificate of suitability with any appendices is submitted, then an outline of the route of synthesis is sufficient 3. The manufacturer of the finished product should know the full details of the synthesis of the substance so that they are able to conduct a full set of tests on each batch. The results of such testing should be presented for at least two batches. The last option can be used only if the quality of API is described in a pharmacopoeia		
Specifications		
Pharmacopoeial requirements: copy of the monograph and tests, additional specifications, certificates of analysis, two batches, including results for impurities		
Non-pharmacopoeia: tests and limits, methods, results of validation		
Stability testing Results of stability, physical as well as chemical tests, methodology used (WHO guidelines or ICH guidelines), validation		

Table *continued*

	YES	NO
Finished product		
Formulation Formulation and administration unit, excipients not present in final formulation, the qualitative and quantitative composition, overages, function(s) of each excipient, ranges in the content of excipients justified and explained		
Sites of manufacture Name and street address of each facility. Indicate the activity, alternative manufacturers, major production step(s) – certificate issued, product information approved, summary basis of approval		
Manufacturing procedure Outline of manufacturing and packaging Copy of the master formula and a copy of a manufacturing record Details of sterilization Stages of sampling and in-process control tests		
Specifications for excipients Pharmacopoeia: copy of the monograph, test methods referenced Additional specifications Non-pharmacopoeia: list of tests and for each excipient, including solvents, liquids to adjust pH, coatings, capsule shell, and inked imprint (on the dosage form), description of test methods, microbiological limits, colours EU/FDA/Japan		
Specifications for the finished product Two specifications: at release and end of shelf-life List general characteristics, specific standards: tests and limits for results for the finished product must be provided Analytical test procedures described (physicochemical properties, identity of API) Quantitative determination of active, deviations, purity tests, pharmaceutical tests, colouring antimicrobial or chemical preservatives, results of validation studies, comments on the choice of routine tests and standards provided Copy of pharmacopoeia monograph and verification data Results of batch analysis (inc. date of manufacture, place of manufacture, batch size and use of batch tested)		
Container/closure system(s) and other packaging Detailed description (inc. liner or wadding, details of composition); describe other (e.g. outer) packaging; state materials and specifications for part in contact with the product, or if protective. Parenteral: BP, EP, JP or USP		
Stability testing Results for each pack, methodology, validated (accuracy and precision recorded) Related compounds and decomposition: sensitivity, accelerated and real-time data, accelerated 40 °C and 75% RH for six months, real time 30 °C and 70% RH		

Table *continued*

	YES	NO
Container labelling Name, active ingredients, amount of each, batch number, expiry date, storage conditions, directions, warnings or precautions, name and address of the manufacturer, excipients known to be a safety concern		
Product information Copy approved by competent authority		
Patient information and package inserts Copies of package inserts and information for distribution		
Justification for any differences Arguments provided and/or data to support, validation data. Only minor differences are likely to be acceptable		
Interchangeability Multisource (generic): bioequivalence study. Bioequivalence of all oral preparations except aqueous solutions. Orally or parenterally administered aqueous solutions: chemical–pharmaceutical characteristics. Comparative clinical trial using clinical or pharmacodynamic end-points can be presented. End-points justified and validated for the compound and trial should be designed to show equivalence. Trial showing the absence of significant difference cannot be accepted Bioequivalence study report included		
Report Study design, investigators, study site, study dates, preparations used, characterization of study subjects, study procedures, drug determination methods, measured drug concentrations, calculation methodology of pharmacokinetic parameters, statistical methodology and results of statistical calculations		
Summary of pharmacology, toxicology and efficacy of the product New active ingredients and new combinations of active ingredients: full safety and efficacy (EU, FDA, Japan)		

☐ Accept ☐ Reject ☐ Hold

Reasons for rejecting or holding an application: _____

Addendum C: Product information receipt

Dear ...

Prequalification of manufacturers and suppliers of drug products

Thank you for submitting a product file after having indicated your company's interest in supplying drug products as part of the prequalification process of drug products to the United Nations organizations and interested procurement agencies.

We herewith acknowledge receipt of your product information sent to this office as part of the prequalification process.

The product information submitted has been screened to assess completeness of the submission in accordance with the guidelines that were sent to you after receiving your Expression of Interest (EOI) in participating in the prequalification programme.

Kindly note that your submission is now pending the full assessment. It is possible that an inspection of the manufacturing site(s) will be performed in due course. Details of this will be advised to you once all the necessary arrangements have been completed.

OR

Kindly note that your submission was found to be incomplete. We therefore regret to inform you that no further evaluation will take place with regards to your product file, and that the manufacturer will be not be included in the prequalification process. Would you kindly contact this office within 30 days to enable us to make the necessary arrangements for the return of the information already submitted.

OR

Kindly note that your submission was found to be incomplete. It is missing the following information.

If you provide the missing data within X days, and it is of satisfactory quality, then your submission will go forward to full assessment.

Your cooperation is appreciated.

Addendum D: Product assessment report

Access to drugs and diagnostics of acceptable quality
Pilot procurement quality and sourcing project

Product number:		
Product name (API):		
Manufacturer:		
Product manufactured and registered/licensed in EU, Japan or USA	YES ¹	NO ²

This product evaluation report consists of two parts. Both parts should be completed as part of the assessment. The report should be written in clear unambiguous language referring to shortcomings or lack of data submitted, as communication with the manufacturer may result from the assessment.

Part One should be completed by at least three evaluators from different countries, responsible for assessing product quality including pharmaceutical and analytical aspects. (The report should be no longer than six pages.)

Part Two should be completed by an evaluator responsible for the assessment for bioavailability. (The report should be no longer than two pages.)

The report should be signed off by the person responsible for the evaluation and assessment of the product files.

Part I: Quality aspects

¹ Product licensed/registered in the EU, Japan or the USA. Review the data submitted and comment (see also guidelines):

A WHO-type certificate of a pharmaceutical product (CPP) issued by one of the regulatory authority of ICH regions (EU, Japan, USA)
The summary of product characteristics (SmPC)
Assessment report(s) issued by the respective regulatory authority
WHO-type batch certificate from the manufacturer

Table *continued*

The packaging of the product is the same as those approved by the drug regulatory authorities of the ICH regions
The product information is the same as on the WHO-type CPP for at least:
Formulation
Strength
Specifications

² Product not licensed/registered in the EU, Japan or the USA. Review the data submitted and comment:

Details of the product
Regulatory situation in other countries
Active pharmaceutical ingredient(s) (API) Properties of the API(s)
Sites of manufacture
Route(s) of synthesis
Specifications API described in a pharmacopoeia (specify the pharmacopoeia, its edition, and any supplement if relevant). The latest edition of the relevant pharmacopoeia should always be used. API not described in a pharmacopoeia
Stability testing

<i>Table continued</i>
Finished product
Formulation
Sites of manufacture
Manufacturing procedure
Specifications for excipients
Specifications for the finished product
Container/closure system(s) and other packaging
Stability testing
Container labelling
Product information
Patient information and package inserts
Justification for any differences of the product in the country or countries issuing the submitted WHO-type certificate(s)

Evaluator (name):	Signature:	Date:
1		
2		
3		

Part II: Bioavailability (safety and efficacy)

(See also guidelines)

Bioequivalence study report
Summary of pharmacology, toxicology and efficacy

Evaluator (name):	Signature:	Date:
1		
2		
3		

Addendum E: Product-specific problem report

Access to drugs and diagnostics of acceptable quality
Pilot procurement quality and sourcing project

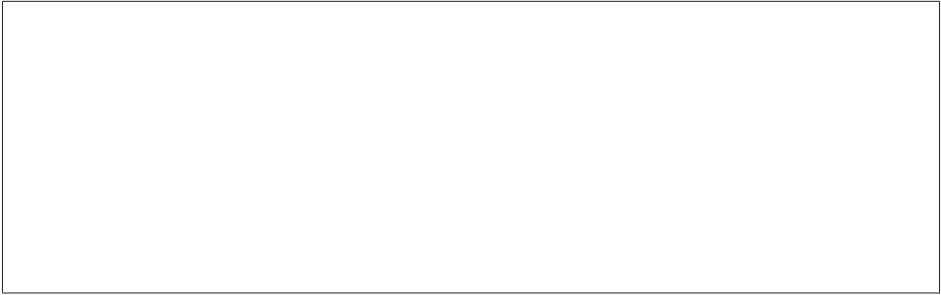
API:	

This product-specific problem report should highlight any specific problems identified during the evaluation of products. No mention should be made of the specific manufacturer’s product. The objective is to identify any problems associated with a specific product containing a specific API, or specific to any dosage form.

Dosage form:	

Problems

General recommendations



Appendix 8

Quality system recommendations for pharmaceutical inspectorates

For a guide to Quality systems requirements for national good manufacturing practice inspectorates, see: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-sixth report*. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 8.

Appendix 9

Technical questionnaire for pharmaceutical manufacturers

1. General information on the manufacturer

Name, address, telephone, telefax, Internet address of the company:

Name	
Postal address	
Physical address	
Telephone	
Fax number	
Web site URL	
Contact email address	

2. Affiliates

If the company is owned by another company, or belongs to a group of companies, Please describe your position within the structure: _____

3. Regulatory issues

3.1 Good manufacturing practice (GMP)

Indicate the GMP standards (WHO, PIC/EU, FDA or other) with which the company complies: _____

Provide a copy of the latest inspection report or certificate whichever is appropriate.

3.2 Manufacturing licence for medicinal products

Please list the pharmaceutical dosage forms you are licensed to manufacture by the national regulatory authority and attach a copy of the manufacturing licence(s):

3.3 Inspection

Date of last inspection by a national or other competent drug regulatory authority:

Drug regulatory authority	Date

Please attach a copy of the last inspection report(s) or certificates for review on a confidential basis.

4. Manufacturing

4.1 Manufacturing site

Please state all the names and addresses at which manufacturing of pharmaceutical products to be prequalified takes place, and indicate in which year the factory was built. Include dates of upgrading and adaptation, as well as a description of the activity:

Name	Physical address	Year built and recent upgrades	Activity (e.g. all, compression, packaging, etc.)

4.2 Personnel

Please indicate the name, qualification and years of experience of the following key staff:

Position	Name	Qualification	Experience
Managing Director			
Technical Director			
Production Manager			
Quality Control Manager			
Quality Assurance Manager			

Number of personnel in total: _____

Number of personnel in production: _____

Number of personnel in quality assurance/control: _____

4.3 Ventilation system

Please indicate whether the manufacturing areas are equipped with controlled ventilation systems ☐ Yes ☐ No

If “Yes”, please give a brief description of the ventilation system. (*A diagram complementing the description can be submitted.*)

If “No”, explain reasons: _____

4.4 Quality control

Instrumentation?

Chemical laboratory in-house ☐ contracted out ☐

Biological laboratory in-house ☐ contracted out ☐

Microbiological laboratory in-house ☐ contracted out ☐

4.5 Contract manufacture

Do you undertake contract manufacture for other companies? ☐ Yes ☐ No

If “Yes”, please indicate the type of products (e.g. pesticides, antibiotics, hormones, cytotoxics, etc.) _____

Do you subcontract to other companies? ☐ Yes ☐ No

If “Yes”, please list products and/or services that are subcontracted: _____

4.6 Sterile products

Do you manufacture sterile products? ☐ Yes ☐ No

Give a brief description of the method of sterilization used: _____

4.7 Beta-lactam, highly sensitizing compounds, hormones, cytotoxic products

Do you manufacture penicillins or other beta-lactam, highly sensitizing compounds, hormones or cytotoxic products? ☐ Yes ☐ No

If yes, does this production take place in a separate building provided with its own dedicated air-handling system? ☐ Yes ☐ No

4.8 Complaints and recalls

Do you have a recall procedure, which enables you to recall any product effectively and promptly within 24 hours from the distribution points or market? ☐ Yes ☐ No

Do you have a procedure for handling complaints? ☐ Yes ☐ No

Does it cover analysis of trends? ☐ Yes ☐ No

Please list significant product complaints and any recalls during the last three years:

Product	List complaints		
	Year 1	Year 2	Year 3

4.9 Research and development activities

Please indicate the type of activities and annual investment: _____

4.10 Production capacity

Product	No. of units per year	Last year's production units
Tablets		
Capsules		
Ampoules		
Vials, liquids		

Table *continued*

Vials, dry powder		
Vials, lyophilized		
Ointments		
Liquids		
Powder for oral suspensions		
Suppositories		
Penicillin, tablets/capsules		
Penicillin, powder for oral suspension		
Penicillin, powder for injection		
Other, specify		

Are production capacity figures based on one or more shifts?

(Tick appropriate box)

☐ One ☐ Two ☐ Three

4.11 Stock

Do you maintain a permanent stock?

☐ Yes ☐ No

4.12 Quality systems (including quality management and quality assurance)

Give a brief description of the quality management system, with specific reference to aspects such as procurement agency, documentation infrastructure, validation, training, statistical analysis, and other related aspects: _____

5. Products

5.1 Product licences

Please enclose a list of all products manufactured by your company for which you seek prequalification and which are authorized for sale. For each licensed product, please complete the table below and categorize as shown.

If possible, please attach an indicative price list.

Product	Marketed in the domestic market (Yes or No)	For export only (Yes or No)	Licences are held in the following countries	Name of contract manufacturer and country

5.2 Documentation

The following product documentation must be made available upon request for each product offered. Please indicate if this documentation is NOT available for any of the products on the list shown under point 5.1:

Product composition – master formula _____

Starting materials specification _____

Manufacturing and packaging specification _____

In-process test specifications and methods _____

Finished product specification _____

Packaging and labelling specifications _____

Analytical procedures _____

Upon request, “the common product questionnaire” must be completed and returned.

5.3 Samples

Are you willing to provide product samples and batch documentation (on a confidential basis) when requested? ☐ Yes ☐ No

5.4 Starting materials

List starting materials manufactured by the company or by affiliates, and indicate in the table below whether approved drug master files (DMF) or Certificates of suitability of the Monograph of the European Pharmacopoeia (CEP) are available.

Starting material	DMF (Mark ✓, and state number)	CEP (Mark ✓)

5.5 Stability studies and shelf-life

Do you perform initial and continuous stability studies on your products?

☐ Yes ☐ No

Give a brief description of the stability procedure and programme. If “No”, explain reasons: _____

What type(s) of studies do you carry out?

Type (Mark with ✓)		Test conditions	
		Temperature (indicate)	Relative humidity (indicate)
	Accelerated studies		
	Real-time studies		

Explain if necessary: _____

How do you determine the shelf-life of your products? _____

5.6 Bioequivalence

Have you conducted in vivo bioequivalence studies for some of your products?

☐ Yes ☐ No

If “yes”, list the products studied and the reference products:

Product	Reference product	Country of study

5.7 Retention samples

Do you keep retention samples?

☐ Yes ☐ No

Samples:	Yes	No	Retention period	Storage conditions
Every finished product				
Active pharmaceutical ingredients				
Excipients				

6. Audit

Can we or any other representative designated by us perform a GMP audit of the manufacturing site?

☐ Yes ☐ No

Can (a) representative(s) from the national regulatory authority participate as observer(s) in the audit

☐ Yes ☐ No

May we share the inspection report with the other procurement agencies “signatory” to this questionnaire?

☐ Yes ☐ No

Is a site master file (PIC or WHO format) available upon request?

☐ Yes ☐ No

Will any required additional information be provided if we wish to perform an audit of the company?

☐ Yes ☐ No

7. Other information

Contact person (commercial issues):

Name:	
Telephone no.:	
Fax:	
email:	

Contact person (quality issues):

Name:	
Telephone no.:	
Fax:	
email:	

Any additional information: _____

I hereby certify that the information given in this questionnaire and the attachments is correct.

 Date

 Signature

 Name

 Position in company

Appendix 10

Example of a standard operating procedure for planning of inspections

1. Title

Inspection, planning of site inspections

	Signature	Date
Prepared by		1 July 2006
Authorized by		

2. Policy and objective

- 2.1 Manufacturing sites should be inspected as part of the prequalification process. To enable the procurement agency to perform the inspections, they should be properly planned.
- 2.2 The objective is proper planning of site inspections to ensure that products will be sourced only from manufacturers that comply with international standards.
- 2.3 Proper planning of inspections should save time and resources (e.g. financial and human) through procurement agency planning.

3. Responsibility

Head of the Section or Department
Project Manager
Evaluator

4. Action

- 4.1 When assessing product information, make a list of all the products received (see Addendum A). Complete the table.
- 4.2 On the basis of the outcome of the assessment of the product information, decide which manufacturers should be inspected for prequalification.
- 4.3 Dossiers lacking information, or of unacceptably low quality, may lead to the manufacturing site failing to qualify for the inspection.

- 4.4 Group all the manufacturers in one country together to ensure that when a trip is undertaken to one country, more than one manufacturer can be included in the inspection trip where relevant.
- 4.5 Consult a map to see where the sites are located and plan the trip so as to prevent unnecessary loss of time through travelling.
- 4.6 Plot the sites on a table (calendar) and allocate at least 3 days for inspection of each manufacturing site, depending on the dosage forms manufactured and the size of the facilities.
- 4.7 Write a letter to the company informing them of the tentative date allocated for the site inspection. Request the company to indicate whether the dates are suitable to them, and also request them to submit a site master file.
- 4.8 Appoint inspectors for the inspection team. There should be at least two inspectors on the team, including the representative from WHO.
- 4.9 Send a letter to the national regulatory authority inviting an inspector from the inspectorate to participate in the inspection.
- 4.10 Inform the inspectors of the proposed dates for the inspection.
- 4.11 When the manufacturer confirms the dates for inspection confirm the date with the company and request the information listed in Addendum B.
- 4.12 Confirm the dates with the inspectors.
- 4.13 Send the inspectors copies of the SOPs needed to perform the inspections, as well as the terms of reference, confidentiality clause, no conflict of interest declaration and agreement for performance of work.
- 4.14 Make the relevant bookings (air travel, transport in the country where the inspection will be performed and hotel accommodation).

5. Addenda

Addendum A: Summary list of dossiers received

Addendum B: Manufacturer information

6. Distribution and retrieval

The record of distribution and retrieval of the SOP should be entered in a table; see the model below.

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

The history of changes to the SOP should be entered in a table; see the model below.

Date	Reason for change

Addendum A: Summary list of dossiers received

[illegible]

Addendum B: Manufacturer information

1. General information

Name	
Physical address of head office	
Postal address	
Telephone number	
Fax number	
Contact person	
Email address	

2. Manufacturing licence

Please attach the manufacturing licence.

3. Product list

Please attach a list of products manufactured at this particular manufacturing site.

4. Inspections by the national regulatory authority

Date of last inspection by the national regulatory authority (NRA)	
List the NRA of other countries that have inspected the site, and dates of inspection	Country Date

5. Manufacturing and testing

Physical address of manufacturing sites for the products indicated in the submission	
Telephone number	
Fax number	
Physical address of quality control laboratories (chemical and microbiological) used for testing the products in the submission	
Telephone number	
Fax number	
Email	

6. Recalls

Please list the products and reasons for implementing a product recall in the last 5 years.

Product and batch number (INN, strength and dosage form)	Reason	Date of recall

7. Complaints

If the company has had any product complaints in the last year, please complete the table below.

Products and batch number (INN, strength and dosage form)	Complaint and source	Corrective action taken

8. Site master file (SMF)

If the SMF for the manufacturing site was submitted previously:

Date submitted	
SMF number	

If the SMF has not yet been submitted to WHO, please attach it now. Please note that the SMF must conform to the requirements specified previously.

9. Audit/inspection

We herewith grant WHO permission to perform the inspection of the manufacturing site to assess compliance with good manufacturing practice, for the purpose of the prequalification of the manufacturing site and product.

I declare that the information given above is true and correct.

Signature: _____

Date: _____

Name: _____

Position: _____

Appendix 11

Example of a standard operating procedure for preparing for an inspection

1. Title

Preparation for an inspection

	Signature	Date
Prepared by		11 May 2006
Authorized by		

2. Policy and objective

- 2.1 Each manufacturer should be inspected by the procurement agency to assess compliance with good manufacturing practices.
- 2.2 All inspectors should follow the SOP in preparing for the inspection(s).
- 2.3 The objective is to ensure that a standardized procedure is followed by all inspectors when preparing for the inspections to prevent inspections being performed by different inspectors in different ways. This should ensure consistency in performance between inspectors.

3. Responsibility

Project Manager

Inspectors

4. Action

All actions described here are taken from the details provided by the WHO publication *Quality assurance of pharmaceuticals*, Volume 2, Chapter 4: Inspection of pharmaceutical manufacturers and inspection of drug distribution channels. These guidelines or other similar systems operated by national drug regulatory agencies should be followed in detail.

- 4.1 Once the inspection has been allocated to the inspector, he or she should plan for the performance of the inspection according to the steps outlined below.

- 4.2 Verify the objective of the inspection that is to be carried out.
- 4.3 Clarify which type of inspection will be performed, e.g. routine GMP or follow-up inspection.
- 4.4 Decide whether the inspection will cover the entire factory or just part of it.
- 4.5 Determine what the scope and depth of the inspection will be to enable you to prepare for it properly. (For a company producing sterile products, prepare by reviewing the guidelines for sterile product manufacture in addition to the general GMP guidelines.)
- 4.6 Scrutinize the product information for the products in the prequalification procedure manufactured at this manufacturing site.
- 4.7 Decide how long it will take to carry out the inspection and plan the date when the inspection will take place.
- 4.8 Inform the manufacturer(s) in question of the proposed date for the inspection.
- 4.9 Ensure that the proposed date for the inspection is suitable for all members of the inspection team.
- 4.10 Decide on a chief or lead inspector to coordinate and lead the inspection.
- 4.11 The lead inspector will be the main spokesperson during the closing or exit meeting at the end of an inspection, and has the overall responsibility for the inspection report.
- 4.12 Inform other interested parties of the proposed or planned inspection, e.g. a regional office of the procurement agency or agency, or the national regulatory authority.
- 4.13 Review documentation relating to the manufacturer to be inspected such as a completed questionnaire.
- 4.14 In case of a follow-up inspection, and where the procurement agency or agency has a company file in which general correspondence and previous inspection reports are filed, review the correspondence.
- 4.15 If a site master file (SMF) exists and is available, study the SMF and make notes to be followed up during the inspection (e.g. available equipment, SOPs and records)
- 4.16 Study the layout and design of the manufacturing facility, and some of the systems the manufacturer has in place to ensure quality in manufacture of products.

- 4.17 Look at the information provided on the manufacturing licence and product licence. Make notes of the aspects that need to be inspected to confirm compliance with licence conditions, and to verify data during the inspection.
- 4.18 Review the reports of previous inspections, reports of adverse drug experiences and complaints, if any exist, as investigations and corrective action taken by the manufacturer should be verified during inspections.
- 4.19 For a special inspection, review records of the company in relation to complaints and recalls, and regulatory test results (surveillance) where available.
- 4.20 If an annual report is available, scrutinize the report and note the information in relation to financial aspects of the company, personnel issues and products manufactured.
- 4.21 If any complaints had been received about the manufacturer or products previously supplied, review the contents of the complaint, investigation, outcome and corrective action.
- 4.22 If self-inspection/internal audit reports were requested from the manufacturer, review the contents. (Such reports are normally not requested as some manufacturers consider that the inspectors should assess GMP compliance themselves, and not look at the company's own findings of inspections. Requesting such reports would be dependent on the policy of the procurement agency.)
- 4.23 Study the diagram of the facility to get a better understanding of the flow of material, personnel and processes in the facility.
- 4.24 If any manuals and/or procedures were submitted by the manufacturer, review these and prepare specific questions relating to the quality policy, validation policy and procedure for performing certain activities.
- 4.25 Draw up a checklist or aide-memoire of points to be verified during the inspection.
- 4.26 Draw up a programme for the inspection. Produce an outline of what will be covered each day and clarify what each member of the team will be doing every day or half-day of the visit. Indicate in the programme which sections or departments will be inspected, and when (for an example, see Addendum A).
- 4.27 Distribute the programme to the team members. In the case of an announced inspection, inform the company of the proposed inspection programme.

5. Addenda

Addendum A: Example of an inspection plan

6. Distribution and retrieval

The record of distribution and retrieval of the SOP should be entered in a table; see the model below.

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

The history of changes to the SOP should be entered in a table; see the model below.

Date	Reason for change

Addendum A: Example of an inspection plan

Manufacturer	
Address	
Date	
Inspectors	

Day 1

Time	Activity
08:30	Arrival
08:45	Opening meeting and company presentation
09:15	Receiving area and stores
10:15	Sampling
11:00	Tea
11:15	Weighing
12:00	Packaging components
13:00	Lunch
14:00	Manufacturing (organize time depending on the dosage form(s))
17:00	Summary of the day's observations

Day 2

08:30	Manufacturing, continued
10:00	Tea
10:15	Quality control
12:00	Heating, ventilation and air-conditioning, water and other utilities
13:00	Lunch
14:00	Documentation
17:00	Summary
17:30	Closing meeting

Appendix 12

Example of a standard operating procedure for performing an inspection

1. Title

Performance of inspection

	Signature	Date
Prepared by		1 July 2006
Authorized by		

2. Policy and objective

- 2.1 Each manufacturer should be inspected by the procurement agency to assess compliance with good manufacturing practices.
- 2.2 All inspectors should follow the SOP for performing inspections.
- 2.3 The objective is to ensure that a standardized procedure is followed by all inspectors when performing inspections to prevent inspections being performed by different inspectors in different ways. This should ensure consistency in performance between inspectors.
- 2.4 One of the objectives is to control and enforce the general standards of production for products that may be sourced as a result of the prequalification procedure.
- 2.5 Through sequential examination of production and control activities of the manufacturer, the manufacturer of pharmaceutical products may be included on the prequalification list as a manufacturer of pharmaceutical products for possible supply of specified products to procurement agencies and other agencies.
- 2.6 During inspections, the performance of manufacture of products and data submitted in the relevant product information files should be verified.

3. Responsibility

Project Manager

Inspectors

4. Action

All actions described here are taken from the details provided in the WHO publication *Quality Assurance of Pharmaceuticals*, Volume 2, Chapter 4: Inspection of pharmaceutical manufacturers and inspection of drug distribution channels. These guidelines or other similar systems operated by national drug regulatory authorities should be followed in detail.

4.1 Clarification and definitions

4.1.1 Different types of inspections are identified in the WHO text referred to above. These include:

- routine inspection;
- concise inspection;
- follow-up inspection;
- special inspection;
- quality systems review.

4.2 The performance of the inspection is dependent on the type of inspection; however, in principle, the basic aspects of this procedure can be followed for performance of an inspection.

4.3 A routine inspection is a full review of all aspects and components of GMP within a facility. It is appropriate to perform a routine inspection under the following circumstances:

- when there is a new expression of interest (EOI) from a manufacturer or a newly established manufacturer;
- when the listing on the prequalification list is due for renewal;
- if there have been significant changes such as new products or new product lines; modification to manufacturing methods or processes; or changes in key personnel, premises and/or equipment;
- if an inspection has not been carried out within the past 3–5 years.

4.4 A concise inspection is the evaluation of limited aspects relating to GMP compliance within a facility. (It is known as an abbreviated inspection in some countries.) A limited number of GMP requirements are selected by the inspector to serve as indicators of overall GMP compliance by the manufacturer. The inspector also has to identify and evaluate any significant changes that could have been introduced by the manufacturer since the last inspection.

4.4.1 Collectively, the selected indicators and the changes identified indicate the manufacturer's attitude towards GMP.

4.4.2 A concise inspection is appropriate under the following circumstances:

- where a manufacturer has a consistent record of compliance with GMP through routine inspections in the past;
- where a sample of aspects can be taken as a good indication of the overall level of compliance with GMP.

4.4.3 However, if the concise inspection uncovers evidence that the level of GMP compliance has fallen, a more comprehensive or full GMP inspection should be performed soon after the concise inspection.

4.5 A follow-up inspection is also referred to as a re-inspection or a reassessment of the manufacturer.

4.5.1 A follow-up inspection is performed specifically to monitor the result of corrective actions of the manufacturer following a previous inspection.

4.5.2 Depending on the nature of the defects and the work required, the follow-up inspection could be carried out between 6 weeks and 6 months after the original inspection took place.

4.5.3 The follow-up inspection is limited to specific GMP requirements that have not been observed or that have been inadequately implemented by the manufacturer.

4.6 There are a number of circumstances in which special visits or inspections may be necessary. A special inspection is undertaken to do spot checks. Spot checks could focus on one product, a group of related products, or specific operations e.g. mixing or labelling. If there have been complaints about a specific product that suggest there may be defects, a special inspection could be performed to investigate the quality defects of the product. If there has been a product recall, this can also trigger an inspection, as would adverse drug reactions. In the above cases, the inspection would focus on the specific product or aspect of production that is suspect. A special inspection could also be performed to gather specific information, or to investigate specific operations of the manufacturer.

4.7 The purpose of a quality systems review is to review the manufacturer's quality system and to ascertain whether it has been shown to operate satisfactorily.

4.8 Plan the inspection to ensure that all areas for assessment are covered in the allocated timeframe. The length of time needed for an inspection is determined by a number of factors, including the type of inspection to be performed, the number of inspectors, the size of the company and the purpose of the inspection or visit.

4.9 An inspection can be performed over a period of a few days to several weeks.

- 4.10 The time taken will also depend on the size of the inspection team. One or more inspectors can perform the inspection as part of an inspection team.
- 4.11 If necessary, appoint a specialist to accompany the team during the inspection, e.g. for particular dosage forms, chemistry or another aspect, e.g. the manufacture of biologicals.

5. Addenda

Addendum A: Inspection programme

Addendum B: Documentation required for verification during the inspection

6. Distribution and retrieval

The record of distribution and retrieval of the SOP should be entered in a table; see the model below.

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

The history of changes to the SOP should be entered in a table; see the model below.

Date	Reason for change

Addendum A: Inspection programme

Manufacturer	
Address	
Date	
Inspectors	

Day 1

08:30	Arrival
08:35	Opening meeting
08:45	Company presentation
09:00	Receiving area and stores
10:30	Tea
10:45	Sampling and weighing areas
11:15	Packaging material stores and control
12:30	Lunch
13:15	Manufacturing areas
15:30	Tea
15:45	Manufacturing (cont.)
16:30	Summary of findings, day 1

Day 2

08:30	Arrival
08:35	Manufacturing area (cont.)
10:30	Tea
10:45	Laboratories
12:30	Lunch
13:15	Laboratories (cont.)
15:30	Tea
15:45	Utilities
16:30	Summary of findings, day 2

Day 3

08:30	Arrival
08:35	Utilities (cont.)
10:30	Tea
10:45	Documentation
12:30	Lunch
13:15	Documentation (cont.)
15:30	Tea
15:45	Preparation for closing meeting
16:00	Closing meeting

Addendum B: Documentation required for verification during the inspection

1. Organigram
2. Job descriptions
3. Quality policy (e.g. quality manual)
4. Validation policy (e.g. validation master plan or programme)
5. Raw material specifications (for specific products)
6. Packaging material specifications
7. Manufacturing formula and method masters
8. Packing instructions master
9. Batch manufacturing records (verification against master documents)
10. SOP index
11. SOP: self inspection
12. SOP: recalls
13. SOP: complaints plus records
14. SOP: batch number allocation
15. SOP: planned preventive maintenance
16. SOP and record: planned preventive maintenance of specific equipment
17. SOP: training (plus record of personnel)
18. SOP: environmental monitoring plus records
19. SOP: water sampling and testing plus records
20. Validation protocol and report for specific products
- 21.
- 22.
- 23.
- 24.
- 25.
- 26.
- 27.
- 28.
- 29.
- 30.

Appendix 13

Example of a checklist for good manufacturing practices

It is recommended that inspectors prepare an aide-memoire to remind them of points to be checked during an inspection.

Aide-memoires can be prepared to cover one or more aspects, e.g.

- production
- quality control
- utilities
- lyophilization.

The aide-memoire should contain key words to remind the inspector of aspects to be inspected.

An example of an aide-memoire is shown below.

Example: Aide-memoire for inspection of the lyophilization process:

Points to check	Notes
Dissolving Filtration Filling and stoppering Transfer Loading Freezing Vacuum Heating Stoppering Capping	
Validation: Design qualification (DQ) Installation qualification (IQ) Operational qualification (OQ) Commissioning Process qualification (PQ) Media fills Air samples Surface swabs Operator swabs Daily clothing	

Table *continued*

Points to check	Notes
Simulate process with media (not freeze) Smoke test (transport area) Transport Frequent fill volume Pre-cooling of shelves (no ice)	
Freezing Cycle Rate – (slow = crystals, polymorphism) Manner Drying temp. < eutectic point Determine eutectic point, consistent Shelf loading variations <i>Validate:</i> shelf temperature product temperature condenser temperature pressure (chamber) pressure (condenser) time, temperature, pressure leakage in contamination (thermal fluid, oil) cleaning	
Cycle Eutectic point determination Scale up Vial size Batch size	
Sterilization of lyophilizer Moist heat used Each cycle Residue if applicable Biological Indicators Design: single door (double door, air class!)	

Appendix 14

Guidance on good manufacturing practices: model inspection report

Model inspection report

Section 1. General information

Name of organization:	
Website (link):	
Physical address:	
Postal address:	
Tel.:	
Fax:	
Contact person:	
Email address:	
Activities:	Prequalification ☐ Purchasing ☐ Receiving and storage ☐ Distribution ☐ Reassessment ☐
Date of assessment/inspection (dd/mm/yyyy):	
Products and/or product category (e.g. pharmaceuticals, diagnostics, medical devices)	
Name of inspector:	

Section 2. Summary

<i>General information about the procurement agent and site</i>
<i>History of inspections</i>
<i>Focus of the inspection and areas inspected</i>
<i>Summary of findings</i>
General activities:
Prequalification:
Purchasing:
Receiving and storage:
Distribution (including the ability to supply the needed products in quantities required):

Table continued

Reassessment:

Section 3. Observations and deficiencies/noncompliance

Note: Module I should be used in all cases of assessment of a procurement agency. Modules 2 to 6 may be used depending on the activities performed by the procurement agency.

	Module I: General requirements	Classification (C, M, O)
1.		
2.		
3.		
4.		
5.		
	Module II: Prequalification	
6.		
7.		
8.		
9.		
10.		
	Module III: Purchasing	
11.		
12.		
13.		
14.		

Table *continued*

	Module IV: Receiving and storage	
15.		
16.		
17.		
18.		
	Module V: Distribution	
19.		
20.		
21.		
22.		
	Module VI: Reassessment	
23.		
24.		
25.		
26.		

(C) Critical observation: An observation relating to any activity, action or omission thereof, by the procurement agency, in relation to product(s), that may result in a significant risk to the user.

(M) Major observation: A non-critical observation that:

- may have a negative impact on a product in relation to prequalification, purchasing, storage, distribution or requalification; and/or
- indicates a major deviation from the model quality assurance system (MQAS); and/or
- consists of several other deficiencies, none of which on its own may be major, but which may together represent a major deficiency and should be explained and reported as such.

(O) Other observation: An observation that cannot be classified as either critical or major, but indicates a departure from the recommendations in the MQAS (including good storage practices (GSP) and good distribution practices (GDP)).

Section 4. Outcome of the inspection (select one of the following options)

Based on the areas inspected, the personnel met and the documents reviewed, and considering the findings of the inspection, including the observations listed above – the agency was considered to be operating in compliance with the MQAS for the following activities (select the appropriate one(s)) prequalification, purchasing, storage, distribution, requalification).

Or

Based on the areas inspected, the personnel met and the documents reviewed, and considering the findings of the inspection, including the observations listed above – the agency was considered not yet to be operating at an acceptable level of compliance with the MQAS for the following activities (select the appropriate one(s)) prequalification, purchasing, storage, distribution, requalification). The corrective and preventive actions (CAPAs) will be reviewed after which a conclusion will be made as to whether the procurement agency is operating in compliance with the MQAS. (A reinspection may be considered before the conclusion is reached.)

Or

Based on the areas inspected, the personnel met and the documents reviewed, and considering the findings of the inspection, including the observations listed above – the agency was considered to be operating at an unacceptable level of compliance with the MQAS for the following activities (select the appropriate one(s)): prequalification, purchasing, storage, distribution, requalification).

Signature: _____

Date: _____

(Name): _____

(Print)

Appendix 15

Good storage practices

For a guide to good storage practices for pharmaceuticals, see: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-seventh report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series No. 908), Annex 9.

Appendix 16

Good trade and distribution practices

For a guide to good trade and distribution practices for pharmaceutical starting materials, see: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-eighth report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 917), Annex 2.

8.4 Good trade and distribution practices for pharmaceutical starting materials

Annex 6, WHO Technical Report Series, 996, 2016

Introduction	1294
1. Quality management	1295
2. Organization and personnel	1296
3. Premises	1297
4. Procurement, warehousing and storage	1298
5. Equipment	1300
6. Documentation	1300
7. Repackaging and relabelling	1302
8. Complaints	1304
9. Recalls	1305
10. Returned goods	1305
11. Handling of non-conforming materials	1306
12. Dispatch and transport	1306
13. Contract activities	1307
References	1307

Introduction

Good manufacturing practices for active pharmaceutical ingredients were published in 2000 by The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), in ICH Q7 (1). Section 17 of this ICH text includes guidelines for agents, brokers, traders, distributors, repackers and relabellers. This section was written based on the outcome of the World Health Organization (WHO) investigation into deaths resulting from the intentional relabelling of industrial grade ethylene glycol as pharmaceutical grade material. This material was subsequently formulated into a paediatric medicine that caused many deaths. Section 17 of this good manufacturing practice (GMP) guide for active pharmaceutical ingredients (APIs) applies to any party other than the original manufacturer which may trade and/or take possession, repack, relabel, manipulate, distribute or store an API or API intermediate. The scope of ICH Q7 does not include excipients.

Following a number of incidents involving diethylene glycol and a World Health Assembly resolution (WHA52.19), WHO published the *Good trade and distribution practices for pharmaceutical starting materials* in 2004 (2). At the time of publication of these guidelines, WHO had not yet adopted the text from ICH Q7 as GMP for APIs. The WHO guidance for excipients (3), published in 1999, did not cover trade and distribution practices for excipients.

In 2010, WHO published *Good manufacturing practices for active pharmaceutical ingredients* (4), which reflect the text from ICH Q7 and include Section 17 of that document, to replace the existing WHO GMP for APIs.¹

The WHO Expert Committee on Specifications for Pharmaceutical Preparations discussed the revision of the *Good trade and distribution practices for pharmaceutical starting materials* at several meetings. The scope of this WHO guidance on *Good trade and distribution practices for pharmaceutical starting materials* is applicable to any ingredient that is used in the manufacture of a medicinal product, including APIs, excipients and any others.

Note: Material deriving from non-pharmaceutical grades, such as food, industrial or technical grades, should not be designated as pharmaceutical grade when it is not produced under the required manufacturing conditions and quality system. For finished pharmaceutical products (FPPs), details can be found in the WHO good distribution practices for pharmaceutical products (5).

¹ It is important to note that any party that engages in repackaging or blending of an API is considered to be a manufacturer and must submit appropriate registration documents for such manufacturing. He or she must also comply with the GMP for APIs as stated in WHO Technical Report Series, No. 957, Annex 2, 2010 (4).

1. Quality management

1.1 Within an organization, quality assurance serves as a management tool. In contractual situations, quality assurance also serves to generate confidence in the supplier. There should be a documented quality policy describing the overall intentions and direction of the distributor regarding quality, which should be formally expressed and authorized by management. The quality policy should clearly indicate that the distributor implements and maintains good trade and distribution practices (GTDP) as described in these guidelines, within the organization and its services.

1.2 Quality management should include:

- an appropriate infrastructure or “quality system”, encompassing the organizational structure, procedures, processes and resources. The size, structure and complexity of the distributor and its activities should be taken into consideration when developing or modifying the quality system;
- an independent quality unit (or designee), which is responsible for all quality-related matters;
- an appropriate quality risk management (QRM) system to enable a systematic process for the assessment, control, communication and review of risks to the quality of the product. The extent of application of the QRM system should reflect the operations performed;
- a validation/qualification system to ensure that the resulting product is capable of meeting the requirements for the specified application;
- systematic actions necessary to ensure adequate confidence that a material (or service) and relevant documentation will satisfy given requirements for quality – the totality of these actions is termed quality assurance;
- a clear documented procedure for selecting, approving, disqualifying and re-approving suppliers of pharmaceutical starting materials and services;
- a robust deviation management and change control programme designed to ensure that quality is continually assessed and maintained: these should include a customer notification where appropriate;
- a system ensuring traceability of products and associated documentation throughout the entire supply chain.

1.3 The system should cover for example, but not be limited to, the quality assurance principles in these guidelines.

1.4 All parties involved in the manufacture and supply chain must exercise responsibility to ensure the quality and safety of the materials and products, and that they are fit for their intended use in accordance with their specifications.

- 1.5 The responsibilities placed on any one individual should not be so extensive as to present any risk to quality. In the event of a supplier having a limited number of staff, some duties may be delegated or contracted out to designated persons who are appropriately qualified. There should, however, be no gaps or unexplained overlaps related to the application of GTDP for pharmaceutical starting materials as described in these guidelines.
- 1.6 Where electronic commerce (e-commerce) is used, defined procedures and adequate systems should be in place to ensure confidence in the quality of the material and its traceability.
- 1.7 Authorized release procedures should be in place to ensure that when material is released for its intended purpose, it is of an appropriate quality, meets its specifications and is sourced from approved suppliers.
- 1.8 Implementation of QRM principles using appropriate tools such as hazard analysis and critical control point (HACCP); inspection and certification of compliance with an appropriate quality system such as applicable International Organization for Standardization (ISO) series, and recognition of compliance with national and/or regional standards by external bodies is recommended. However, this should not be seen as a substitute for the implementation of these guidelines or for conforming, for example, to pharmaceutical GMP and good storage practices (GSP) requirements, as applicable.
- 1.9 A system should be in place for the performance of regular internal audits with the aim of continuous improvement. The findings of the audit and any corrective and preventive actions taken, including verification of their effectiveness, should be documented and brought to the attention of the responsible management.

2. Organization and personnel

- 2.1 There should be an adequate organizational structure and a sufficient number of personnel should be employed to carry out all the tasks for which the supplier is responsible.
- 2.2 Individual responsibilities should be clearly defined, understood by the individuals concerned and recorded in writing (as job descriptions or in a contract). Certain activities, such as supervision of performance of activities in accordance with local legislation, may require special attention. Personnel should be suitably qualified, trained and authorized to undertake their duties and responsibilities.
- 2.3 All personnel should be aware of the principles of the appropriate guidelines, including but not limited to GTDP.

- 2.4 Personnel should receive initial and continuing training relevant to their tasks. Training should be provided by qualified trainers in accordance with a training programme. The effectiveness of training should be verified where appropriate. Training records should be maintained. All personnel should be motivated to support the establishment and maintenance of quality standards.
- 2.5 Personnel dealing with hazardous materials (such as highly active, toxic, infectious or sensitizing materials) should be given specific training and should be provided with the necessary protective equipment. Documented policies and procedures for the use of personal protective equipment should be followed to decrease exposure of workers working directly with products and those in the immediate environment.
- 2.6 Personnel who may be exposed to materials from open containers should maintain good hygiene, have no open wounds and should wear appropriate protective garments, gloves, masks and goggles.

3. Premises

- 3.1 Premises, including laboratory facilities, must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid contamination, cross-contamination, mix ups, build-up of dust, dirt or waste and, in general, any adverse effect on the quality of materials.
- 3.2 Measures should be in place to prevent unauthorized persons from entering the premises.
- 3.3 Premises should be designed, equipped and maintained so as to afford maximum protection against the entry of insects, rodents or other animals. A pest control programme should be implemented and maintained. Its effectiveness should be monitored.
- 3.4 Suitable supporting facilities and utilities (such as air control, ventilation and lighting) should be in place and appropriate to the activities performed, in order to avoid contamination, cross-contamination and degradation of the material. Utilities that could affect product quality should be identified and monitored.
- 3.5 If sampling of pharmaceutical starting materials is performed, the sampling area should be separate and in a controlled environment. Sampling should only be performed in a storage area if it can be conducted in such a way that there is no risk of contamination or cross-contamination. Adequate cleaning procedures should be in place for the sampling areas.

4. Procurement, warehousing and storage

Note: GSP are applicable in all circumstances in which, and in all areas where, materials are stored.

- 4.1 Materials should be purchased from approved suppliers in accordance with mutually agreed formal specifications.
- 4.2 Actions should be taken to minimize the risk of falsified or non-conforming materials entering the supply chain.
- 4.3 There should be authorized procedures describing the activities relating to the receipt, storage and distribution of materials. Steps should be taken to ensure and document that the arriving consignment is correct and that the products originate from approved suppliers. Deliveries should be examined to check that containers have not been damaged, altered or tampered with, and that closures and security seals are intact.
- 4.4 Storage areas should have sufficient capacity to allow orderly storage of the various categories of materials.
- 4.5 Receipt and dispatch bays should be equipped with the means to protect materials from adverse environmental conditions. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned before storage if appropriate. Upon receipt, material should be segregated until released by the quality unit.
- 4.6 Segregated areas should be provided for the storage of received, quarantined, rejected, recalled and returned material, including materials with damaged packaging. Any system replacing physical segregation, such as electronic segregation based on a computerized system, should provide equivalent security and should be appropriately qualified and validated.
- 4.7 The storage areas should be kept clean and dry.
- 4.8 Segregated areas and materials should be appropriately identified.
- 4.9 The required storage conditions, as specified for the material, should be maintained within acceptable limits at all times during storage. Appropriate checks to confirm that required shipping conditions have been met should be conducted as soon as possible after receipt.

The product should be transferred to appropriate storage facilities immediately after checks to be made in the goods receiving area have been conducted.

- 4.10 Where special storage conditions are required (e.g. particular temperature, humidity or protection from light) these should be provided, monitored and recorded as appropriate.
- 4.11 Highly active materials, narcotics, other dangerous drugs and substances presenting special risks of abuse, fire or explosion should be stored in safe, dedicated and secure areas. In addition and where applicable, international conventions and national legislation are to be adhered to.
- 4.12 Special attention should be given to the design, use, cleaning and maintenance of all equipment for bulk handling and storage, such as tanks and silos.
- 4.13 Products should be packed in such a way as to avoid breakage, contamination, tampering or theft. The packing should be adequate to maintain the quality of the product during transport. If special shipping conditions have to be met they should be defined, provided and controlled. The containers in which products are shipped should be sealed and should clearly indicate the authenticity of the product and its supplier.
- 4.14 Spillages should be cleaned up as soon as possible to prevent possible cross-contamination and hazard.
- 4.15 Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, closed containers in enclosed areas, taking into account the relevant national legislation.
- 4.16 A default system should be in place to ensure that those materials due to expire first are sold or distributed first (earliest expiry/first out). Where no expiry dates are specified for the materials, the first in/first out principle should be applied.
- 4.17 A process should be in place to ensure that materials that have reached their expiry or retest date should be withdrawn immediately from saleable stock. Materials with a retest date should be retested according to the appropriate specifications. Materials with an expiry date should not be retested or used after that date.
- 4.18 Stock inventory should be checked regularly, at least for quantity, overall condition and retesting or expiration dates. Any discrepancies should be investigated.
- 4.19 Controls should be in place to ensure that the correct product is picked, packed and distributed. The material should have an appropriate remaining shelf life. All batch numbers should be recorded.
- 4.20 Storage areas should be clean and free from accumulated waste and from vermin. A written sanitation programme should be available, indicating the frequency of cleaning and the methods to be used to clean the premises and storage areas.

5. Equipment

- 5.1 Equipment must be located, designed, constructed, adapted, qualified, used, cleaned and maintained to suit the operations to be carried out. Its layout, design and use should aim to minimize the risk of errors and permit effective cleaning and maintenance so as to avoid cross-contamination, build-up of dust or dirt and any adverse effect on the quality of materials.
- 5.2 Defective equipment should not be used and should either be removed or labelled as defective. Equipment should be disposed of in such a way as to prevent any misuse.
- 5.3 The status of the equipment should be readily identifiable.
- 5.4 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.
- 5.5 All services, piping and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases, liquids and other materials.
- 5.6 Balances and other measuring equipment of an appropriate range and precision should be available and should be calibrated in accordance with a suitable schedule.
- 5.7 Dedicated equipment should be used where appropriate when handling and/or processing pharmaceutical starting materials. Where non-dedicated equipment is used cleaning validation should be performed.
- 5.8 Closed equipment should be used when possible. If open equipment is used, suitable measures should be taken to prevent contamination.
- 5.9 Procedures should be in place for the operation and maintenance of equipment. Lubricants and other materials used on surfaces that come into direct contact with the materials should be of the appropriate grade, e.g. food-grade oil, and should not alter the quality of the materials.
- 5.10 Washing and cleaning equipment should be chosen and used such that it cannot be a source of contamination.

6. Documentation

- 6.1 Documents, in particular instructions and procedures relating to any activity that might have an impact on the quality of materials, should be designed, completed, reviewed and distributed with care. Documents should be completed, approved, signed and dated by appropriate authorized persons and should not be changed

without authorization. Specifications for materials, including packaging materials, should be available, reviewed and revised on a regular basis.

- 6.2 Documents should have unambiguous contents: their title, nature and purpose should be clearly stated. They should be laid out in an orderly manner and be easy to check.
- 6.3 Certificates of analysis (COAs) issued by the original manufacturer should be provided. If additional testing is done, all COAs should be provided.

COAs should document product traceability back to the manufacturer by naming the original manufacturer and the manufacturing site. COAs should indicate which results were obtained by testing the original material and which results came from skip-lot testing or other testing and should specify the organization responsible for issuing the COA.

- 6.4 Before any material is sold or distributed, the supplier should ensure that the COAs and results are available and that the results meet the required specifications.
- 6.5 The original manufacturer and the intermediaries handling the material should always be traceable and transparent; and this information should be made available to authorities and end-users, downstream and upstream, when requested.
- 6.6 Depending upon risk assessment, and in accordance with the national requirements, quality agreements should form the basis of the relationship for all parties involved in the supply chain. The agreements should include mechanisms to allow transfer of information, e.g. quality or regulatory information and change control.
- 6.7 Labels applied to containers should be clear, unambiguous, permanently fixed and should be printed in the company's agreed format. The information on the label should be indelible.
- 6.8 Each container should be identified by labelling bearing at least the following information:
 - the name of the pharmaceutical starting material (including grade and reference to pharmacopoeias where relevant);
 - if applicable, the International Nonproprietary Name (INN);
 - the amount (weight or volume);
 - the batch number assigned by the original manufacturer or the batch number assigned by the repacker, if the material has been repacked and relabelled;
 - the retest date or expiry date (where applicable);

- the storage conditions;
- handling precautions, where necessary;
- identification of the original manufacturing site;
- name and contact details of the supplier.

6.9 Relevant storage and handling information and safety data sheets should be available.

6.10 Records should be kept and must be readily available upon request in accordance with GMP and GSP (6).

7. Repackaging and relabelling

7.1 Operations, such as combining into a homogeneous batch, repackaging and/or relabelling, are manufacturing processes and are not recommended. In circumstances where they are to be conducted, their performance should be in compliance with GMP.

Note: It is important to note that any party who engages in repackaging or blending of an API is considered to be a manufacturer and must submit appropriate registration documents for such manufacturing. They must also comply with the GMP for APIs as set out in WHO Technical Report Series, No. 957, Annex 2, 2010 (4).

7.2 Special attention should be given to the following points:

- prevention of contamination, cross-contamination and mix ups;
- appropriate environmental conditions for dispensing, packaging and sampling;
- security of stocks of labels, line clearance checks, online inspections, destruction of excess batch-printed labels and label reconciliation;
- good sanitation and hygiene practices;
- maintaining batch integrity (mixing of different batches of the same solid material should normally not be done);
- as part of batch records, all labels that were removed from the original container during operations, and a sample of the new label, should be kept;
- if more than one batch of labels is used in one operation, samples of each batch should be kept;
- maintaining product identity, integrity and traceability.

7.3 Upon receipt, packaging materials should be placed in quarantine and should not be used prior to release. There should be procedures for the inspection, approval and release of the packaging materials.

- 7.4 When different batches of a material from the same original manufacturing site are received by a distributor and combined into a homogeneous batch, the conformity of each batch with its specification should be confirmed before it is added.
- 7.5 Only materials from the same manufacturing site, received by a distributor and conforming to the same specifications, can be mixed. If different batches of the same material are mixed to form a homogeneous batch it should be defined as a new batch, tested and supplied with a batch certificate of analysis. In such cases the customer should be informed that the material supplied is a mixture of manufacturers' batches.
- 7.6 In all cases, traceability back to the manufacturer should be documented by identifying the original manufacturer of the specific batch of the material and its manufacturing site.
- 7.7 If batches are combined or mixed, the oldest batch should determine the expiry or retest date assigned to the combined or mixed batch.
- 7.8 If the integrity and quality of the batch is maintained during repackaging and relabelling, then the original COA of the original manufacturer should be provided.

If retesting is done, both the original and the new COA should be provided as long as the batch integrity is maintained. The batch referred to on the new COA should be traceable to the original COA.
- 7.9 Repackaging of materials should be carried out using approved packaging materials for which the quality and suitability have been established as being equal to or better than those of the original container.
- 7.10 The reuse of containers should be discouraged unless they have been cleaned using a validated procedure. Recycled containers should not be used unless there is evidence that the quality of the material packed in them will not be adversely affected.
- 7.11 Materials should be repackaged only if efficient environmental control exists to ensure that there is no possibility of contamination, cross-contamination, degradation, physicochemical changes and/or mix ups. The quality of air supplied to the area should be suitable for the activities performed, e.g. there should be efficient filtration.
- 7.12 Suitable procedures should be followed to ensure proper label control.
- 7.13 Containers of repackaged material and relabelled containers should bear both the name of the original manufacturing site and the name of the distributor/repacker.

- 7.14 Procedures should be in place to ensure maintenance of the identity and quality of the material by appropriate means, both before and after repackaging operations.
- 7.15 Each batch of repackaged material should be tested to ensure that the material conforms to documented specifications.
- 7.16 There should be a procedure to ensure that appropriate repackaging documentation, in addition to the test results, is evaluated prior to release of the repackaged material.
- 7.17 Sampling, analytical testing and batch release procedures should be in accordance with GMP.
- 7.18 Only official pharmacopoeial methods or validated analytical test methods should be used for the analysis. Where alternatives to the test methods specified in a monograph are used to provide test results, those alternative methods should be demonstrated to be suitable and equivalent.
- 7.19 Out-of-specification test results should be investigated and documented.
- 7.20 Samples of pharmaceutical starting materials in appropriate quantities should be kept for at least one year after the expiry or retest date, or for three years after distribution is complete.
- 7.21 The repacker and relabeller should ensure that the stability of the material is not adversely affected by the repackaging or relabelling. Stability studies to justify assigned expiration or retest dates should be conducted if the pharmaceutical starting material is repackaged in a container different from that used by the original manufacturer. It is recognized that some excipients may not need additional stability studies.

8. Complaints

- 8.1 All complaints and other information concerning potentially defective materials must be carefully reviewed according to written procedures that describe the action to be taken and specify the criteria on which a decision to recall a product should be based. Records of complaints should be retained and evaluated for trends at defined intervals.
- 8.2 Any complaint concerning a material defect should be recorded and thoroughly investigated to identify the origin or reason for the complaint (e.g. the repackaging procedure or the original manufacturing process). Corrective and preventive actions should be taken where appropriate, and recorded.

- 8.3 If a defect in a pharmaceutical starting material is discovered or suspected, consideration should be given to whether other batches should be checked.
- 8.4 Where necessary, appropriate follow-up action, possibly including a recall, should be taken after investigation and evaluation of the complaint.
- 8.5 The manufacturer and customers should be informed if action is needed following possible faulty manufacturing, packaging, deterioration or any other serious quality problems with a pharmaceutical starting material.

9. Recalls

- 9.1 There should be a system for recalling promptly and effectively from the market, materials known or suspected to be defective.
- 9.2 The original manufacturer should be informed in the event of a recall.
- 9.3 There should be detailed written procedures for the organization of any recall activity. These procedure(s) should be regularly reviewed and updated.
- 9.4 All recalled materials should be stored in a secure area while their fate is decided.
- 9.5 In the event of serious or potentially life-threatening situations, all customers and competent authorities in all countries to which a given material may have been distributed should be promptly informed of any intention to recall the material.
- 9.6 All records should be readily available to the designated person(s) responsible for recalls. These records should contain sufficient information on materials supplied to customers (including exported materials).
- 9.7 The effectiveness of the arrangements for recalls should be evaluated at regular intervals.

10. Returned goods

- 10.1 Goods returned to the supplier should be appropriately identified and quarantined. The conditions under which returned goods have been stored and shipped should be evaluated to determine the quality of the returned goods.
- 10.2 The quality unit or designee should decide on the disposition of the returned goods following a formal and documented investigation process. Corrective and preventive actions should be taken where appropriate.

11. Handling of non-conforming materials

- 11.1 Non-conforming materials should be handled in accordance with a procedure that will prevent their introduction or reintroduction into the market. Records covering all activities, including destruction, disposal, return and reclassification, should be maintained.
- 11.2 An investigation should be performed to establish whether any other batches are also affected. Corrective and preventive measures should be taken where necessary.
- 11.3 The disposition of the material, including downgrading to other suitable purposes, should be documented.
- 11.4 Non-conforming materials should never be blended with materials that do comply with specifications.

12. Dispatch and transport

- 12.1 Materials should be loaded, unloaded and transported in a manner that will ensure the maintenance of controlled conditions where applicable (e.g. temperature, protection from the environment). The transport process should not adversely affect the materials. Any carrier used for transport should be approved according to a written procedure unless the carrier has been selected by the customer.
- 12.2 Requirements for special transport and/or storage conditions should be stated on the label and/or in the transport documentation. If the pharmaceutical starting material is intended to be transferred outside the control of the manufacturer's materials management system, the name and address of the manufacturer, quality of contents, special transport conditions and any special legal requirements should also be included on the label and/or in the transport documentation.
- 12.3 The supplier of the materials should ensure that the contract acceptor for transportation of the materials is aware of and provides the appropriate storage and transport conditions, e.g. through audits.
- 12.4 Procedures should be in place to ensure proper cleaning and prevention of cross-contamination when liquids (tanks) and bulk or packed materials are transported.
- 12.5 The bulk transport of pharmaceutical starting materials requires numerous precautions to avoid contamination and cross-contamination. The best practice is to use dedicated equipment, tanks or containers.
- 12.6 Packaging materials and transportation containers should be suitable to prevent damage to the pharmaceutical starting materials during transport.

- 12.7 For bulk transport, validated cleaning procedures should be used between loadings, and a list of restricted previous cargoes must be supplied to the transport companies.
- 12.8 Steps should be taken to prevent unauthorized access to the materials being transported.
- 12.9 General international requirements regarding safety aspects (e.g. prevention of explosion and of contamination of the environment) should be observed.

13. Contract activities

- 13.1 Any activity performed, as referenced in the GMP and GTDP guidelines, delegated to another party, should be agreed upon in a written contract.
- 13.2 The contract giver should evaluate the proposed contract acceptor's compliance with GTDP before entering into an agreement.
- 13.3 All contract acceptors should comply with the requirements in these guidelines. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.
- 13.4 There should be a written and approved contract or formal agreement between the contract giver and contract acceptor that addresses and defines in detail the responsibilities with respect to GTDP and which party is responsible for which quality measures.
- 13.5 Subcontracting may be permissible under certain conditions, subject to approval by the contract giver, especially for activities such as sampling, analysis, repacking and relabelling.

References

- 1. ICH harmonised tripartite guideline: Good manufacturing practice guide for active pharmaceutical ingredients – Q7. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2000.
- 2. Good trade and distribution practices for pharmaceutical starting materials. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-eighth report. Geneva: World Health Organization; 2004: Annex 2 (WHO Technical Report Series, No. 917; https://iris.who.int/bitstream/handle/10665/42851/WHO_TRS_917.pdf?sequence=1&isAllowed=y).
- 3. Good manufacturing practice: supplementary guidelines for the manufacture of pharmaceutical excipients. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-fifth report. Geneva: World Health Organization; 1999: Annex 5 (WHO Technical Report Series, No. 885; https://iris.who.int/bitstream/handle/10665/42145/WHO_TRS_885.pdf?sequence=1&isAllowed=y).

4. Good manufacturing practices for active pharmaceutical ingredients. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 2 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y).
5. WHO good distribution practices for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 5 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y).
6. Guide to good storage practices for pharmaceuticals. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-seventh report. Geneva: World Health Organization; 2003: Annex 9 (WHO Technical Report Series, No. 908; https://iris.who.int/bitstream/handle/10665/42613/WHO_TRS_908.pdf?sequence=1&isAllowed=y).

8.5 Good storage and distribution practices for medical products

Annex 7, WHO Technical Report Series, 1025, 2020 (revised)

1. Introduction	1310
2. Scope	1311
3. Glossary	1311
4. General principles	1316
5. Quality management	1317
6. Quality risk management	1318
7. Management review	1318
8. Complaints	1318
9. Returned goods	1319
10. Recalls	1320
11. Self-inspection	1321
12. Premises	1321
13. Stock control and rotation	1325
14. Equipment	1325
15. Qualification and validation	1325
16. Personnel	1326
17. Documentation	1327
18. Activities and operations	1328
19. Outsourced activities	1333
20. Substandard and falsified products	1334
21. Inspection of storage and distribution facilities	1334
References	1335
Further reading	1336
Appendix 1 Recommended storage conditions	1338

1. Introduction

- 1.1 Storage and distribution are important activities in the supply chain management of medical products. Various people and entities may be responsible for the handling, storage and distribution of medical products. Medical products may be subjected to various risks at different stages in the supply chain, for example, purchasing, storage, repackaging, relabelling, transportation and distribution.
- 1.2 Substandard and falsified products are a significant threat to public health and safety. Consequently, it is essential to protect the supply chain against the penetration of such products.
- 1.3 This document sets out steps to assist in fulfilling the responsibilities involved in the different stages within the supply chain and to avoid the introduction of substandard and falsified products into the market. The relevant sections should be considered as particular roles that entities play in the storage and distribution of medical products.
- 1.4 This guideline is intended to be applicable to all entities involved in any aspect of the storage and distribution of medical products, from the premises of the manufacturer of the medical product to his or her agent, or the person dispensing or providing medical products directly to a patient. This includes all entities involved in different stages of the supply chain of medical products; manufacturers and wholesalers, as well as brokers, suppliers, distributors, logistics providers, traders, transport companies and forwarding agents and their employees.
- 1.5 The relevant sections of this guideline should also be considered for implementation by, amongst others, governments, regulatory bodies, international procurement organizations, donor agencies and certifying bodies, as well as all health-care workers.
- 1.6 This guideline can be used as a tool in the prevention of distribution of substandard and falsified products. It should, however, be noted that these are general guidelines that may be adapted to suit the prevailing situations and conditions in individual countries. National or regional guidelines may be developed to meet specific needs and situations in a particular region or country.
- 1.7 To maintain the quality of medical products, every party that is active in the supply chain has to comply with the applicable legislation and regulations. Every activity in the storage and distribution of medical products should be carried out according to the principles of good manufacturing practices (GMP) (1) or applicable standard such as ISO 13485 for medical devices (2); good storage practices (GSP) (3); and good distribution practices (GDP) (4), as applicable.

- 1.8 This guideline does not deal with dispensing to patients, as this is addressed in the *Joint FIP/WHO* (International Pharmaceutical Federation/World Health Organization) *guidelines on good pharmacy practice* (GPP) (5).
- 1.9 This guideline should also be read in conjunction with other WHO guidelines, for example those listed at the end of the document under References and Further reading.

2. Scope

- 2.1 This document lays down guidelines for the storage and distribution of medical products. It is closely linked to other existing guidelines recommended by the WHO Expert Committee on Specifications for Pharmaceutical Preparations, for example those listed at the end of the document under References and Further reading.
- 2.2 Depending on the national and regional legislation, these guidelines may apply equally to pharmaceutical products for human and veterinary use, and other medical products, where applicable.
- 2.3 The document does not specifically cover GMP aspects of finished products in bulk, distribution of labels, or packaging, as these aspects are considered to be covered by other guidelines. The principles for the distribution of starting materials (active pharmaceutical ingredients [APIs] and excipients) are also not covered here. These are laid down in the WHO document *Good trade and distribution practices for pharmaceutical starting materials* (6).

3. Glossary

The definitions given below apply to the terms used in this guideline that are not defined in existing WHO terms and definitions databases. They may have different meanings in other contexts and documents.

active pharmaceutical ingredient (API). Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when used in the production of a drug, becomes an active ingredient of that drug. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

auditing. An independent and objective activity designed to add value and improve an organization's operations by helping it to accomplish its objectives, using a systematic, disciplined approach to evaluate and improve the effectiveness of risk management, control and governance processes.

batch. A defined quantity of pharmaceutical products processed in a single process or series of processes, so that it is expected to be homogeneous.

batch number. A distinctive combination of numbers and/or letters that uniquely identifies a batch, for example, on the labels, its batch records and corresponding certificates of analysis.

broker. A person or organization that arranges transactions in relation to the sale or purchase of medical products that consist of negotiating, independently and on behalf of another legal or natural person, and that do not include physical handling.

consignment. The quantity of medical products supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include pharmaceutical products belonging to more than one batch.

container. The material employed in the packaging of a medical product. Containers include primary, secondary and transportation containers. Containers are referred to as primary if they are intended to be in direct contact with the product. Secondary containers are not intended to be in direct contact with the product.

contamination. The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a starting material, intermediate or pharmaceutical product during handling, production, sampling, packaging or repackaging, storage or transportation.

contract. Business agreement for the supply of goods or performance of work at a specified price; this may include quality elements in the agreement, or in a separate contract.

corrective and preventative actions (CAPA). A system for implementing corrective and preventive actions resulting from an investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings and trends from process performance and product quality monitoring.

cross-contamination. Contamination of a starting material, intermediate product or finished pharmaceutical product or medical product with another starting material or product, during production, storage and transportation.

distribution. The procuring, purchasing, holding, storing, selling, supplying, importing, exporting or movement of medical products, with the exception of dispensing or providing medical products directly to a patient or his or her agent.

excipient. A substance, other than the active ingredient, which has been appropriately evaluated for safety and is included in a drug delivery system, to aid in the processing of the drug delivery system during its manufacture; protect, support or enhance stability,

bioavailability, or patient acceptability; assist in product identification; or enhance any other attribute of the overall safety and effectiveness of the drug during storage or use.

expiry date. The date given on the individual container (usually on the label) of a medical product, up to and including the date on which the product is expected to remain within specifications if stored correctly. It is established for each batch by adding the shelf-life to the date of manufacture.

falsified product. A product that has been deliberately and/or fraudulently misrepresented as to its identity, composition or source. Such deliberate/fraudulent misrepresentation refers to any substitution, adulteration or reproduction of an authorized product, or the manufacture of a product that is not an authorized product.

“Identity” shall refer to the name, labelling or packaging or to documents that support the authenticity of an authorized product. “Composition” shall refer to any ingredient or component of the product in accordance with applicable specifications authorized/recognized by the national regulatory authority (NRA). “Source” shall refer to the identification, including name and address, of the marketing authorization holder, manufacturer, importer, exporter, distributor or retailer, as applicable (7).

first expiry/first out (FEFO). A distribution procedure that ensures that the stock with the earliest expiry date is distributed and/or used before an identical stock item with a later expiry date is distributed and/or used.

forwarding agent. A person or entity engaged in providing, either directly or indirectly, any service concerned with clearing and forwarding operations in any manner to any other person; this includes a consignment agent.

good distribution practices (GDP). That part of quality assurance that ensures that the quality of a medical product is maintained by means of adequate control of the numerous activities that occur during the trade and distribution process, as well as providing a tool to secure the distribution system from falsified, unapproved, illegally imported, stolen, substandard, adulterated and/or misbranded medical products.

good manufacturing practices (GMP). That part of quality assurance that ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

good pharmacy practice (GPP). The practice of pharmacy aimed at providing and promoting the best use of medicines and other health-care services and products by patients and members of the public. It requires that the welfare of the patient is the pharmacist's prime concern at all times.

good practices (GXP). The group of good practice guides governing the preclinical, clinical, manufacture, testing, storage, distribution and post-market activities for

regulated medical products, such as good laboratory practices (GLP), good clinical practices (GCP), good manufacturing practices (GMP), good pharmacy practice (GPP), good distribution practices (GDP) and other good practices.

good storage practices (GSP). That part of quality assurance that ensures that the quality of medical products is maintained by means of adequate control throughout the storage thereof.

heating, ventilation and air conditioning systems. Heating, ventilation and air conditioning, also referred to as environmental control systems.

importation. The act of bringing or causing any goods to be brought into a customs territory (national territory, excluding any free zone).

intermediate product. Partly processed product that must undergo further manufacturing steps before it becomes a bulk finished product.

labelling. The process of identifying a medical product, including the following information, as appropriate: name of the product; active ingredient(s), type and amount; batch number; expiry date; special storage conditions or handling precautions; directions for use, warnings and precautions; and names and addresses of the manufacturer and/or supplier.

manufacture. All operations of purchase of materials and products, production, packaging, labelling, quality control, release, and storage of medical products and the related controls.

marketing authorization. A legal document issued by the NRA for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy, performance (where applicable) and quality. It must set out, inter alia, the name of the product, the pharmaceutical dosage form; the quantitative formula (including excipients) per unit dose (using International Nonproprietary Names or national generic names where they exist); the shelf-life and storage conditions; and packaging characteristics, or other details as required by the product category. It specifies the information on which authorization is based (e.g. “The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence”). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization and the period of validity of the authorization. Once a product has been given marketing authorization, it is included on a list of authorized products – the register – and is often said to be “registered” or to “have registration”. Market authorization may occasionally also be referred to as a “licence” or “product licence”.

material. A general term used to denote starting materials (APIs and excipients), reagents, solvents, process aids, intermediates, packaging materials and labelling materials.

medical products. Products including, but not limited to, finished pharmaceutical products, medical devices including in vitro diagnostic medical devices, and vaccines.

packaging material. Any material, including printed material, employed in the packaging of a medical product, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary, according to whether or not they are intended to be in direct contact with the product.

pedigree. A complete record that traces the ownership of, and transactions relating to, a medical product as it is distributed through the supply chain.

pharmaceutical product. Any product intended for human use, or veterinary product intended for administration to food-producing animals, presented in its finished dosage form, which is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required; products that may be sold to patients without a prescription; biologicals; and vaccines. It does not, however, include medical devices.

product recall. A process for withdrawing or removing a medical product from the distribution chain because of defects in the product, complaints of serious adverse reactions to the product and/or concerns that the product is or may be falsified. The recall might be initiated by the manufacturer, importer, wholesaler, distributor or a responsible agency.

production. All operations involved in the preparation of a medical product, from receipt of materials through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

quality assurance. A wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that medical products are of the quality required for their intended use.

quality risk management. A systematic process for the assessment, control, communication and review of risks to the quality of medical products in the supply chain.

quality system. An appropriate infrastructure, encompassing the organizational structure, procedures, processes, resources and systematic actions necessary to ensure adequate confidence that a product (or services) will satisfy given requirements for quality.

quarantine. The status of medical products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing.

retest date. The date when a material should be re-examined to ensure that it is still suitable for use.

sampling. Operations designed to obtain a representative portion of a medical product, based on an appropriate statistical procedure, for a defined purpose, for example, acceptance of consignments or batch release.

self-inspection. An internal procedure followed to evaluate the entity's compliance with GSP and GDP, as well as GXP in all areas of activities, designed to detect any shortcomings and to recommend and implement necessary corrective actions.

shelf-life. The period of time during which a medical product, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf-life is used to establish the expiry date of each batch.

standard operating procedure (SOP). An authorized written procedure giving instructions for performing operations that are not necessarily specific to a given product but of a more general nature (e.g. equipment operation, maintenance and cleaning, validation, cleaning of premises, environmental control, sampling and inspection).

storage. The storing of medical products up to the point of use.

substandard products. "Substandard" medical products (also called "out of specification") are authorized by NRAs but fail to meet either national or international quality standards or specifications – or, in some cases, both.

supplier. A person or entity engaged in the activity of providing products and/or services.

transit. The period during which medical products are in the process of being carried, conveyed or transported across, over or through a passage or route to reach their destination.

vehicles. Trucks, vans, buses, minibuses, cars, trailers, aircraft, railway carriages, boats and other means that are used to convey medical products.

4. General principles

- 4.1 There should be collaboration between all entities, including governments, customs agencies, law enforcement agencies, regulatory authorities, manufacturers, distributors and entities responsible for the supply of medical products to patients, to ensure the quality and safety of medical products; to prevent the exposure of patients to substandard and falsified products; and to ensure that the integrity of the distribution chain is maintained.

- 4.2 The principles of GSP and GDP should be included in national legislation and guidelines for the storage and distribution of medical products in a country or region, as applicable, as a means of establishing minimum standards. The principles of GSP and GDP are applicable to:
- medical products moving forward in the distribution chain from the manufacturer;
 - medical products that are moving backwards in the chain, for example, as a result of the return or recall thereof; and
 - donations of medical products.

5. Quality management

- 5.1 Entities involved in the storage and distribution of medical products should have a comprehensively designed, documented and correctly implemented quality system that incorporates GSP, GDP, principles of quality risk management and management review.
- 5.2 Senior management has the ultimate responsibility to ensure that an effective quality system is established, resourced, implemented and maintained.
- 5.3 The quality system should ensure that:
- GSP and GDP are adopted and implemented to ensure that the quality of medical products is maintained throughout their shelf-life in the supply chain; and medical products are appropriately procured, stored, distributed and delivered (in compliance with the legislation) to the appropriate recipients (see Section 18.1);
 - operations are clearly specified in written procedures;
 - responsibilities are clearly specified in job descriptions;
 - all risks are identified and necessary, effective controls are implemented;
 - processes are in place to assure the management of outsourced activities;
 - there is a procedure for self-inspection and quality audits;
 - there is a system for quality risk management;
 - there are systems for managing returns, complaints and recalls; and
 - there are systems to manage changes, deviations and corrective and preventive actions (CAPAs).
- 5.4 There should be an authorized, written quality policy describing the overall intentions and requirements regarding quality. This may be reflected in a quality manual.

- 5.5 There should be an appropriate organizational structure. This should be presented in an authorized organizational chart. The responsibility, authority and interrelationships of personnel should be clearly indicated.
- 5.6 Roles and responsibilities should be clearly defined and understood by the individuals concerned, and recorded as written job descriptions.
- 5.7 The quality system should include appropriate procedures, processes and resources.

6. Quality risk management

- 6.1 There should be a system to assess, control, communicate and review risks identified at all stages in the supply chain.
- 6.2 The evaluation of risk should be based on scientific knowledge and experience and ultimately be linked to the protection of the patient.
- 6.3 Appropriate controls should be developed and implemented to address all risks. The effectiveness of the controls implemented should be evaluated at periodic intervals.

7. Management review

- 7.1 There should be a system for periodic management review. The review should include at least:
 - senior management;
 - review of the quality system and its effectiveness by using quality metrics and key performance indicators;
 - identification of opportunities for continual improvement; and
 - follow-up on recommendations from previous management review meetings.
- 7.2 Minutes and related documentation from management review meetings should be available.

8. Complaints

- 8.1 There should be a written procedure for the handling of complaints. In the case of a complaint about the quality of a medical product or its packaging, the original manufacturer and/or marketing authorization holder should be informed as soon as possible.

- 8.2 All complaints should be recorded and appropriately investigated. The root cause should be Identified, and the impact (e.g. on other batches or products) risk-assessed. Appropriate CAPAs should be taken.
- 8.3 Where required, the information should be shared with the NRA and a recall initiated where appropriate.
- 8.4 A distinction should be made between complaints about a medical product or its packaging and those relating to distribution.
- 8.5 The relevant information, such as the results of the investigation of the complaint, should be shared with the relevant entities.
- 8.6 Medical product quality problems and suspected cases of substandard or falsified products identified should be handled according to relevant authorized procedures. The information should be shared with the manufacturer and appropriate national and/or regional regulatory authorities, without delay.

9. Returned goods

- 9.1 Returned medical products should be handled in accordance with authorized procedures.
- 9.2 All returned medical products should be placed in quarantine upon receipt. The status of the goods should be clear. Precautions should be taken to prevent access and distribution until a decision has been taken with regard to their disposition. The particular storage conditions applicable to the medical products should be maintained until their disposition.
- 9.3 Medical products returned should be destroyed unless it is certain that their quality is satisfactory, after they have been critically assessed in accordance with a written and authorized procedure.
- 9.4 The nature of the medical product, any special storage conditions it requires, its condition and history and the time lapse since it was issued, should all be taken into account in this assessment. Where any doubt arises over the quality of the medical product, it should not be considered suitable for reissue or reuse. Any action taken should be appropriately recorded.
- 9.5 When handling returned goods, the following considerations at least should be taken:
 - a risk-based process should be followed when deciding on the fate of the returned goods. This should include, but not be limited to, the nature of

the product, storage conditions, condition of the product history, time-lapse since distribution and the manner and condition of transport while being returned;

- the terms and conditions of the agreement between the parties; and
- examination of the returned goods, with decisions taken by suitably qualified, experienced and authorized persons.

- 9.6 Where products are rejected, authorized procedures should be followed, including safe transport.
- 9.7 Destruction of products should be done in accordance with international, national and local requirements regarding disposal of such products, and with due consideration to the protection of the environment.
- 9.8 Records of all returned, rejected and destroyed medical products should be kept for a defined period, in accordance with national requirements.

10. Recalls

- 10.1 There should be a written procedure, in compliance with national or regional requirements, to effectively and promptly recall medical products.
- 10.2 The effectiveness of the procedure should be checked annually and updated as necessary.
- 10.3 The original manufacturer and/or marketing authorization holder, or other relevant contract party, should be informed in the event of a recall.
- 10.4 Information on a recall should be shared with the appropriate national or regional regulatory authority.
- 10.5 All recalled products should be secure, segregated, transported and stored under appropriate conditions. These should be clearly labelled as recalled products. The particular storage conditions applicable to the product should be maintained where possible.
- 10.6 All customers and competent authorities of all countries to which a given medical product may have been distributed should be informed promptly of the recall of the product.
- 10.7 All records, including distribution records, should be readily accessible to the designated person(s) responsible for recalls. These records should contain sufficient information on products supplied to customers (e.g. name, address, contact detail, batch numbers, quantities and safety features – including exported products).

- 10.8 The progress of a recall process should be recorded and a final report issued, which includes a reconciliation between delivered and recovered quantities of medical products.

11. Self-inspection

- 11.1 The quality system should include self-inspections. These should be conducted to monitor the implementation, compliance with and effectiveness of SOPs, as well as compliance with regulations, GSP, GDP and other appropriate guidelines.
- 11.2 Self-inspections should be conducted periodically, according to an annual schedule.
- 11.3 The team conducting the inspection should be free from bias and individual members should have appropriate knowledge and experience.
- 11.4 The results of all self-inspections should be recorded. Reports should contain all observations made during the inspection and presented to the relevant personnel and management.
- 11.5 Necessary CAPAs should be taken and their effectiveness should be reviewed within a defined timeframe.

12. Premises

General

- 12.1 Premises should be suitably located, designed, constructed and maintained, to ensure appropriate operations such as receiving, storage, picking, packing and dispatch of medical products.
- 12.2 There should be sufficient space, lighting and ventilation to ensure required segregation, appropriate storage conditions and cleanliness.
- 12.3 Sufficient security should be provided and access should be controlled.
- 12.4 Appropriate controls and segregation should be provided for products requiring specific handling or storage conditions, such as radioactive materials, products containing hazardous substances and products to be stored under controlled temperature and relative humidity conditions.
- 12.5 Where possible, receiving and dispatch bays should be separate, to avoid mix-ups. Bays should protect products from weather conditions.
- 12.6 Activities relating to receiving and dispatch should be done in accordance with authorized procedures. Areas should be suitably equipped for the operations.

- 12.7 Premises should be kept clean. Cleaning equipment and cleaning agents should not become possible sources of contamination.
- 12.8 Premises should be protected from the entry of birds, rodents, insects and other animals. A rodent and pest control programme should be in place.
- 12.9 Toilets, washing, rest and canteen facilities should be separate from areas where products are handled. Food, eating, drinking and smoking should be prohibited in all areas where medical products are stored or handled.

Receiving area

- 12.10 Each incoming delivery should be checked against the relevant documentation, to ensure that the correct product is delivered from the correct supplier. This may include, for example, the purchase order, containers, label description, batch number, expiry date, product and quantity.
- 12.11 The consignment should be examined for uniformity of the containers and, if necessary, should be subdivided according to the supplier's batch number should the delivery comprise more than one batch. Each batch should be dealt with separately.
- 12.12 Each consignment should be carefully checked for possible contamination, tampering and damage. A representative number of containers in a consignment should be sampled and checked according to a written procedure. Any suspect containers or, if necessary, the entire delivery, should be quarantined for further investigation.
- 12.13 Receiving areas should be of sufficient size to allow the cleaning of incoming medical products.
- 12.14 When required, samples of medical products should be taken by appropriately trained and qualified personnel and in strict accordance with a written sampling procedure and sampling plans. Containers from which samples have been taken should be labelled accordingly.
- 12.15 Following sampling, the goods should be subject to quarantine. Batch segregation should be maintained during quarantine and all subsequent storage.
- 12.16 Materials and products requiring transport and storage under controlled conditions of temperature and relative humidity, as applicable, should be handled as a priority. The transportation temperature data, where appropriate, should be reviewed upon receipt, to ensure that the required conditions had been maintained. Where applicable, cold-chain materials and products should be handled according to the approved conditions by the authority, or as recommended by the manufacturer, as appropriate.

- 12.17 Medical products should not be transferred to saleable stock until an authorized release is obtained.
- 12.18 Measures should be taken to ensure that rejected medical products cannot be used. They should be segregated and securely stored while awaiting destruction or return to the supplier.

Storage areas

- 12.19 Precautions should be taken to prevent unauthorized persons from entering storage areas.
- 12.20 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of medical products.
- 12.21 Storage areas should be appropriately designed, constructed, maintained or adapted. They should be kept clean and there should be sufficient space and lighting.
- 12.22 Storage areas should be maintained within acceptable and specified temperature limits. Where the labels show special storage conditions are required (e.g. temperature, relative humidity), these should be provided, controlled, monitored and recorded.
- 12.23 Materials and medical products should be stored off the floor, away from walls and ceilings, protected from direct sunlight and suitably spaced, to permit ventilation, cleaning and inspection. Suitable pallets should be used and kept in a good state of cleanliness and repair.
- 12.24 A written sanitation programme should be available, indicating the frequency of cleaning and the methods to be used to clean the premises and storage areas.
- 12.25 There should be appropriate procedures for the clean-up of any spillage, to ensure complete removal of any risk of contamination.
- 12.26 Where the status is ensured by storage in separate areas, these areas should be clearly marked and their access restricted to authorized personnel. Any system replacing physical separation and labelling or demarcation should provide equivalent security. For example, computerized systems can be used, provided that they are validated to demonstrate security of access (8).
- 12.27 Sampling should be done under controlled conditions and conducted in such a way that there is no risk of contamination or cross-contamination. Adequate cleaning procedures should be followed after sampling.

- 12.28 Certain materials and products, such as highly active and radioactive materials, narcotics and other hazardous, sensitive and/or dangerous materials and products, as well as substances presenting special risks of abuse, fire or explosion (e.g. combustible liquids and solids and pressurized gases), should be stored in a dedicated area that is subject to appropriate additional safety and security measures, and in accordance with national legislation.
- 12.29 Materials and medical products should be handled and stored in such a manner as to prevent contamination, mix-ups and cross-contamination.
- 12.30 Materials and medical products should be stored in conditions that assure that their quality is maintained. Stock should be appropriately rotated. The “first expired/first out” (FEFO) principle should be followed.
- 12.31 Narcotic medical products should be stored in compliance with international conventions, national laws and regulations on narcotics.
- 12.32 Broken or damaged items should be withdrawn from usable stock and separated.
- 12.33 There should be a written procedure for fire control, including prevention of fire, fire detection and fire drills. Fire-detection and firefighting equipment should be available and should be serviced regularly.

Storage conditions

- 12.34 The storage conditions for medical products should be in compliance with their labelling and information provided by the manufacturer.
- 12.35 Heating, ventilation and air conditioning systems should be appropriately designed, installed, qualified and maintained, to ensure that the required storage conditions are upheld (9).
- 12.36 Mapping studies for temperature, and relative humidity where appropriate, should be done, for example in storage areas, refrigerators and freezers (10).
- 12.37 Temperature and relative humidity, as appropriate, should be controlled and monitored at regular intervals. Data should be recorded and the records should be reviewed. The equipment used for monitoring should be calibrated and be suitable for its intended use. All records pertaining to mapping and monitoring should be kept for a suitable period of time and as required by national legislation.

Note: See Appendix 1 for recommended storage conditions.

13. Stock control and rotation

- 13.1 Records of stock levels for all medical products in store should be maintained, in either paper or electronic format. These records should be updated after each operation (e.g. entries, issues, losses, adjustments). These records should be kept for a suitable period of time and as required by national legislation. Periodic stock reconciliation should be performed at defined intervals, by comparing the actual and recorded stock.
- 13.2 The root cause for stock discrepancies should be identified and appropriate CAPAs taken to prevent recurrence.
- 13.3 When damaged containers are received, this should be brought to the attention of the person responsible for quality. Any action taken should be documented. (These containers should not be issued unless the quality of the medical products has been shown to be unaffected.)
- 13.4 All stock should be checked at regular intervals, to identify those items that are close to their retest or expiry date. Appropriate action should be taken, such as removal of these items from useable stock.

14. Equipment

- 14.1 Equipment, including computerized systems, should be suitable for its intended use. All equipment should be appropriately designed, located, installed, qualified and maintained.
- 14.2 Computerized systems should be capable of achieving the desired output and results.
- 14.3 Where electronic commerce (e-commerce) is used, i.e. electronic means for any of the steps, defined procedures and adequate systems should be in place to ensure traceability and confidence in the supply chain and products concerned.
- 14.4 Electronic transactions (including those conducted via the Internet) relating to the distribution of medical products should be performed only by authorized persons, according to defined and authorized access and privileges.
- 14.5 Where GXP systems are used, these should meet the requirements of WHO or other appropriate guidelines on computerized systems (8, 11).

15. Qualification and validation

- 15.1 The scope and extent of qualification, and validation where appropriate, should be determined using documented risk management principles.

- 15.2 Premises, utilities, equipment and instruments, processes and procedures should be considered.
- 15.3 Qualification and validation should be done following procedures and protocols. The results and outcome of the qualification and validation should be recorded in reports. Deviations should be investigated and the completion of the qualification and validation should be concluded and approved.

16. Personnel

- 16.1 There should be an adequate number of personnel.
- 16.2 Personnel should have appropriate educational qualification, experience and training relative to the activities undertaken.
- 16.3 A designated person within the organization, with appropriate qualification and training, should have the defined authority and responsibility for ensuring that a quality management system is implemented and maintained. This person should preferably be independent from the person responsible for operations and should ensure compliance with GSP and GDP.
- 16.4 Personnel should have the authority and resources needed to carry out their duties and to follow the quality systems, as well as to identify and correct deviations from the established procedures.
- 16.5 There should be arrangements in place to ensure that management and personnel are not subjected to commercial, political, financial or other pressures or conflict of interest that may have an adverse effect on the quality of service provided or on the integrity of medical products.
- 16.6 Safety procedures should be in place relating to all relevant personnel and property, environmental protection and product integrity.
- 16.7 Personnel should receive initial and continued training in accordance with a written training programme. The training should cover the requirements of GSP and GDP (as applicable), as well as on-the-job training. Other topics should be included, such as product security, product identification and the detection of falsified products.
- 16.8 Personnel dealing with hazardous products (such as highly active materials, radioactive materials, narcotics and other hazardous, environmentally sensitive and/or dangerous pharmaceutical products, as well as products presenting special risks of abuse, fire or explosion) should be given specific training.

- 16.9 Personnel should be trained in, and observe high levels of, personal hygiene and sanitation.
- 16.10 Records of all training, attendance and assessments should be kept.
- 16.11 Personnel handling products should wear garments suitable for the activities that they perform. Personnel dealing with hazardous pharmaceutical products, including products containing materials that are highly active, toxic, infectious or sensitizing, should be provided with protective garments as necessary.
- 16.12 Appropriate procedures relating to personnel hygiene, relevant to the activities to be carried out, should be established and observed. Such procedures should cover health, hygiene and the clothing of personnel.
- 16.13 Procedures and conditions of employment for employees, including contract and temporary staff, and other personnel having access to medical products, must be designed and implemented to assist in minimizing the possibility of such products coming into the possession of unauthorized persons or entities.
- 16.14 Codes of practice and procedures should be in place to prevent and address situations where persons involved in the storage and distribution of medical products are suspected of, or found to be implicated in, any activities relating to the misappropriation, tampering, diversion or falsification of any product.

17. Documentation

- 17.1 Documentation includes all procedures, records and data, whether in paper or electronic form. Documents should be appropriately designed, completed, reviewed, authorized, distributed and kept as required. Documents should be readily available.
- 17.2 Written procedures should be followed for the preparation, review, approval, use of and control of all documents relating to the policies and activities for the process of storage and distribution of medical products.
- 17.3 Documents should be laid out in an orderly fashion and be easy to complete, review and check. The title, scope, objective and purpose of each document should be clear.
- 17.4 All documents should be completed, signed and dated as required by authorized person(s) and should not be changed without the necessary authorization.
- 17.5 Documentation should be prepared and maintained in accordance with the national legislation and principles of good documentation practices (11).

- 17.6 Records should be accurate, legible, traceable, attributable and unambiguous. Electronic data should be backed-up in accordance with written procedures. Records should be maintained for the back-up and restoration of data.
- 17.7 Procedures for the identification, collection, indexing, retrieval, storage, maintenance, disposal of and access to all applicable documentation should be followed.
- 17.8 Documents should be reviewed regularly and kept up-to-date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version.
- 17.9 All records should be stored and retained using facilities that prevent unauthorized access, modification, damage, deterioration and/or loss of documentation during the entire life-cycle of the record. Records must be readily retrievable.
- 17.10 Comprehensive records should be maintained for all receipts, storage, issues and distribution. The records should include, for example:
 - date (e.g. receipt or dispatch, as appropriate);
 - name and description of the product;
 - quantity received, or supplied;
 - name and address of the supplier and customer;
 - batch number(s);
 - expiry date;
 - suitability of the supplier;
 - qualification of suppliers; and
 - customer qualification.
- 17.11 All containers should be clearly labelled with at least the name of the medical product, batch number, expiry date or retest date, and the specified storage conditions.

18. Activities and operations

- 18.1 All activities and operations should be conducted in accordance with national legislation, GSP, GDP and associated guidelines.
- 18.2 Storage and distribution of medical products should be done by persons authorized to do so, in accordance with national legislation.
- 18.3 Activities and operations should be performed in accordance with documented procedures.

- 18.4 Automated storage and retrieval systems and operations should comply with current GSP, GDP and GXP guidelines, as well as the recommendations in this guideline.

Receipt

- 18.5 Medical products should be procured from appropriately authorized suppliers.
- 18.6 Deliveries should be examined for damage, seal intactness, signs of tampering, labelling, completeness of order and other related aspects (e.g. availability of a certificate of analysis, where applicable), at the time of receiving.
- 18.7 Containers and consignments that do not meet acceptance criteria at the time of receipt should be labelled, kept separate and investigated. This includes suspected falsified products.

Storage

- 18.8 Medical products requiring specific storage conditions, or controlled access (e.g. narcotics), should be processed without delay and stored in accordance with their requirements.
- 18.9 Appropriate controls should be implemented to prevent contamination and/or mix-ups during storage.
- 18.10 Controls and procedures should be in place to prevent and handle spillage and breakage.

Repackaging and relabelling

- 18.11 Repackaging and relabelling of materials and products are not recommended. Where repackaging and relabelling occur, these activities should only be performed by entities appropriately authorized to do so and in compliance with the applicable national, regional and international requirements, and in accordance with GMP.
- 18.12 Procedures should be in place for the controlled disposal of original packaging, to prevent re-use thereof.

Distribution and transport

- 18.13 Medical products should be transported in accordance with the conditions stated on the labels and described by the manufacturer. The risk to the quality of the medical product during transport and distribution should be eliminated or minimized to an acceptable level.

- 18.14 Product, batch and container identity should be maintained at all times.
- 18.15 All labels should remain legible.
- 18.16 Distribution records should be sufficiently detailed to allow for a recall when required.
- 18.17 Drivers of vehicles should be identified and present appropriate documentation to demonstrate that they are authorized to transport medical products.
- 18.18 Vehicles should be suitable for their purpose, with sufficient space and appropriately equipped to protect medical products.
- 18.19 The design and use of vehicles and equipment must aim to minimize the risk of errors and permit effective cleaning and/or maintenance, to avoid contamination, build-up of dust or dirt and/or any adverse effect on the quality of the products.
- 18.20 Where feasible, consideration should be given to adding technology, such as global positioning system (GPS) electronic tracking devices and engine-kill buttons to vehicles, which would enhance the security and traceability of vehicles with products.
- 18.21 Where possible, dedicated vehicles and equipment should be used for medical products. Where non-dedicated vehicles and equipment are used, procedures should be in place to ensure that the quality of the products will not be compromised. Defective vehicles and equipment should not be used. These should either be labelled as such or removed from service.
- 18.22 There should be procedures in place for the operation and maintenance of all vehicles and equipment.
- 18.23 Equipment and materials used for the cleaning of vehicles should not become a source of contamination or have an adverse effect on product quality.
- 18.24 Vehicles used for transportation of medical products should be qualified, where applicable, to demonstrate their capability to maintain the required transport conditions. There should be a maintenance programme for the cooling/heating system.
- 18.25 Appropriate environmental conditions should be maintained, monitored and recorded. All monitoring records should be kept for a defined period of time, as required by national legislation. Records of monitoring data should be made available for inspection by the regulatory or other oversight body.
- 18.26 Instruments used for monitoring conditions, for example, temperature and humidity, within vehicles and containers should be calibrated at regular intervals.

- 18.26 Rejected, recalled and returned products, as well as those suspected as being falsified, should be securely packaged, clearly labelled and accompanied by the appropriate supporting documentation.
- 18.27 Measures should be in place to prevent unauthorized persons from entering and/or tampering with vehicles and/or equipment, as well as to prevent the theft or misappropriation thereof.
- 18.28 Shipment containers should have no adverse effect on the quality of the medical products and should offer adequate protection to materials and these products. Containers should be labelled indicating, for example, handling and storage conditions, precautions, contents and source, and safety symbols, as appropriate.
- 18.29 Special care should be taken when using dry ice and liquid nitrogen in shipment containers, owing to safety issues and possible adverse effects on the quality of medical products.
- 18.30 Written procedures should be available for the handling of damaged and/or broken shipment containers. Particular attention should be paid to those containing potentially toxic and hazardous products.

Dispatch

- 18.31 There should be documented, detailed procedures for the dispatch of products.
- 18.32 Medical products should only be sold and/or distributed to persons or entities that are authorized to acquire such products in accordance with the applicable national legislation and marketing authorization. Written proof of such authorization, or an import permit or equivalent where there is no marketing authorization, must be obtained prior to the distribution of products to such persons or entities.
- 18.33 Dispatch and transportation should be undertaken only after the receipt of a valid order, which should be documented.
- 18.34 Records for the dispatch of products should be prepared and should include information such as, but not limited to:
 - date of dispatch;
 - complete business name and address (no acronyms), type of entity responsible for the transportation, telephone number, names of contact persons;
 - status of the addressee (e.g. retail pharmacy, hospital or community clinic);
 - a description of the products, including, for example, name, dosage form and strength (if applicable);

- quantity of the products, i.e. number of containers and quantity per container (if applicable);
 - applicable transport and storage conditions;
 - a unique number to allow identification of the delivery order; and
 - assigned batch number and expiry date (where not possible at dispatch, this information should at least be kept at receipt, to facilitate traceability).
- 18.35 Records of dispatch should contain sufficient information to enable traceability of the product. Such records should facilitate the recall of a batch of a product, if necessary, as well as the investigation of falsified or potentially falsified products. In addition, the assigned batch number and expiry date of products should be recorded at the point of receipt, to facilitate traceability.
- 18.36 Vehicles and containers should be loaded carefully and systematically on a last-in/first-out (LIFO) basis, to save time when unloading, to prevent physical damage and to reduce security risks. Extra care should be taken during loading and unloading of cartons, to avoid damage.
- 18.37 Medical products should not be supplied or received after their expiry date, or so close to the expiry date that this date is likely to be reached before the products are used by the consumer (12).
- 18.38 Medical products and shipment containers should be secured in order to prevent or to provide evidence of unauthorized access. Vehicles and operators should be provided with additional security where necessary, to prevent theft and other misappropriation of products during transportation.
- 18.39 Medical products should be stored and transported in accordance with procedures such that:
- the identity of the product is not lost;
 - the product does not contaminate and is not contaminated by other products;
 - adequate precautions are taken against spillage, breakage, misappropriation and theft; and
 - appropriate environmental conditions are maintained, for example, using cold-chain for thermolabile products.
- 18.40 Written procedures should be in place for investigating and dealing with any failure to comply with storage requirements, for example, temperature deviations. If a deviation has been noticed during transportation, by the person or entity responsible for transportation, this should be reported to the supplier, distributor

and recipient. In cases where the recipient notices the deviation, it should be reported to the distributor.

- 18.41 Transportation of products containing hazardous substances or narcotics and other dependence-producing substances, should be transported in safe, suitably designed, secured containers and vehicles. In addition, the requirements of applicable international agreements and national legislation should be met.
- 18.42 Spillages should be cleaned up as soon as possible, in order to prevent possible contamination, cross-contamination and hazards. Written procedures should be in place for the handling of such occurrences.
- 18.43 Damage to containers and any other event or problem that occurs during transit must be recorded and reported to the relevant department, entity or authority and investigated.
- 18.44 Products in transit must be accompanied by the appropriate documentation.

19. Outsourced activities

- 19.1 Any activity relating to the storage and distribution of a medical product that is delegated to another person or entity should be performed by the appropriately authorized parties, in accordance with national legislation and the terms of a written contract.
- 19.2 There should be a written contract between the entities. The contract should define the responsibilities of each entity (contract giver and contract acceptor) and cover at least the following:
 - compliance with this guideline and the principles of GSP and GDP;
 - the responsibilities of all entities for measures to avoid the entry of substandard and falsified products into the distribution chain;
 - training of personnel;
 - conditions of subcontracting subject to the written approval of the contract giver; and
 - periodic audits.
- 19.3 The contract giver should assess the contract acceptor before entering into the contract, e.g. through on-site audits, documentation and licensing status review.
- 19.4 The contract giver should provide to the contract acceptor all relevant information relating to the material and medical products.

- 19.5 The contract acceptor should have adequate resources (e.g. premises, equipment, personnel, knowledge, experience and vehicles, as appropriate) to carry out the work.
- 19.6 The contract acceptor should refrain from performing any activity that may adversely affect the materials or products handled.

20. Substandard and falsified products

- 20.1 The quality system should include procedures to assist in identifying and handling medical products that are suspected to be substandard and/or falsified.
- 20.2 Where such medical products are identified, the holder of the marketing authorization, the manufacturer and the appropriate national, regional and international regulatory bodies (as appropriate), as well as other relevant competent authorities, should be informed.
- 20.3 Such products should be stored in a secure, segregated area and clearly identified to prevent further distribution or sale. Access should be controlled.
- 20.4 Records should be maintained reflecting the investigations and action taken, such as disposal of the product. Falsified products should not re-enter the market.

21. Inspection of storage and distribution facilities

- 21.1 Storage and distribution facilities should be inspected by inspectors authorized by national legislation. This should be done at determined, periodic intervals.
- 21.2 Inspectors should have appropriate educational qualifications, knowledge and experience (13).
- 21.3 An inspection should normally be conducted by a team of inspectors.
- 21.4 Inspectors should assess compliance with national legislation, GSP, GDP and related guidelines (GXP), as appropriate.
- 21.5 Inspections should cover the premises, equipment, personnel, activities, quality system, qualification and validation and other related aspects, as contained in this guideline.
- 21.6 An inspection report should be prepared and provided to the inspected entity within a defined period of time from the last day of the inspection. Observations may be categorized based on risk assessment.

- 21.7 CAPA for observations listed as non-compliances in the inspection report, with the national legislation and guidelines, should be submitted for review by the inspectors within the defined period, as stated by the inspectors.
- 21.8 Inspections should be closed with a conclusion after the review of the CAPAs.

References

1. WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986; https://iris.who.int/bitstream/handle/10665/112733/WHO_TRS_986_eng.pdf?sequence=1&isAllowed=y, accessed 5 December 2019).
2. ISO 13485:2016(en). Medical devices – quality management systems – requirements for regulatory purposes (<https://www.iso.org/obp/ui/#iso:std:iso:13485:ed-3:v1:en>, accessed 5 December 2019).
3. Guide to good storage practices for pharmaceuticals. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-seventh report. Geneva: World Health Organization; 2003: Annex 9 (WHO Technical Report Series, No. 908; https://iris.who.int/bitstream/handle/10665/42613/WHO_TRS_908.pdf?sequence=1&isAllowed=y, accessed 5 December 2019).
4. WHO good distribution practices for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 5 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y, accessed 5 December 2019).
5. Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 8 (WHO Technical Report Series, No. 961; https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1, accessed 5 December 2019).
6. Good trade and distribution practices for pharmaceutical starting materials. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 6 (WHO Technical Report Series, No. 996; <https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>, accessed 5 December 2019).
7. Member State mechanism on substandard/spurious/false-labelled/falsified/counterfeit medical products. Report by the Director-General. In: Seventieth World Health Assembly, Geneva, 22–31 May 2017. Geneva: World Health Organization; 2017 (A70/23; http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_23-en.pdf, accessed 6 December 2019).
8. Good manufacturing practices: guidelines on validation. Appendix 5. Validation of computerized systems. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; <https://iris.who.int/bitstream/handle/10665/312316/9789241210287-eng.pdf?sequence=1&isAllowed=y>, accessed 29 January 2020).

9. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 2 (WHO Technical Report Series, No. 1019; <https://iris.who.int/bitstream/handle/10665/312316/9789241210287-eng.pdf?sequence=1&isAllowed=y>, accessed 5 December 2019).
10. Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 9 (WHO Technical Report Series, No. 961; https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1, accessed 5 December 2019).
11. Guidance on good data and record management practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 5 (WHO Technical Report Series, No. 996; <https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>, accessed 5 December 2019).
12. Policy on remaining shelf life of medical products. Geneva: World Health Organization; 2019 (working document QAS/19.788).
13. Quality systems requirements for national inspectorates. Geneva: World Health Organization; 2019 (working document QAS/19.811/Rev.1).

Further reading

- WHO guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 981; https://iris.who.int/bitstream/handle/10665/81144/WHO_TRS_981_eng.pdf?sequence=1&isAllowed=y, accessed 5 December 2019).
- ICH harmonised tripartite guideline. Quality risk management Q9. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2005 (<https://www.ich.org/page/quality-guidelines>).
- ISO 31000:2018(en). Risk management – guidelines.
- ISO 14971:2019(en). Medical devices – application of risk management to medical devices (<https://www.iso.org/obp/ui/#iso:std:iso:14971:ed-3:v1:en>, accessed 5 December 2019).
- WHO guidance on testing of “suspect” falsified medicines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. Geneva: World Health Organization; 2018: Annex 5 (WHO Technical Report Series, No. 1010; <https://iris.who.int/bitstream/handle/10665/272452/9789241210195-eng.pdf?sequence=1&isAllowed=y>, accessed 5 December 2019).
- Guidelines on import procedures for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 5 (WHO Technical Report Series, No. 1019; <https://iris.who.int/bitstream/handle/10665/312316/9789241210287-eng.pdf?sequence=1&isAllowed=y>, accessed 29 January 2020).

- Good practices of national regulatory authorities in implementing the collaborative registration procedures for medical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 6 (WHO Technical Report Series, No. 1019; <https://iris.who.int/bitstream/handle/10665/312316/9789241210287-eng.pdf?sequence=1&isAllowed=y>, accessed 29 January 2020).
- Guidelines for medicine donations, 3rd ed. Geneva: World Health Organization; 2011 (https://apps.who.int/iris/bitstream/handle/10665/44647/9789241501989_eng.pdf?sequence=1, accessed 5 December 2019).
- Guidelines for safe disposal of unwanted pharmaceuticals in and after emergencies: interagency guidelines. Geneva: World Health Organization; 1999 (WHO/EDM/PAR/99.2; https://iris.who.int/bitstream/handle/10665/42238/WHO_EDM_PAR_99.2.pdf?sequence=1&isAllowed=y, accessed 5 December 2019).
- Model quality assurance system for procurement agencies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 3 (WHO Technical Report Series, No. 986; https://iris.who.int/bitstream/handle/10665/112733/WHO_TRS_986_eng.pdf?sequence=1&isAllowed=y, accessed 5 December 2019).
- Good manufacturing practices: guidelines on validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; <https://iris.who.int/bitstream/handle/10665/312316/9789241210287-eng.pdf?sequence=1&isAllowed=y>, accessed 29 January 2020).
- Guidelines on the international packaging and shipping of vaccines. Geneva: World Health Organization; 2019 (https://iris.who.int/bitstream/handle/10665/69368/WHO_IVB_05.23_eng.pdf?sequence=1, accessed 5 December 2019).

Appendix 1

Recommended storage conditions

Note: Appropriate conditions should be provided for medical products during storage and distribution. Conditions should be maintained as stated on their labels (or as described by the manufacturers as applicable) during storage and distribution. Statements such as “store at ambient conditions” should be avoided. Where possible, actual limits should be specified by the manufacturers, such as “store below 25 °C”. See Table A7.1 below.

Table A7.1

Recommended limits for descriptive storage conditions^a

Label description	Recommended limits
Store at controlled room temperature	15 to 25 °C
Store in a cold or cool place	8 to 15 °C
Store in a refrigerator	5 ± 3 °C
Store in a freezer	–20 ± 5 °C
Store in deep freezer	–70 ± 10 °C
Store in a dry place	No more than 60% relative humidity
Protect from moisture	No more than 60% relative humidity
Store under ambient conditions	Store in well-ventilated premises at temperatures of between 15 °C and 30 °C and no more than 60% relative humidity. Extraneous odours, other indications of contamination and intense light must be excluded.
Protect from light	To be maintained in the original manufacturer's light-resistant containers.
Chilled	5 ± 3 °C

^a These limits are recommended values and are based on pharmacopoeia limits and guidelines.

8.6 Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

Annex 9, WHO Technical Report Series, 961, 2011

Abbreviations	1343
Background	1343
Key to conventions used	1344
Glossary	1344
1. Importation	1348
1.1 Port handling and customs clearance	1348
1.1.1 Port of entry	1348
1.1.2 Offloading	1348
1.1.3 Temporary storage at port of entry	1348
1.1.4 Customs clearance	1348
2. Warehousing sites	1349
2.1 Site layout	1349
2.1.1 Natural hazards	1349
2.1.2 Site access	1349
2.2 Site security	1349
2.3 Site cleanliness	1349
3. Storage buildings	1349
3.1 Construction standards	1349
3.2 Accommodation and layout	1350
3.3 Loading and receiving bays	1350
3.3.1 Loading bays	1350
3.3.2 Receiving bays	1350
3.4 Goods assembly and quarantine areas	1350
3.4.1 Goods assembly areas	1350
3.4.2 Holding area for incoming goods	1351
3.4.3 Quarantine area	1351
3.5 Environmental control of ancillary areas	1351
3.6 Building security	1352
3.6.1 General building security	1352
3.6.2 Controlled and hazardous substances areas	1352

3.7	Fire protection	1352
3.7.1	Fire protection equipment	1352
3.7.2	Fire prevention, detection and control procedures	1353
3.8	Building hygiene	1353
3.8.1	Building cleanliness	1353
3.8.2	Pest control	1353
3.9	Power supply	1354
3.9.1	Uninterrupted power supply	1354
3.9.2	Power failure contingency plan	1354
3.10	Building maintenance	1354
4.	Temperature-controlled storage	1355
4.1	Normative references	1355
4.2	Storage capacity of temperature-controlled stores	1355
4.3	Temperature-controlled storage	1355
4.4	Temperature-controlled storage for controlled and hazardous products	1357
4.5	Temperature and humidity control and monitoring in storage	1357
4.5.1	Temperature control	1357
4.5.2	Temperature monitoring	1357
4.5.3	Humidity control	1359
4.5.4	Humidity monitoring	1359
4.6	Alarm systems	1359
4.6.1	Temperature alarms	1359
4.6.2	Humidity alarms	1360
4.7	Qualification of temperature-controlled stores	1361
4.8	Cleanliness of temperature-controlled stores	1361
4.9	Refrigeration equipment maintenance	1362
4.10	Calibration and verification of control and monitoring devices	1362
4.10.1	Calibration of temperature control and monitoring devices	1362
4.10.2	Calibration of humidity control and monitoring devices	1363
4.10.3	Alarm equipment verification	1363
5.	Materials handling	1363
5.1	Materials handling equipment	1363
6.	Transport and delivery	1363
6.1	Normative references	1363
6.2	Product stability profiles	1364
6.3	Transport route profiling and qualification	1364
6.4	Temperature-controlled transport	1364
6.4.1	Air and sea transport	1364
6.4.2	Temperature-controlled road vehicles operated by common carriers	1365
6.4.3	Temperature-controlled road vehicles generally	1365
6.4.4	Transport of controlled TTSPs and TTSPs with high illicit value	1366
6.5	Temperature and humidity control and monitoring during transit	1366
6.5.1	Temperature control in temperature-controlled road vehicles	1366
6.5.2	Temperature monitoring in temperature-controlled road vehicles	1367
6.5.3	Humidity monitoring in temperature-controlled road vehicles	1367
6.5.4	Temperature monitoring in passive and active shipping containers	1368

6.6	Qualification of temperature-controlled road vehicles	1368
6.7	Calibration and verification of transport monitoring devices	1369
6.7.1	Calibration of transport temperature control devices	1369
6.7.2	Calibration of transport temperature monitoring devices	1369
6.7.3	Calibration of transport humidity monitoring devices	1369
6.7.4	Verification of transport alarm equipment	1369
6.8	Shipping containers	1369
6.8.1	Container selection generally	1369
6.8.2	Uninsulated containers	1370
6.8.3	Qualification of insulated passive containers	1370
6.8.4	Qualification of active containers	1370
6.9	Shipping container packing	1371
6.10	Product handling during packing and transport	1371
6.11	Cleaning road vehicles and transport containers	1372
6.12	Transport of returned and recalled TTSPPs	1372
6.12.1	Transport of returned TTSPPs	1372
6.12.2	Transport of recalled TTSPPs	1373
7.	Labelling	1373
7.1	Normative references	1373
7.2	Labelling	1373
7.2.1	Labelling generally	1373
7.2.2	Labelling air-freighted shipments	1373
8.	Stock management	1374
8.1	Stock control systems	1374
8.1.1	General stock control systems and procedures	1374
8.1.2	Stock control procedures for controlled and hazardous TTSPPs	1374
8.2	Incoming goods	1375
8.2.1	Product arrival checks	1375
8.2.2	Actions following arrival checks	1375
8.3	Outgoing goods (external deliveries)	1376
8.3.1	Management of outgoing goods	1376
8.3.2	Actions following dispatch	1376
8.4	Product complaint procedures	1376
8.5	Suspect product procedures	1377
8.5.1	Suspect products	1377
8.6	Product return, recall, withdrawal and disposal procedures	1377
8.6.1	Return procedures	1377
8.6.2	Recall procedures	1378
8.6.3	Disposal procedures	1378
8.7	Traceability or stock tracking	1379
9.	General procedures and record-keeping	1379
9.1	Emergencies and contingency planning	1379
9.2	General record-keeping	1379
9.2.1	Record-keeping	1379
9.2.2	Content of records	1380
9.2.3	Record review and retention	1381

9.3	Temperature and humidity records	1381
9.3.1	Temperature records	1381
9.3.2	Humidity records	1381
10.	Environmental management	1382
10.1	Normative references	1382
10.2	Environmental management of refrigeration equipment	1382
11.	Quality management	1382
11.1	Normative references	1382
11.2	Organizational structure	1383
11.3	Quality systems	1383
11.3.1	Quality system	1383
11.3.2	Self inspections	1384
11.3.3	Contractors subject to service level agreements	1384
11.4	Management of documents and standard operating procedures	1384
11.4.1	Standard operating procedures	1384
11.5	Document control	1385
12.	Personnel/training	1385
12.1	Training	1385
12.1.1	General training	1385
12.1.2	Specialist training	1386
	Key references	1386
	Further reading	1388
	Task force membership	1388

Abbreviations

CAPA	corrective and preventive action (procedures)
DCVMN	Developing Countries Vaccine Manufacturers Network
EEFO	earliest-expiry-first-out. Used in this document as equivalent to FEFO (first to expire-first-out)
FIFO	first-in-first-out
GDP	good distribution practice
GMP	good manufacturing practice
GPS	global positioning system
GSP	good storage practice
HVAC	heating ventilating and air-conditioning (system)
IATA	International Air Transport Association
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IQ	installation qualification
PCCIG	Pharmaceutical Cold Chain Interest Group
PDA	Parenteral Drug Association
SKU	stock-keeping unit
SLA	service level agreement
SMS	short message service
SOP	standard operating procedure
TTSP	time- and temperature-sensitive pharmaceutical product
UPS	uninterrupted power supply
USP	United States Pharmacopeia

Background

These guidelines set out the principal requirements for the safe storage and distribution of time- and temperature-sensitive pharmaceutical products (TTSPs). They are based upon existing regulations and best practice guidance from a wide range of international sources (see References), while accepting that local legislation and regulations will

continue to take precedence. The target audience includes regulators, logisticians and pharmaceutical professionals in industry, government and the international agencies.

The document has been prepared in close consultation with the WHO Task Force on Regulatory Oversight on Pharmaceutical Cold Chain Management which has been central to the review process. A full list of members is given at the end of this annex.

The intention is that the guidance in this document should be directly applicable in less-developed countries as well as in the industrialized world. To this end, supplementary materials will be developed to show how the requirements can practicably be achieved, particularly in resource-constrained settings. Experience with vaccine supply chain assessments in many less-developed countries demonstrates that the mandatory standards set out in this document can be achieved, and that some countries are also capable of meeting many of the optional requirements.

The document is designed to give a balanced overview of the major aspects of good storage and distribution practice for TTSPs. As such it deliberately includes references to requirements which can be found in general guides to good manufacturing practice (GMP), good storage practice (GSP) and good distribution practice (GDP). The purpose is not to supplant these source materials, but to ensure that the reader is aware of the relevant GMP, GSP and GDP implications when seen from the particular and specialized perspective of TTSP management.

Key to conventions used

The following conventions are used in the requirements clauses:

- The imperative voice is used to denote a mandatory or highly desirable requirement. For example: “Ensure that...”, “Provide...” and the like.
- The words “where possible” or “preferably” are used to denote an optional but desirable requirement.
- Many clauses are followed by a brief explanation setting out the underlying reason for including the clause.

Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

active systems

Actively powered systems using electricity or other fuel source to maintain a temperature-controlled environment inside an insulated enclosure under thermostatic regulation (e.g. cold rooms, refrigerators, temperature-controlled trucks, refrigerated ocean and air containers).

change control

The processes and procedures to manage system changes.

common carrier

A seller of distribution services.

controlled or hazardous time- and temperature-sensitive pharmaceutical products

Time- and temperature-sensitive pharmaceutical products (TTSPPs) with high illicit value: poisons, narcotics, psychotropic products, inflammable or explosive substances and radioactive materials.

dunnage

Loose packing material used to protect TTSPPs from damage during transport.

external distribution

Transport of TTSPPs through various steps in the customer's supply chain (i.e. transport from a pharmaceutical manufacturer's distribution centre to commercial customers (including wholesalers, retailers and buying groups), to clinical facilities or direct to the patient).

installation qualification

The process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its specifications and that it functions within predetermined limits when operated in accordance with the operating instructions.

internal distribution

Transport of a TTSP within a pharmaceutical manufacturer's internal supply chain (i.e. all internal transports from manufacturing facility to packaging facility to warehouse to distribution centre).

net storage capacity

The total volume available for storing TTSPPs, taking account of the type of load support system employed (floor-standing pallets, adjustable pallet racking or shelving units), as modified by the utilization factor that can be achieved in the store.

passive systems

Systems which maintain a temperature-controlled environment inside an insulated enclosure, with or without thermostatic regulation, using a finite amount of pre-conditioned coolant in the form of chilled or frozen gel packs, phase change materials, dry ice or others.

pests

Includes birds, bats, rodents and insects whose uncontrolled presence affects hygiene and cleanliness.

pharmaceutical product

Any product intended for human use or veterinary product intended for administration to food-producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. It does not, however, include medical devices.¹

qualification

Documented testing that demonstrates, with a high degree of assurance, that a specific process will meet its predetermined acceptance criteria.²

refrigeration equipment

The term “refrigeration” or “refrigeration equipment” means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity.

service level agreement (SLA)

A service level agreement or contract is a negotiated agreement between the customer and service provider that defines the common understanding about materials or service quality specifications, responsibilities, guarantees and communication mechanisms. It can either be legally binding, or an information agreement. The SLA may also specify the target and minimum level performance, operation or other service attributes.³

standard operating procedure (SOP)

A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness.

storage temperature

The temperature range listed on the TTSP label, and within the regulatory documentation, for long-term storage.

storage unit temperature/humidity distribution

The range and pattern of temperatures and/or humidity within a temperature-controlled storage unit during normal operation.

¹ Definition from *Revision of WHO good distribution practices for pharmaceutical products*. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report*. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 5.

² Definition from the Parenteral Drug Association (PDA) Technical Report No. 39, 2007.

³ Definition from International Air Transport Association (IATA), Chapter 17, 9th ed., June 2009.

suspect product

A TTSPP whose presentation and/or pharmacological formulation indicates that it has not been manufactured by the company named on the packaging. A TTSPP that shows visible or pharmacological evidence of tampering.

temperature-controlled

Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits.

temperature excursion

An excursion event in which a TTSPP is exposed to temperatures outside the range(s) prescribed for storage and/or transport. Temperature ranges for storage and transport may be the same or different; they are determined by the product manufacturer, based on stability data.

temperature-modified

Includes any environment in which the temperature is predictably maintained at a level different from that of the surrounding environment, but is not actively or passively controlled within precise predefined limits.

time- and temperature-sensitive pharmaceutical product (TTSPP)

Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

transport temperature profile

Anticipated ambient temperature variation and duration to which a TTSPP may be exposed during transport.

utilization factor

The percentage of the total volume available for storing TTSPPs that can reliably be achieved in practice, taking account of the types of stock-keeping unit (SKU), the types of load support system and the stock management systems used in the store.

validation

Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting predetermined acceptance criteria.⁴

⁴ Definition from PDA Technical Report No. 39, 2007.

1. Importation

1.1 Port handling and customs clearance

1.1.1 Port of entry

Import TTSPPs through a port of entry that is equipped to handle such products. Where this is not possible, ensure that arrangements are in place to provide the necessary level of protection and security.

Reason: To minimize the risk of damage.

1.1.2 Offloading

As soon as possible after arrival, remove TTSPP shipments from the wharf or airport apron to a safe and suitable temperature-controlled storage location.

Reason: To minimize the risk of theft and to avoid exposure to adverse ambient conditions.

1.1.3 Temporary storage at port of entry

Store TTSPP shipments in a secure warehouse under the conditions recommended by the product manufacturer, until the shipment has been authorized for removal by customs.⁵

Reason: To avoid risk of theft or damage during temporary storage.

1.1.4 Customs clearance

Draw up procedures and memoranda of understanding to ensure that TTSPP shipments are cleared through customs as rapidly as possible. This can be facilitated by a pre-clearance procedure carried out by the local health agency, clearing agent or freight forwarder in collaboration with customs. Alternatively the clearance process should be conducted by customs staff, supported by personnel with suitable pharmaceutical training, especially when clearance involves the opening and resealing of temperature-controlled packaging.

Reason: To avoid delays during customs clearance that may cause temperature excursions and place TTSPPs at risk.

⁵ In some situations, arrangements can be made for formal customs clearance to take place away from the port of entry — for example, at a national vaccine store. In situations where the port of entry is not equipped with suitable cold storage facilities, this can reduce the risk of temperature excursions.

2. Warehousing sites

2.1 Site layout

2.1.1 Natural hazards

Select and/or develop storage sites to minimize risks from natural hazards such as floods, landslides and earthquakes and extreme weather conditions such as hurricanes and tornadoes.

Reason: To protect against loss of valuable pharmaceutical products, to ensure continued supply to patients in the market and to protect personnel working in the store.

2.1.2 Site access

Provide vehicular access to storage buildings sufficient to accommodate the largest vehicles visiting the site, including emergency vehicles.

Reason: To ensure convenient operation of the facility.

2.2 Site security

Provide perimeter protection to ensure security of the grounds and storage buildings against anticipated risks.

Reason: To protect against vandalism, theft and other illegal incursions. Security arrangements should be appropriate to the site location and the value of goods stored there.

2.3 Site cleanliness

Keep the site free of accumulated dust, dirt, waste and debris. Ensure that pests are kept under control within the site area. Collect waste in designated closed containers and arrange for safe disposal at frequent intervals.

Reason: To help protect storage buildings against ingress by dust, dirt and pests.

3. Storage buildings

3.1 Construction standards

Construct or procure storage buildings that are:

- purpose-designed for the storage of TTSPPs, or well-adapted for this purpose;
- designed to suit the prevailing climate, making maximum use of passive heating, cooling and ventilation;

- designed and equipped to minimize the consumption of electricity and other fuel sources;
- constructed using materials and finishes that are robust, easy to clean and which are selected to minimize long-term maintenance;
- constructed using locally available materials and building technologies; and
- built to minimize hiding and nesting places for pests.

Reasons: Storage in unsuitable and poorly-designed buildings places TTSPPs at risk and increases storage costs. Buildings constructed using inappropriate materials and technologies are difficult to operate and maintain in resource-constrained settings.

3.2 Accommodation and layout

Ensure that the storage buildings are well laid out and contain all the necessary storage areas, goods assembly, receiving and dispatch bays and office accommodation needed for efficient operation of the TTSP store.

3.3 Loading and receiving bays

3.3.1 Loading bays

Ensure that receiving and dispatch bays are designed to avoid conflict between incoming and outgoing goods and are protected from direct sunlight, dust, dirt, rain, snow and wind, and from extremes of heat, cold and solar radiation that could damage TTSPPs, and measures are taken to minimize pest activity in these areas.

Reason: Protection against damage and maintenance of product quality.

3.3.2 Receiving bays

Provide receiving areas with suitable equipment to clean reusable transport containers after their contents have been unloaded, and before the containers are stored for re-use.

Reason: Protection against contamination of outgoing TTSPPs.

3.4 Goods assembly and quarantine areas

3.4.1 Goods assembly areas

Provide sufficient space to receive, assemble and pack TTSPPs for dispatch under temperature-modified conditions. Preferably, these areas should be physically close to the temperature-controlled storage area.

Reason: Protection of TTSPPs during arrival, order assembly and dispatch.

3.4.2 Holding area for incoming goods

Provide a temperature-controlled holding area for incoming TTSPs pending their acceptance into the main storage area. The holding area may be a physically separated zone, or it may be defined using a suitable stock control information system, or by a combination arrangement. Where goods are held in bond in the warehouse, awaiting customs clearance, they must be physically separated and secured.

Reason: Incoming items may need inspection and/or regulatory clearance, including laboratory testing.

3.4.3 Quarantine area

Provide a quarantine area for the isolation of returned, faulty, recalled and otherwise withdrawn goods pending a decision on disposal or re-stocking by the qualified person or department. Materials within quarantine areas must be clearly identified with their status.

- with temperature control, for items returned for re-stocking;
- with temperature control, for items recalled for testing;
- without temperature control, for items awaiting disposal.

The quarantine area may be a physically separated zone, or it may be defined using a suitable stock control information system, or by a combination arrangement.

Reason: Items for re-stocking, testing and disposal should be kept separate to avoid the risk of inappropriate use.

3.5 Environmental control of ancillary areas

Ensure, where possible, that ancillary areas where TTSPs are temporarily held during arrival, order assembly or dispatch are:

- maintained within the temperature range specified for the goods being handled;
- maintained within the humidity range specified for goods that are adversely affected by high relative humidity and are not sufficiently protected by their packaging;⁶
- protected from undue exposure to direct sunlight;
- protected from the weather;
- protected against dust, dirt and waste accumulation;

⁶ Active environmental control of ancillary areas may not be needed if all TTSPs are kept in temperature-controlled packaging and/or humidity-protective packaging when passing through these areas.

- adequately ventilated;
- adequately lit to enable operations to be carried out accurately and safely;
- monitored during the times when TTSPPs are handled; and monitored during the times when TTSPPs are handled (see 4.5.1-4.5.4).

Reason: Protection of TTSPP quality during arrival, order assembly or dispatch.

3.6 Building security

3.6.1 General building security

Ensure that buildings used to store TTSPPs have sufficient security to prevent unauthorized access and to prevent misappropriation of goods.

Reason: To protect against vandalism, theft and other illegal incursions. Security arrangements should be appropriate to the site location and to the value of goods stored there.

3.6.2 Controlled and hazardous substances areas

Ensure that all areas that are used to store controlled or hazardous TTSPPs are:

- dedicated, securely locked facilities that comply fully with all legislative and regulatory requirements applicable in the country where the store is located;
- only accessible to authorized staff;
- protected by automatic intruder and/or fire and smoke, and/or chemical and/or radiological sensor alarm systems appropriate to the type(s) of product being stored;⁷
- designed to be explosion-proof, where explosive TTSPPs are stored;⁸ and
- continuously monitored by security staff.

Reason: Protection of property and life.

3.7 Fire protection

3.7.1 Fire protection equipment

Provide suitable fire detection and fire-fighting equipment, including fire hydrants, in all TTSPP storage areas and ensure that:

⁷ Zoned sprinkler systems are recommended to control fires and to localize product damage in the event of system activation.

⁸ Explosion-proof stores must have a blast roof or wall. Preferably, explosive substances should be stored in an independent building, well separated from the main store.

- systems and equipment are appropriate for the class of occupancy and product storage arrangements and are approved by the local fire authority; and
- equipment is regularly serviced in accordance with the equipment manufacturers' recommendations and local regulations.

Reason: Protection of property and life.

3.7.2 Fire prevention, detection and control procedures

Follow standard operating procedures (SOPs) for fire prevention, detection and control. Train staff and carry out regular fire drills. Prohibit smoking in all areas.

Reason: Protection of property and life.

3.8 Building hygiene

3.8.1 Building cleanliness

Implement a cleaning programme for all areas:

- do not allow the accumulation of dust, dirt and waste, including packaging waste;
- take precautions against spillage or breakage, and cross-contamination;
- collect waste in designated closed containers and arrange for safe disposal at frequent intervals;
- do not permit consumption of food or beverages other than in designated areas; and
- maintain cleaning records to demonstrate compliance.

Reason: Protection against damage and contamination of TTSPs and to minimize the risk of pest infestation.

3.8.2 Pest control

Implement a programme to keep all areas free of pests. This should include enclosed receiving and loading bays. Maintain records to demonstrate compliance with a robust pest control programme.

Reason: Protection against damage and contamination of TTSPs.

3.9 Power supply

3.9.1 Uninterrupted power supply

Where possible, and where necessary,⁹ ensure that all temperature- controlling equipment for TTSP storage (i.e. refrigerators, freezers, building management systems, heating, ventilation and air-conditioning (HVAC) systems, compressors, air-handling units, monitoring systems, alarms and related computer equipment) are connected to an uninterrupted power supply (UPS) system. Where a generator and associated control equipment is used it should:

- be able to manage the combined start-up load of all connected temperature-controlling and temperature-monitoring equipment;¹⁰
- not exceed the defined parameters of the mains power supply;
- be equipped with automatic mains failure start-up and automatic shutdown when power is restored; and
- have adequate fuel tank capacity and sufficient fuel to cover a prolonged power outage.

Regularly test and service UPS equipment and generators. Maintain records to demonstrate compliance.

Reason: Loss prevention.

3.9.2 Power failure contingency plan

Develop and maintain a contingency plan to protect TTSPs in the event of power failure which places products at risk. Alternative emergency cooling systems (e.g. liquid nitrogen or dry ice) are acceptable.

Reason: Loss prevention.

3.10 Building maintenance

Implement a planned preventive maintenance programme to ensure that storage buildings and building utilities are well maintained. Keep records to demonstrate compliance with the programme.

Reason: To ensure that storage buildings continue to protect stored products against damage.

⁹ UPS systems may be unnecessary in countries with a very reliable electricity supply. In smaller stores in countries where electricity is only available for a limited period each day, or is entirely absent, an alternative approach to UPS is to use refrigeration equipment with extended holdover capacity, for example, ice-lined refrigerators, or gas, kerosene or solar-powered refrigerators.

¹⁰ The installed capacity of the UPS system can be minimized by fitting electronic controls which reduce compressor start-up loads.

4. Temperature-controlled storage

4.1 Normative references

- EN 60068-3 parts 5, 6, 7 and 11: *Environmental testing. Guidance. Confirmation of the performance of temperature chambers*
- International Air Transport Association (IATA) *Perishable cargo regulations chapter 17*. 10th ed, July 2010
- USP <1079> *Good storage and shipping practices*
- USP <1118> *Monitoring devices — time, temperature and humidity*

4.2 Storage capacity of temperature-controlled stores

Ensure that the net storage capacity of the temperature-controlled stores is sufficient to accommodate peak TTSP stock levels and their associated transit temperature protection components (i.e. freezer blocks, flexible ice blankets, refrigerated gel packs, phase change materials and insulated packaging, if retained), under correct temperature conditions and in a manner which enables efficient and correct stock management operations to take place.

Reason: To avoid the risks associated with overstocking and to ensure that good warehousing practices can be adopted (i.e. first in-first out (FIFO) or earliest expiry-first out (EEFO)). Overstocking makes FIFO or EEFO handling difficult or impossible and hinders accurate physical stock counts.

4.3 Temperature-controlled storage

Ensure that TTSPs are stored in temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers which comply with the following requirements.

Temperature-controlled rooms, cold rooms and freezer rooms should be:

- capable of maintaining the temperature range defined by the system set points over the full annual ambient temperature range experienced at the store location;
- preferably equipped with an auto-defrost circuit which has a minimal effect on temperature within the unit during the defrost cycle and maintains temperature within specification for this period;
- equipped with a low temperature protection circuit in cold climates where there is a risk of breaching the low temperature set point for TTSPs that are damaged by exposure to low temperatures;
- connected to a UPS as described in clause 3.9.1;

- equipped with a calibrated continuous temperature monitoring system with sensors located at points representing greatest temperature variability and temperature extremes;
- preferably equipped with continuous humidity monitoring devices with sensors located at points representing humidity extremes;
- equipped with alarms to indicate temperature excursions and/or refrigeration failure;
- fitted with lockable doors, or an access control system, as necessary; locks must have a safety device so that doors can be freely opened from the inside; and
- qualified as defined in clause 4.7.

Refrigerators and freezers should be:

- purpose-designed for the storage of TTSPPs; household-style units are only acceptable if they have been independently tested and found to comply with the temperature control requirements of a recognized standard for pharmaceutical refrigerators and freezers;
- capable of maintaining the temperature range specified by the TTSPP manufacturer over the full annual ambient temperature range experienced at the storage site;
- equipped with calibrated temperature monitoring devices appropriate to the level of risk but preferably capable of continuous recording and with sensor(s) located at a point or points within the cabinet which most accurately represents the temperature profile of the equipment during normal operation;
- preferably equipped with alarms to indicate temperature excursions and/or refrigeration failure;
- fitted with lockable doors or lids, or access control system, as necessary; and
- qualified and/or tested as defined in clause 4.7.

Reason: To maintain labelled TTSPP storage temperatures during long-term storage.

4.4 Temperature-controlled storage for controlled and hazardous products

Ensure that controlled and hazardous TTSPs are securely stored:

- Provide dedicated temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers for these TTSPs, in separate secure areas, as described in clause 3.6.2.
- Alternatively, but only if acceptable to the regulatory authority, bulk stocks of TTSPs with high illicit-value may be stored in a securely locked section of a general temperature-controlled storage area.

Reason: To protect this category of TTSPs against theft and misuse and to safeguard workers and general storage areas in the event of an accident involving hazardous substances.

4.5 Temperature and humidity control and monitoring in storage

4.5.1 Temperature control

Provide thermostatic temperature control systems for all temperature- controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPs. Comply with the following minimum requirements:

- system able continuously to maintain air temperatures within the set point limits throughout the validated storage volume;
- control sensors accurate to ± 0.5 °C or better;
- control sensors calibrated as described in clause 4.10.1;
- control sensors located in areas where greatest variability in temperature is expected to occur in order to maximize available safe storage volume;
- control sensors positioned at the hot and cold spots determined by temperature mapping, even if affected by door opening, unless recommendations are being made not to store products in such areas; and
- control sensors independent of the temperature monitoring system.

4.5.2 Temperature monitoring

Provide air temperature monitoring systems and devices for all temperature- controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPs. Comply with the following minimum requirements:

General requirements

- Monitoring sensors accurate to $\pm 0.5\text{ }^{\circ}\text{C}$ or better for electronic devices and $\pm 1\text{ }^{\circ}\text{C}$ or better for alcohol, bi-metal gas or vapour pressure thermometers.
- Monitoring sensors calibrated as described in clause 4.10.1.
- Monitoring sensors located in areas where greatest variability in temperature is expected to occur within the qualified and/or tested storage volume as defined in clause 4.7.
- Monitoring sensors positioned so as to be minimally affected by transient events such as door opening.
- Temperature monitoring devices, temperature traces or electronic temperature records manually checked at least twice a day, in the morning and evening, seven days a week, including public holidays.

Temperature-controlled rooms, cold rooms and freezer rooms

- Provide a temperature record with a minimum recording frequency of six times per hour for each monitoring sensor position.
- Provide documentation for each monitoring sensor position which can be stored and accessed.
- Continue to operate independently in the event of a power failure.¹¹

Refrigerators and freezers

- Preferably, connect refrigerators and freezers to a multipoint monitoring system with a minimum recording frequency of six times per hour for each sensor position which can operate independently in the event of a power failure.
- Alternatively use battery-powered portable temperature monitoring devices with a minimum recording frequency of six times per hour.
- The least preferred option is a thermometer or maximum/minimum thermometer.
- Provide documentation for each appliance which can be stored and accessed.

¹¹ Where there is no UPS, the autonomy period for the device should be matched to the maximum length of anticipated power outages.

Reasons: To maintain labelled TTSP temperatures during long-term storage. Thermometers provide only limited and discontinuous temperature information. For this reason, continuous recording devices are preferable.

4.5.3 Humidity control

Provide humidity control in temperature-controlled rooms that are used to store TTSPs which are adversely affected by high relative humidity and are not sufficiently protected by their packaging. Such products are typically labelled “store in a dry place”, or carry similar wording and require a humidity-controlled environment.

4.5.4 Humidity monitoring

Provide humidity monitoring systems and devices in temperature-controlled rooms that are used to store TTSPs which require a humidity-controlled environment. Comply with the following minimum requirements:

- sensors accurate to $\pm 5\%$ RH;
- sensors calibrated as per clause 4.10.2;
- sensors located to monitor worst-case humidity levels within the qualified storage volume defined in clause 4.7;
- sensors positioned so as to be minimally affected by transient events such as door opening;
- provides a humidity record with a minimum recording frequency of six times per hour for each sensor position;
- provides documentation for each sensor position which can be stored and accessed; and
- continues to operate independently in the event of a power failure.¹²

Reason: To maintain labelled TTSP humidity conditions during long-term storage.

4.6 Alarm systems

4.6.1 Temperature alarms

Provide temperature alarm systems for temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPs. Comply with the following minimum requirements:

¹² Where there is no UPS the autonomy period for the device should be matched to the maximum length of anticipated power outages.

General requirements

- Sensors accurate to ± 0.5 °C.
- Sensors calibrated as described in clause 4.10.1.
- Sensors located to monitor worst-case temperatures within the validated storage volume defined in clause 4.7; where the alarm system is not integrated with the temperature monitoring system, sensors should be located close to the temperature monitoring sensors.
- Sensors positioned so as to be minimally affected by transient events such as door opening.

Temperature-controlled rooms, cold rooms and freezer rooms

- High/low alarms set points to trigger appropriately located visual alarm(s).
- Preferably there should also be appropriately located audible alarm(s) in addition to the visual alarm(s).
- Preferably there should be an automatic telephone dial-up or SMS text warning system to alert on-call personnel when an alarm is triggered outside working hours.

Refrigerators and freezers

- Preferably there should be a visual and/or audible alarm system; this may be integrated with a portable continuous temperature monitoring device.

Reason: Loss prevention.

4.6.2 Humidity alarms

Provide humidity alarm systems for temperature-controlled rooms used to store TTSPs that require a humidity-controlled environment. Comply with the following minimum requirements:

- sensors accurate to $\pm 5\%$ relative humidity (RH);
- sensors calibrated as described in clause 4.10.2;
- sensors located to monitor worst-case humidity levels within the validated storage volume defined in clause 4.7; where the alarm system is not integrated with the humidity monitoring system, sensors should be located close to the humidity monitoring sensors;
- sensors positioned so as to be minimally affected by transient events such as door opening;

- high/low alarms set points to trigger appropriately located visual alarm(s);
- preferably there should also be appropriately located audible alarm(s) in addition to the visual alarm(s); and
- preferably there should be an automatic telephone dial-up or SMS text warning system to alert on-call personnel when an alarm is triggered outside working hours.

Reason: Loss prevention.

4.7 Qualification of temperature-controlled stores

Qualify new temperature-controlled storage areas and new refrigeration equipment before it becomes operational. The qualification procedure should:

- demonstrate the air temperature profile throughout the storage area or equipment cabinet, when empty and in a normal loaded condition;
- define zones which should not be used for storage of TTSPPs (for example areas in close proximity to cooling coils, cold air streams or heat sources); and
- demonstrate the time taken for temperatures to exceed the designated limits in the event of power failure.

Fully document the initial qualification. Carry out additional qualification exercises whenever modifications are made to the storage area that may increase loading or affect air circulation, or when changes are made to the refrigeration equipment, such as a change in the set point. Consider the need for requalification whenever temperature and/or humidity monitoring shows unexplained variability that is greater than normal.

Qualification may not be required for equipment which requires little or no site assembly or commissioning, such as vaccine refrigerators and freezers that have been independently tested and found suitable for the storage of TTSPPs. Independent testing must be carried out between the chosen set points and under the ambient temperature conditions to which the equipment will be exposed during operation. Prequalified equipment of this type must be correctly installed in each location in accordance with written guidance.

Reason: To ensure that labelled TTSPP temperatures can be maintained during long-term storage and that the facility can demonstrate to the regulatory authorities and other interested parties that due diligence has been observed.

4.8 Cleanliness of temperature-controlled stores

Implement a cleaning and decontamination programme for all temperature-controlled rooms:

- Ensure that floor areas are fully accessible for cleaning. Do not store goods directly on the floor.
- Do not permit storage of any non-pharmaceutical products except transport-related items such as icepacks, gel packs and the like.
- Do not allow the accumulation of dust, dirt and waste, including packaging waste.
- Take precautions against spillage or breakage, and cross-contamination.
- Do not allow accumulation of frost and ice, particularly ice contaminated by spillages.
- Collect waste in designated closed containers and arrange for safe disposal at frequent intervals.

Maintain cleaning records to demonstrate compliance.

Reason: Protection against damage and contamination of TTSPPs and hazards to workers, arising from spillage or breakage.

4.9 Refrigeration equipment maintenance

Implement a maintenance programme for all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers:

- Carry out regular planned preventive maintenance on all temperature-controlling equipment.
- Make arrangements to ensure that emergency maintenance is carried out within a time period that does not place TTSPPs at risk of damage.
- Ensure that there is a contingency plan to move products stored in non-functioning equipment to a safe location before damage to the product occurs in the event that equipment cannot be repaired in a timely manner.

Maintain records to demonstrate compliance.

Reason: Loss prevention.

4.10 Calibration and verification of control and monitoring devices

4.10.1 Calibration of temperature control and monitoring devices

Calibrate devices against a certified, traceable reference standard at least once a year, unless otherwise justified. Calibration should demonstrate the accuracy of the unit across the entire temperature range over which the device is designed to be used. Single-use devices that are supplied with a manufacturer's calibration certificate do not need to be re-calibrated.

4.10.2 Calibration of humidity control and monitoring devices

Calibrate devices against a certified, traceable reference standard at least once a year unless otherwise justified. Single-use devices that are supplied with a manufacturer's calibration certificate do not need to be re-calibrated.

4.10.3 Alarm equipment verification

Check functionality of temperature and humidity alarms at least once every six months at the designated set points.

Maintain records to demonstrate compliance.

Reason: To ensure that labelled TTSP storage temperatures and humidity control can be maintained during long-term storage and that the store can demonstrate to the regulatory authorities and other interested parties that due diligence has been observed.

5. Materials handling

5.1 Materials handling equipment

Where powered materials handling equipment is used in temperature- controlled rooms, cold rooms or freezer rooms, select equipment which is certified for safe use in confined spaces.

Reason: Protection of the workforce.

6. Transport and delivery

6.1 Normative references

- Directive 94/62/EC. *European Parliament and Council Directive of 20 December 1994 on packaging and packaging waste.*1994.
- EN 13428:2004. *Packaging. Requirements specific to manufacturing and composition. Prevention by source reduction.*
- EN 13430:2004. *Packaging. Requirements for packaging recoverable by material recycling.*
- EN 13431:2004. *Packaging. Requirements for packaging recoverable in the form of energy recovery, including specification of minimum inferior calorific value.*
- EN 13432:2000. *Packaging. Requirements for packaging recoverable through composting and biodegradation. Test scheme and evaluation criteria for the final acceptance of packaging.*

- IATA *Perishable Cargo Regulations Chapter 17*, 9th Edition, July 2009.
- *Isothermal and refrigerating containers for health products — Thermal performance qualification method.*
- ISTA — 5B: *Focused Simulation Guide for Thermal Performance Testing of Temperature Controlled Transport Packaging.*
- ISTA — 7D: *Thermal Controlled Transport Packaging for Parcel Delivery System Shipment. Basic Requirements: atmospheric conditioning, vibration and shock testing.*
- WHO Technical Report Series, No. 937, 2006. Annex 5: *Good distribution practices for pharmaceutical products.*

6.2 Product stability profiles

Transport TTSPPs in such a manner that transport temperatures meet local regulatory requirements at the sending and receiving sites and/or so that temperature excursions above or below the manufacturer's labelled storage temperature range do not adversely affect product quality. Product stability data must demonstrate the acceptable temperature excursion time during transport.

Reason: Protection of TTSPPs against degradation.

6.3 Transport route profiling and qualification

Profile and qualify transport routes:

- Select the most suitable methods for protecting TTSPPs against anticipated ambient temperature and humidity conditions throughout the year.
- Use suitable methods, including published standards, weather data, laboratory tests and field tests to select suitable transport equipment and shipping containers.

Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.4 Temperature-controlled transport

6.4.1 Air and sea transport

Ensure that any carrier contracted to transport TTSPPs by air or by sea operates under the terms of a formal service level agreement (SLA) drawn up between the parties. The carrier is to be made responsible for maintaining load temperatures within the transport temperature profile defined for each product.

Reason: To ensure that the carrier is made responsible for maintaining load temperatures within the transport temperature profile defined for each product and that compliance can be demonstrated to the contracting organization, the regulatory authorities and other interested parties.

6.4.2 Temperature-controlled road vehicles operated by common carriers

Temperature control in vehicles operated by a common carrier must be qualified and the details and responsibilities for this process should be set out in a formal SLA drawn up between the parties.

Reason: To ensure that the carrier is made responsible for maintaining load temperatures within the transport temperature profile defined for each product and that compliance can be demonstrated to the contracting organization, the regulatory authorities and other interested parties.

6.4.3 Temperature-controlled road vehicles generally

Ensure that temperature-controlled road vehicles used for the transport of TTSPPs are:

- capable of maintaining the temperature range defined by the system set points over the full annual ambient temperature range experienced over known distribution routes and when the vehicle is in motion, or parked with the main engine stopped;
- equipped with a low temperature protection circuit in cold climates where there is a risk of breaching the low temperature set point for TTSPPs that are damaged by exposure to low temperatures;
- equipped with calibrated temperature monitoring devices with sensors located at points representing temperature extremes;
- equipped with alarms to alert the driver in the event of temperature excursions and/or refrigeration unit failure;
- fitted with doors with security seals and/or security locks that protect against unauthorized access during transit;
- qualified as defined in clause 6.6; and
- regularly calibrated and maintained and records kept to demonstrate compliance.

Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.4.4 Transport of controlled TTSPs and TTSPs with high illicit value

Ensure that controlled TTSPs and TTSPs with high illicit value are transported in the following manner:

- Transport practices comply with all relevant local legislation and regulations.
- Vehicles are equipped with lockable doors and an intruder alarm.
- Vehicles use unique seal lock indicating devices such as cable seal locks with unique identifiers that are tamper-resistant to protect against unauthorized access during transit.¹³
- Security-cleared delivery drivers are employed.
- All deliveries are documented and tracked.
- Signed dispatch and arrival records are kept.
- Shipments are fitted with security equipment appropriate to the product being transported and the assessed security risk, such as global positioning system (GPS) devices located in the vehicle and/or hidden in the product.
- Drivers are informed about the perishability of the product and the maximum acceptable transport time.

Reason: To prevent theft and misappropriation of this category of TTSP and to ensure the security and safety of the driver.

6.5 Temperature and humidity control and monitoring during transit

6.5.1 Temperature control in temperature-controlled road vehicles

Provide thermostatic temperature control systems for all temperature-controlled vehicles used to transport TTSPs. Comply with the following minimum requirements:

- system able continuously to maintain air temperatures within the set point limits throughout the validated storage volume defined in clause 6.6;
- control sensors accurate to ± 0.5 °C;
- control sensors calibrated as described in clause 6.7.1;
- control sensors located to control worst-case temperatures in order to maximize available safe storage volume;
- control sensors positioned in the return air stream; and
- control sensors independent of the temperature monitoring system.

¹³ Refer to ISO/PAS 17712: *Freight containers — Mechanical seals*.

6.5.2 Temperature monitoring in temperature-controlled road vehicles

Provide air temperature monitoring systems and devices for vehicles used to transport TTSPPs. Comply with the following minimum requirements:

- monitoring sensors accurate to ± 0.5 °C;
- monitoring sensors calibrated as described in clause 6.7.2;
- monitoring sensors located to monitor worst-case temperatures within the qualified storage zone defined in clause 6.6;
- monitoring sensors positioned so as to monitor worst-case positions;
- provide a temperature record with a minimum recording frequency of six times per hour for each sensor position;¹⁴ and
- provide documentation which can be stored and accessed.

Establish transit temperature specifications and document transit temperatures for every internal and external shipment.

6.5.3 Humidity monitoring in temperature-controlled road vehicles

Preferably provide humidity monitoring systems and devices for temperature-controlled vehicles which are used to transport TTSPPs that require a humidity-controlled environment. Systems and devices should comply with the following minimum requirements:

- sensors accurate to $\pm 5\%$ RH;
- sensors calibrated as described in clause 6.7.3;
- sensors located to monitor worst-case humidity levels within the qualified storage zone defined in clause 6.6;
- sensors positioned so as to be minimally affected by transient events such as door opening;
- provide a humidity record with a minimum recording frequency of six times per hour for each sensor position; and
- provide documentation which can be stored and accessed.

Establish transit humidity specifications and document transit humidity conditions for internal and external shipments where required.

¹⁴ Recording frequency should take account of the storage capacity of the data logger and the expected transport period.

6.5.4 Temperature monitoring in passive and active shipping containers

Use chemical or electronic freeze indicators, electronic loggers (with or without alarms) and/or other suitable indicators to monitor temperature and/or humidity exposure during internal distribution. Preferably use these devices for external distribution. Monitor and document indicator status upon arrival.

Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.6 Qualification of temperature-controlled road vehicles

Where temperature-controlled vehicles are directly owned and/or operated, qualify each vehicle before it becomes operational, wherever possible. The qualification procedure should:

- demonstrate that the air temperature distribution is maintained within the limits specified throughout the temperature-controlled compartment for both air and product temperatures for commonly used load layouts and at the ambient temperature extremes anticipated during normal operation over known routes;
- demonstrate the humidity distribution throughout the temperature-controlled compartment for commonly used load layouts, where products are being transported that require a humidity-controlled environment;
- define zones within the vehicle's payload area which should not be packed with TTSPPs (for example areas in close proximity to cooling coils or cold air streams);
- demonstrate the time taken for temperatures to exceed the designated maximum in the event that the temperature-controlling unit fails; and
- document the qualification exercise.

An alternative approach is to perform an initial full qualification on each trailer/refrigeration unit type combined with an installation qualification (IQ) for each example when a new vehicle becomes operational.

Carry out additional qualification exercises whenever significant modifications are made to the vehicle. Consider the need for requalification whenever temperature and/or humidity monitoring shows unexplained variability that is greater than normal.

Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.7 Calibration and verification of transport monitoring devices

6.7.1 Calibration of transport temperature control devices

Calibrate devices against a certified, traceable reference standard at least once a year, unless otherwise justified.

6.7.2 Calibration of transport temperature monitoring devices

Calibrate devices against a certified, traceable reference standard at least once a year, unless otherwise justified.

6.7.3 Calibration of transport humidity monitoring devices

Calibrate devices against a certified, traceable, reference standard at least once a year, unless otherwise justified.

6.7.4 Verification of transport alarm equipment

Check functionality of temperature and humidity alarms at the designated set points. Check functionality of security alarm systems. Carry out these checks at least once a year, unless otherwise justified.

Maintain records to demonstrate compliance.

Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.8 Shipping containers

6.8.1 Container selection generally

Select shipping containers that:

- comply with applicable national and international standards relevant to the product type and the chosen transport route and mode(s);
- protect personnel and the general public from hazards arising from spillage, leakage or excessive internal pressure;
- protect the product being transported against mechanical damage and the anticipated ambient temperature range that will be encountered in transit; and
- can be closed in a manner that allows the recipient of the consignment to establish that the product has not been tampered with during transport.

Reason: Quality assurance and safety.

6.8.2 Uninsulated containers

Ensure that uninsulated containers are correctly used, in a manner which protects their contents:

- transport uninsulated containers in a qualified temperature-controlled environment such as an actively or passively temperature-controlled vehicle;
- ensure that the transport system is able to maintain the temperature of the TTSP within the product's stability profile as stated by the product manufacturer and/or to maintain the TTSP within the transit temperature specification requirements specified by the regulatory authorities at both the sending and receiving locations.

Reason: Quality assurance and safety.

6.8.3 Qualification of insulated passive containers

Qualify insulated passive containers, including any and all necessary ancillary packaging such as temperature stabilizing medium, dry ice, ice or gel packs, cool water packs or warm packs, phase change materials, partitions, bubble wrap and dunnage:

- ensure that the qualified packaging system is capable of maintaining the TTSP within the temperature range needed to meet the product stability profile as stated by the product manufacturer. Container qualification should include full details of the packaging assembly, the thermal conditioning regime and the minimum and maximum shipping volume, weight and thermal mass that can safely be accommodated in the container. Qualification should also include the correct placement of temperature monitors where these are used;
- take account of the transport route and of the anticipated ambient temperature profile over the duration of transport, measured from the point of departure to the point of arrival in the recipient's temperature-controlled store.

Reason: To ensure that TTSPs can safely be transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.8.4 Qualification of active containers

Qualify active containers:

- ensure that the container is capable of maintaining the TTSP within the temperature range needed to meet the product stability profile as stated by the product manufacturer;

- take account of the transport route and of the anticipated ambient temperature profile over the duration of transport, measured from the point of departure to the point of arrival in the recipient's temperature-controlled store.

Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.9 Shipping container packing

Pack TTSPP shipping containers to:

- the exact specified configuration to ensure that the correct TTSPP temperature range is maintained;
- minimize the risk of theft and fraud and assure the recipient that the goods have not been tampered with while in transit, for example by using locked containers or shrink-wrapped pallets;
- minimize the risk of mechanical damage during transport;
- protect freeze-sensitive products against temperatures below 0 °C when frozen packs are used;
- protect products against light, moisture and contamination or attack by microorganisms and pests;
- protect products against adverse effects when dry ice is used as a coolant;
- clearly label containers to identify the correct transport temperature range and to show correct orientation for handling; and
- ensure that packages containing dangerous goods (including dry ice) are labelled in compliance with relevant transport regulations and requirements.

Reason: To ensure that shipping containers are systematically used in the manner defined during the container qualification process and that this can be demonstrated to the regulatory authorities and other interested parties.

6.10 Product handling during packing and transport

Handle TTSPPs correctly during packing and transport:

- pack TTSPPs in an area set aside for the assembly and packaging of these products as specified in clause 3.3.1;
- take precautions against spillage or breakage, contamination and cross-contamination;

- deliver TTSPPs to outside recipients by the most suitable mode(s) of transport available in order to minimize delivery time; and
- ensure that patients receiving TTSPP deliveries are given clear advice on correct storage of the product before use.

Reason: To maintain TTSPP quality during transport.

6.11 Cleaning road vehicles and transport containers

Implement a cleaning and decontamination programme for all road vehicles and reusable shipping containers used to transport TTSPPs:

- ensure that all internal surfaces of load compartments are regularly cleaned;
- do not allow the accumulation of dust, dirt and waste, including packaging waste in load compartments, or in reusable shipping containers;
- take precautions against spillage or breakage, and cross-contamination;
- do not allow accumulation of frost and ice in refrigerated vehicles, particularly ice contaminated by spillages; and
- collect waste in designated closed containers and arrange for safe disposal at frequent intervals.

Maintain cleaning records for vehicles and reusable shipping containers to demonstrate compliance.

Reason: Protection against damage and contamination of TTSPPs and hazards to workers arising from spillage or breakage.

6.12 Transport of returned and recalled TTSPPs

6.12.1 Transport of returned TTSPPs

Ensure that that returned TTSPPs are transported under the same conditions as those used for the initial delivery:

- the sender and recipient must work together so that that the product is maintained within the temperature range needed to meet the manufacturer's stated product stability profile;
- take account of the anticipated ambient temperature profile over the duration of transport, measured from the point of departure to the point of return; and
- quarantine returned TTSPPs in temperature-controlled storage pending a decision by the quality control department or qualified person to dispose of the product or to return it to stock.

Reason: To ensure that returned and recalled TTSPPs are maintained within the correct transport temperature profile so that they can safely be re-stocked if a decision to do so is made.

6.12.2 Transport of recalled TTSPPs

Ensure that recalled TTSPPs are:

- marked for disposal as either “recalled” or “withdrawn”;
- transported back from the recipient and quarantined under secure conditions pending a final decision on disposal as described in clause 8.6.3.

7. Labelling

7.1 Normative references

- *IATA Perishable Cargo Regulations Chapter 179th Edition, July 2009. Clauses 17.10.5 and 17.10.6.*

7.2 Labelling

7.2.1 Labelling generally

Label internal shipping and external distribution containers containing TTSPPs as follows:

- identify the product in accordance with all national and international labelling requirements relevant to the container content, transport route and mode(s);
- identify hazardous products in accordance with relevant national and international labelling conventions; and
- indicate the appropriate temperature and humidity ranges within which the product is to be transported and/or stored.

7.2.2 Labelling air-freighted shipments

In cases where TTSPPs are to be air-freighted, the package(s) should be labelled using the standard International Air Transport Association (IATA) time and temperature-sensitive symbol, in accordance with the conditions outlined in Chapter 17 of the IATA Perishable Cargo Regulations. Apply the label to the outer surface of individual shipping packages, overpacks or bulk containers.

Reason: To ensure that products are correctly and safely handled at all points in the supply chain.

8. Stock management

8.1 Stock control systems

8.1.1 General stock control systems and procedures

TTSPS stock control systems and procedures meet the following minimum requirements:

- allow access only to authorized persons;
- record all receipts and dispatches;
- record batch numbers and expiry dates;
- record short-dated and expired products;
- record product status (i.e. released, quarantined, hold, reject);
- record all product returns, recalls, withdrawals, damage and disposals;
- manage the issue of products in EEFO order; and
- take regular physical inventories and reconcile stock records with the actual physical count. Investigate and report on stock discrepancies in accordance with agreed procedures. Preferably physical counts should be made at least twice a year.

Reason: To ensure that accurate and complete stock records are kept at all times.

8.1.2 Stock control procedures for controlled and hazardous TTSPSs

In addition to the requirements set out in clause 8.1.1, implement the following procedures:

- Institute a customer verification process to ensure that all recipients of these products are authorized to receive them.
- Maintain stock records which specifically identify products in these categories.
- Carry out regular audits and make audit reports available to the responsible authorities.
- Comply with all record-keeping procedures specified in local legislation and regulations. Retain product transaction and delivery records for at least the minimum time period required by local regulations.

Reason: To ensure that accurate and complete stock records are kept at all times and to satisfy the requirements of the regulatory authorities.

8.2 Incoming goods

8.2.1 Product arrival checks

Check and record the following for all incoming TTSPPs:

- product name, item code (identifier), strength, and batch/lot number;
- quantity received against order;
- name and address of the supplying site;
- examine containers for tampering, damage or contamination;
- examine expiry dates — accept short-dated products only if prior agreement has been reached with the supplier; do not accept products that have expired or which are so close to their expiry date that this date is likely to occur before use by the consumer;
- delays encountered during transport;
- status of any attached temperature recording device(s) and/or time/temperature indicators; and
- verify that required storage and transport conditions have been maintained.

8.2.2 Actions following arrival checks

- Enter product details, including product name/number, strength, batch numbers, quantities received, expiry dates and acceptance status into the stock recording system.
- Store checked goods under the correct temperature and security regime immediately upon receipt.
- Quarantine defective or potentially defective products, products with incomplete or missing paperwork, products that experienced unacceptable temperature excursions during transport, or products suspected to be counterfeit. Do not release until checks have been completed satisfactorily. All unacceptable temperature excursions should be evaluated to determine their effect on the product.
- Report any defects to the supplying store or holder of the marketing authorization.
- Do not transfer to saleable stock until all relevant disposition procedures have been completed.

Reason: To ensure that incoming TTSPPs are in acceptable condition, accurately recorded and correctly stored and that defective and/or incorrect shipments are followed up with the supplier.

8.3 Outgoing goods (external deliveries)

8.3.1 Management of outgoing goods

Implement outgoing goods procedures to ensure that:

- Transport vehicle conformity, including conformity with SLA or quality assurance (QA) agreements, is checked before loading goods.
- Expired products are never issued.
- Products with short expiry dates are not issued unless the recipient accepts that they can be consumed before the expiry date is reached.
- Products are distributed in strict EEFO order unless a product-based time-temperature exposure indicator, such as a vaccine vial monitor, demonstrates that a batch should be distributed ahead of its EEFO order.
- Details of any temperature monitoring devices packed with the external distributions are recorded.
- Details of outgoing products, including product name/number, strength, batch numbers, expiry dates and quantities distributed, are entered into the stock recording system.

8.3.2 Actions following dispatch

Monitor TTSPPs following dispatch in order to:

- trace products to their intended destination;
- record and retain records to provide assurance of goods arrival status. A suitable delivery report from the carrier is an acceptable alternative; and
- take appropriate action in the event of returns, recalls or complaints.

Reason: To ensure that outgoing TTSPPs are in acceptable condition, that short-dated stock does not accumulate in the store and that evidence is kept to demonstrate that correct quantities are distributed and received in good condition.

8.4 Product complaint procedures

Manage product complaints as follows:

- If a product defect is discovered or suspected in a batch of TTSPPs, cooperate with the regulatory authority to determine whether other batches are affected and recall products if required to do so by the regulatory authority.
- Where complaints or defects relate to a product or its packaging, immediately notify the holder of the marketing authorization for the product.

- Where complaints or defects arise as a result of errors or omissions within the organization, immediately evaluate the causes and take remedial measures to prevent a recurrence.
- Record all complaints and the remedial actions taken. Monitor and analyse trends in the complaint records.

Reason: Protection of the public and of the reputation of the supplying organization.

8.5 Suspect product procedures

8.5.1 Suspect products

Implement systems for identifying and managing suspect products found in the supply chain as follows:

- Physically segregate any suspect TTSPs found in the supply chain and store securely until legal investigations are complete.
- Label them clearly as “Not for use” or other similar phrase;
- Immediately notify the regulatory authority or authorities and any other relevant authorities, as well as the holder of the marketing authorization of the product.
- Cooperate with regulatory authorities to assist with investigating the source of suspect products and implement appropriate remedial action(s).
- Document the decision-making process for disposal or return of condemned or defective TTSPs and make these records available to the relevant authorities.

Reason: Protection of the public, protection of legitimate suppliers and manufacturers and conformity with regulatory requirements.

8.6 Product return, recall, withdrawal and disposal procedures

8.6.1 Return procedures

Manage product returns as follows:

- Quarantine returned TTSPs in a suitable temperature-controlled area and under the security conditions applicable to the product type.
- Do not return to saleable stock unless storage and transport temperature conditions after dispatch from the distribution site have been fully verified and documented, including the return leg to the distribution site.
- Where appropriate, obtain written advice from the holder of the marketing authorization regarding handling and/or disposal of the returned TTSP.

- If returned stock is re-issued, distribute in EEFO order or in accordance with the exposure status of any product-mounted time-temperature indicator device.
- Quarantine returned TTSPPs that have been exposed to unacceptable storage and/or transport temperatures and mark for disposal.
- Maintain records of all returned TTSPPs.

Reason: Protection of the public.

8.6.2 Recall procedures

Manage product recalls as follows:

- Conduct urgent and non-urgent TTSP recall in accordance with an agreed emergency plan.
- Notify the local regulatory authority or authorities.
- Notify overseas regulatory counterparts where the product has been exported.
- Notify all affected customers as applicable.
- Quarantine any remaining inventory of recalled TTSPPs and mark for further investigation before disposal.
- Maintain records of all TTSP recalls, including reconciliation of quantity sold, quantity returned, quantity remaining or quantity consumed.

Reason: Protection of the public and conformity with regulatory requirements.

8.6.3 Disposal procedures

Manage product awaiting board of survey or disposal as follows:

- Ensure that rejected and/or recalled or withdrawn TTSPPs cannot be used, released or cause contamination to other products. Store separately from other products, in accordance with local regulations, to await destruction or return to the supplier.
- Safely dispose of rejected and/or recalled/withdrawn products in accordance with local regulations, including where relevant, regulations covering the disposal of hazardous and controlled drugs.
- Maintain disposal records.

Reason: Protection of the public and the environment.

8.7 Traceability or stock tracking

Ensure that stock and distribution records enable traceability, or stock tracking, of TTSPPs from the point of supply to the end-user or patient.

Traceability should include records of the temperature exposure of the product during internal shipping and storage. These records should include:

- for incoming goods: status of shipping indicators used (if any), status of product-based time-temperature indicators (if any) and physical condition of goods and time of receipt;
- for outgoing goods: type of shipping indicators used (if any), status of product-based time-temperature indicators (if any) and physical condition of goods and time of dispatch.

Monitor, record, and investigate discrepancies.

Reason: To demonstrate that TTSPPs have been correctly distributed and to facilitate product recalls and detect theft and fraud.

9. General procedures and record-keeping

9.1 Emergencies and contingency planning

Make contingency arrangements for the safe storage of TTSPPs in the event of emergencies, including, but not confined to:

- extended power supply outages;
- equipment failure; and
- vehicle breakdown during transport of TTSPPs.

Prepare action plans to deal with products subjected to temperature excursions.

Ensure that the responsible staff know, and have rehearsed, the appropriate actions to be taken in the event of the identified emergency scenarios.

Reason: Loss prevention.

9.2 General record-keeping

9.2.1 Record-keeping

Maintain comprehensive records and ensure that they are laid out in an orderly fashion and are easy to check.

Paper records must be:

- stored and maintained so that they are accessible and easily retrievable;
- labelled, dated and filed for easy identification;

- protected against deterioration and loss due to fire, flood or other hazards;
- kept secure and protected against unauthorized access; and
- signed and dated by authorized persons and not changed without due authorization.

Computer records must be:

- logically filed for easy identification and retrieval;
- kept secure and protected against unauthorized access;
- where feasible, manually signed, dated and scanned or when electronically archived dated, encrypted and with check-sum;¹⁵
- regularly backed-up and archived on media that are independent of the record-keeping computer system(s). Back-up media may be a separate secure server, a separate hard disc, a flash drive or other digital media appropriate to the scale of the operation.

9.2.2 Content of records

Ensure that the following traceability data is recorded for each TTSP batch number, as applicable:

- status of product on arrival;
- temperature and humidity records including records of excursions outside labelled storage and/or transit temperature specification conditions;
- general TTSP stock transactions, including purchase and sale records;
- controlled drug audits;
- audits for products with high illicit value;
- audits for hazardous products;
- stock tracking;
- return, recall, withdrawal and disposal reports, where relevant;
- product complaint reports, where relevant; and
- counterfeit product reports, where relevant.

Maintain all records in accordance with local legislation and regulations.

¹⁵ Electronic records from data loggers are usually encrypted and protected by check-sums. This ensures compliance with FDA Title 21 CFR Part 11: Electronic Records; Electronic Signatures; Final Rule (1997).

9.2.3 Record review and retention

Ensure that records are reviewed and approved on a regular basis by a designated member of the quality management team. Ensure that records are accessible for review by end-users, the regulatory authority and other interested parties. Retain records for the minimum period required under local legislation, but for not less than three years.

Reason: Internal quality control, transparency and external inspection by the regulatory authorities and other interested parties.

9.3 Temperature and humidity records

9.3.1 Temperature records

Monitor and record storage temperatures in all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, as follows:

- Check and record temperatures at least twice daily — in the morning and evening — and preferably continuously.
- Review temperature records monthly and take action to rectify systematic excursions.
- Systematically file temperature records for each storage environment or piece of equipment to ensure traceability. Keep records for at least one year after the end of the shelf-life of the stored material or product, or as long as required by national legislation.

9.3.2 Humidity records

When storing products which are adversely affected by high relative humidity (see clause 4.5.3), monitor and record humidity levels in all temperature-controlled rooms as follows:

- Record humidity at least twice every 24 hours or preferably continuously.
- Check humidity records daily.
- Review humidity records monthly and take action to rectify systematic excursions.
- Systematically file humidity records for each temperature-controlled room to ensure traceability. Keep records for at least one year after the end of the shelf-life of the stored material or product, or as long as required by national legislation.

Reason: Internal quality assurance and availability of records for review by the regulatory authorities and other interested parties.

10. Environmental management

10.1 Normative references

- ISO 14001: 2004. *Environmental management systems — Requirements with guidance for use*.
- *The Montreal Protocol on Substances that Deplete the Ozone Layer*. UNEP, 2000.

10.2 Environmental management of refrigeration equipment

Ensure that all new refrigeration equipment for temperature-controlled storage and transport is specified to:

- use refrigerants that comply with the Montreal Protocol;
- minimize or eliminate the use of refrigerants with high global warming potential (GWP); and
- minimize CO₂ emissions during operation.

Select equipment to minimize whole-life environmental impact and employ best practice to eliminate leakage of refrigerant into the environment during installation, maintenance and decommissioning of refrigeration equipment.

Reason: Compliance with international protocols and accords on climate change and environmental protection.

11. Quality management

11.1 Normative references

- ICH, 2005: *ICH Harmonized Tripartite Guideline: Quality risk management Q9*
- ISO 9000:2005. *Quality management systems — Fundamentals and vocabulary*
- ISO 9001:2008. *Quality management systems — Requirements*
- ISO 9004:2000. *Quality management systems — Guidelines for performance improvements*
- ISO 10005:2005. *Quality management systems — Guidelines for quality plans*
- ISO 19011:2002. *Guidelines for quality and/or environmental management systems auditing*

11.2 Organizational structure

Establish, document and maintain an organizational structure for the TTSP storage and shipping and distribution operations which clearly identifies all key management responsibilities, and the personnel who are accountable.

Reason: Quality management.

11.3 Quality systems

11.3.1 Quality system

Establish, document and maintain a quality system for the management of TTSPs including, the following, as applicable:

- standard quality system(s) and associated auditing procedures;
- written procedures and specifications;
- record storage, record retention and record destruction programme;
- risk management;
- calibration programme;
- stability programme;
- qualification and validation programme;
- deviation and root cause investigation programme;
- corrective and preventive action (CAPA) procedures;
- training programme;
- periodic temperature-controlled process assessment;
- change control programme;
- maintenance programme;
- management controls;
- product return and recall/withdrawal policies, including emergency recalls;
- product complaint policies;
- material destruction programme;
- warehouse and storage programme;
- shipping and distribution programme;
- notification systems for regulatory agencies; boards of health and ministries of health; and
- self-inspection programme and continuous quality improvement.

Carry out annual reviews of the quality management system to ensure that it remains appropriate, relevant, and effective.

Reason: Quality assurance.

11.3.2 Self inspections

Conduct regular self-inspections to ensure continuing compliance with quality management standards GSP and GDP; record results, follow-up with the corrective actions needed to rectify areas of non-compliance and document the changes made.

11.3.3 Contractors subject to service level agreements

Ensure that every contractor with whom there is an SLA provides periodic evidence of compliance with the GSP and/or GDP standards incorporated into the SLA.

Reason: To demonstrate compliance with applicable quality management standards.

11.4 Management of documents and standard operating procedures

11.4.1 Standard operating procedures

Develop and maintain SOPs covering correct storage, internal shipping and external distribution of TTSPPs, including, but not limited to, the following topics:

- security, including management of controlled and hazardous TTSPPs;
- safe handling of TTSPPs;
- temperature monitoring;
- calibration of temperature and humidity monitoring devices and alarm systems;
- qualification and validation procedures, including temperature mapping;
- maintenance of controlled-temperature equipment;
- facility cleaning and pest control;
- facility maintenance;
- product arrival (receiving) procedures and records;
- stock storage and warehousing procedures (put away, replenishment, order fulfilment, packing);
- stock control procedures and records;
- distribution procedures and records;
- management of temperature excursions;

- product return and recall/withdrawal procedures and records;
- product complaint procedures and records;
- safe disposal of damaged, expired and quarantined products and records which are no longer required;
- temperature-controlled packaging and route qualification;
- temperature-controlled vehicle operation, including management of security locks and seals;
- emergency response procedures; and
- environmental management.

Ensure that all documents are clear and unambiguous and that document change control procedures are in place as specified in clause 11.5.

Reason: Quality management and staff training.

11.5 Document control

Ensure that all quality manuals, SOPs and similar documents are:

- authorized by an appropriate person;
- recorded in a document register;
- regularly reviewed and kept up to date, with all changes recorded and authorized;
- version controlled;
- issued to all relevant personnel; and
- withdrawn when superseded.

Withdraw superseded documents and retain record copies for document history files and for the minimum period(s) required by the regulatory authorities and for duty-of-care purposes.

Reason: Good quality management practice.

12. Personnel/training

12.1 Training

12.1.1 General training

Provide regular and systematic training for all relevant personnel responsible for storage, loading and unloading areas used for non-hazardous TTSPs, covering the following:

- applicable pharmaceutical legislation and regulations;
- SOPs and safety issues; and
- response to emergencies.

Ensure that each employee understands his or her specific responsibilities. Provide similar training for drivers who are responsible for transporting these substances. Maintain individual training records to demonstrate compliance and regularly evaluate the effectiveness of training programmes.

Reason: To ensure that all relevant personnel are competent to carry out their duties.

12.1.2 Specialist training

In addition to the training described in clause 12.1.1, provide regular and systematic additional training for relevant personnel responsible for storage, loading and unloading of controlled or hazardous TTSPs. Training should cover the following:

- applicable legislation and regulations;
- security and safety risks; and
- response to emergencies.

Ensure that each employee understands his or her specific responsibilities. Maintain training records to demonstrate compliance and perform effectiveness checks on training. Provide similar training for drivers who are responsible for transporting these substances.

Reason: To ensure that all relevant personnel are competent to handle controlled or hazardous TTSPs.

Key references

- World Health Organization/United Nations Children's Fund/United Nations Development Programme/United Nations Population Fund/World Bank *A model quality assurance system for procurement agencies*. Geneva, World Health Organization, 2007 (WHO/PSM/PAR/2007.3).
- Therapeutic Goods Administration *Australian code of good wholesaling practice for therapeutic goods for human use*. Commonwealth of Australia, Canberra ACT, Draft Revision — June 2006.
- *Protocol for the control of storage temperatures of medicinal products*. London, British Association of Pharmaceutical Wholesalers, 1999.
- The Council of the European Communities. Council Directive 92/25/EEC of 31 March 1992 on the wholesale distribution of medicinal products for human use. *Official Journal L 113*, 30/04/1992 p. 0001 — 0004.
- The Council of the European Communities. EU Council Directive 92/27/EEC of 31 March 1992 on the labelling of medicinal products for human use and on package leaflets. *Official Journal L 113*, 30/04/1992 p. 0008 — 0012.

- State Food and Drug Administration of the People's Republic of China. *Drug administration law of the People's Republic of China*. 2001.
- EU 94/C 63/03. *Guidelines on good distribution practice of medicinal products for human use*. 1994.
- The European Parliament and the Council of the European Union. EU Directive 2004/27/EC. Community code relating to medicinal products for human use. *Official Journal L 136/34/2004*.
- EU Regulation 4/2007. *Good distribution practices for pharmaceutical wholesalers*. 2007.
- GUIDE-0069: *Guidelines for temperature control of drug products during storage and transportation*. Ottawa, Ontario, Health Canada. Health Products and Food Branch Inspectorate, 2005.
- IATA *Perishable Cargo Regulations Chapter 17*. 9th ed, International Air Transport Association, 2009.
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: *ICH Harmonised Tripartite Guideline: Quality Risk Management Q9*. November 2005.
- Irish Medicines Board. *Guide to control and monitoring of storage and transportation temperature conditions for medicinal products and active substances*. Edition IND-003 Version 1, March 2006.
- *Best practices for repositories*. International Society for Biological and Environmental Repositories, 2008.
- Medicines and Healthcare products Regulatory Agency. *Rules and guidance for pharmaceutical manufacturers and distributors*. London, Pharmaceutical Press, 2007.
- PDA: Technical report 39: *Guidance for Temperature Controlled Medicinal Products: Maintaining the quality of temperature-sensitive medicinal products through the transportation environment*. Parenteral Drug Association, 2007.
- *Guidance notes on good distribution practices*. Singapore Health Sciences Authority: 2008.
- Taylor, J. *Recommendations on the control and monitoring of storage and transportation temperatures of medicinal products*. London, Medicines and Healthcare products Regulatory Agency, 2001.
- Ozone Secretariat United Nations Environment Programme. *The Montreal Protocol on Substances that Deplete the Ozone Layer*. Nairobi, UNEP, 2000.
- USP <1079> *Good storage and shipping practices*. United States Pharmacopeia. 2009.
- USP 32-NF 27, *General Notices and requirements*. United States Pharmacopeia 2009.
- USP <1118> *Monitoring Devices—Time, Temperature, and Humidity*. United States Pharmacopeia, 2007.
- *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902; https://iris.who.int/bitstream/handle/10665/42424/WHO_TRS_902.pdf?sequence=1&isAllowed=y).
- *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908; https://iris.who.int/bitstream/handle/10665/42613/WHO_TRS_908.pdf?sequence=1&isAllowed=y).
- *Good trade and distribution practices for pharmaceutical starting materials*. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report*. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 917; https://iris.who.int/bitstream/handle/10665/42851/WHO_TRS_917.pdf?sequence=1&isAllowed=y) Annex 2.
- *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937; https://apps.who.int/iris/bitstream/handle/10665/43443/WHO_TRS_937_eng.pdf?sequence=1).
- *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report*. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y) Annex 5.

Further reading

- **Bishara, R.** A simple answer to cold chain chaos. *World Pharmaceutical Frontiers*, 2008, 5:65–66.
- European Parliament and Council Directive 94/62/EC of 20 December 1994 on packaging and packaging waste. Official Journal L 365 , 31/12/1994 P. 0010 — 0023.
- **Falconer P, Drury J.** *Building and planning for industrial storage and distribution*. Architectural Press, London, 2003.
- Germanischer Lloyd Certification & Cool Chain Association. *Cool Chain Quality Indicator Standard (CCQI)* 20th June 2007, Version 1.5.
- **Kartoglu U, Ganivet S, Guichard S, Aiyar V, Bollen P, Maire D, Altay B.** Use of cool water packs to prevent freezing during vaccine transportation at the country level. *PDA Journal of Pharmaceutical Science and Technology*, 2009, 63:11-26
- Management Sciences for Health. *Managing Drug Supply*. Kumarian Press, pp. 11-26,1997.
- *Regulation (EC) No 2037/2000 of the European Parliament and of the Council of 29 June 2000 on substances that deplete the ozone layer*, Official Journal of the European Communities 29.9.2000.
- **RushtonA, Croucher P, Baker P.** *The handbook of logistics and distribution management*. Kogan Page, London, 2006.
- **Seevers R, Hofer J, Harber P, Ulrich D, Bishara R.** The use of mean kinetic temperature (MKT) in the handling, storage and distribution of temperature sensitive pharmaceuticals. *Pharmaceutical Outsourcing*, May/June 2009: 30-38.
- UNEP,Recovery & recycling systems guidelines: Phasing out ODS in developing countries — refrigeration sector. Paris, 1999.
- United Nations Economic Commission for Europe. ATP handbook. 2008.

Task force membership

Name	Organization	Category	Country
Henry Ames	Sensitech	Temperature monitoring	United States of America
Claude Ammann	Topotarget	Manufacturer	Switzerland
Erik van Asselt	PDA PCCIG	PDA	Netherlands (Kingdom of the)
Anthony Battersby	FBA Health Systems	Consultant	United Kingdom of Great Britain and Northern Ireland
Rafik Bishara	PDA PCCIG	PDA	United States of America
Richard Brown	TGA	Regulatory	Australia
Linda Carducci	Johnson & Johnson	IFPMA	United States of America

Table *continued*

Name	Organization	Category	Country
Gérald Cavalier	Cemafrica	IIR	France
Isabelle Clamou	EFPIA	IFPMA	Belgium
Michael Eakins	USP	Regulatory	United States of America
Chris T Forrest	AstraZenca	IFPMA	United Kingdom of Great Britain and Northern Ireland
Juliman Fuad	BioFarma	Manufacturer	Indonesia
Andreas Giger	Berlinger	Temperature monitoring	Switzerland
Andre Haeusermann	Novartis Pharma	IFPMA	Switzerland
Rodney L Horder	Abbott	IFPMA	United Kingdom of Great Britain and Northern Ireland
Laila Jarrar	Food & Drug Administration	Regulatory	Jordan
Ryoko Krause	IFPMA	IFPMA	Switzerland
Santosh Kutty	CDL Kasauli	Regulatory	India
Gilles Labranque	Sofrigam	IIR	France
Adrien Lehideux	ColdPack	Passive cooling	France
Zhang Lei	National Biotec Group (Chengdu Institute)	DCVMN	China
Eric Lindquist	Organization		
Entropy Solutions	Category		
Passive cooling	Country United States of America		
Kåre Lindroos	Huure	Active cooling	Finland
Gianluca Minestrini	Hoffmann-La Roche	IFPMA	Switzerland
Ali Musa Muhaidat	Vaccine & Sera Department	Ministry of Health	Jordan

Table *continued*

Name	Organization	Category	Country
Fernand Muller	Dometic	Active cooling	Luxembourg
Kevin O'Donnell	IATA	IATA	United States of America
Giralomo Panozzo	ITC/CNR	IIR	Italy
Stefanie Pluschkell	Pfizer	IFPMA	United States of America
Fabian De Paoli	GSK Biologicals	IFPMA	Belgium
Cristiane Frensch Pereira	Bio-Manguinhos	DCVMN	Brazil
Thadeus Prusik	TempTime	Temperature monitoring	United States of America
Eric Raemdonck	IATA	IATA	Canada
Joanie Robertson	PATH	PATH	United States of America
Isabel Rojas	CIGB/ Cuba	DCVMN	Cuba
Wolfram Schlimme	Crucell	IFPMA	Switzerland
Inderjit Sharma	Serum Institute of India Ltd	DCVMN	India
Sarah Skuce	Health Canada	Regulatory	Canada
Engko Sosialine	National Agency of Drug and Food Control	Regulatory	Indonesia
John Taylor	MHRA	Regulatory	United Kingdom of Great Britain and Northern Ireland
Mahboubia Vladakhani	Biological Dept Pharmaceutical & Narcotics	Regulatory	Iran (Islamic Republic of)
Lisette Vromans	Merck	IFPMA	Netherlands (Kingdom of the)

World Health Organization Performance, Quality and Safety Secretariat			
Andrew Garnett	Author — Group leader	Consultant	United Kingdom of Great Britain and Northern Ireland
Ümit Karto_lu	Family and Community Health/Quality, Safety and Standards- Chair	WHO	Switzerland
Denis Maire	Family and Community Health/Quality, Safety and Standards	WHO	Switzerland
World Health Organization			
Lahouari Belgharbi	Family and Community Health/Quality, Safety and Standards	WHO	Switzerland
Ivana Knezevic	Family and Community Health/Quality, Safety and Standards	WHO	Switzerland
Sabine Kopp	Health Systems and Services/ Essential Medicines and Pharmaceutical Policies/ Quality Assurance and Safety: Medicines	WHO	Switzerland

8.7 Technical supplements to Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

Annex 5, WHO Technical Report Series, 992, 2015

1. The technical supplement series	1393
1.1 Topics covered	1393
1.2 Target readership	1394
1.3 Document development and review process	1394
Supplement 1 Selecting sites for storage facilities	1396
Supplement 2 Design and procurement of storage facilities	1398
Supplement 3 Estimating the capacity of storage facilities	1400
Supplement 4 Building security and fire protection	1401
Supplement 5 Maintenance of storage facilities	1403
Supplement 6 Temperature and humidity monitoring systems for fixed storage areas	1404
Supplement 7 Qualification of temperature-controlled storage areas	1406
Supplement 8 Temperature mapping of storage areas	1408
Supplement 9 Maintenance of refrigeration equipment	1410
Supplement 10 Checking the accuracy of temperature control and monitoring devices	1412
Supplement 11 Qualification of refrigerated road vehicles	1413
Supplement 12 Temperature-controlled transport operations by road and by air	1415
Supplement 13 Qualification of shipping containers	1416
Supplement 14 Transport route profiling qualification	1417
Supplement 15 Temperature and humidity monitoring systems for transport operations	1418
Supplement 16 Environmental management of refrigeration equipment	1419

1. The technical supplement series

This series of technical supplements has been written to amplify the recommendations given in *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products* (WHO Technical Report Series, No. 961, 2011, Annex 9).¹ This document sets out the principal requirements for the safe storage and distribution of time- and temperature-sensitive pharmaceutical products (TTSPPs).

The introduction to the guidance documents states that: “... supplementary materials will be developed to show how the requirements can practicably be achieved, particularly in resource constrained settings.” The technical supplements, which make up this volume, are intended to provide this additional material; each one is linked back to a specific clause or clauses in the parent document. All 16 documents are written in a standard format and each contains a reference section with hyperlinks to relevant supporting materials. Most of these materials are available free online. References to print publications are minimized to avoid the difficulties associated with purchasing books and journals.

1.1 Topics covered

Table A5.1 lists the titles of the supplements and the model guidance sections to which each one refers.

Table A5.1

Titles of supplements and model guidance section to which each refers

Title	Section(s)
1. Selecting sites for storage facilities	Section 2
2. Design of storage facilities	Section 2 to 5
3. Estimating the capacity of storage facilities	Section 3.1 to 3.4
4. Security and fire protection in storage facilities	Section 3.7
5. Maintenance of storage facilities	Section 3.10
6. Temperature monitoring of storage areas	Section 4.5.2, 4.5.4
7. Qualification of temperature-controlled storage areas	Section 4.7
8. Temperature mapping of storage areas	Section 4.7

¹ https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1.

Table A5.1 *continued*

Title	Section(s)
9. Refrigeration equipment maintenance	Section 4.9
10. Checking the accuracy of temperature control and monitoring devices	Section 4.10
11. Qualification of refrigerated road vehicles	Section 6.4, 6.5
12. Temperature-controlled transport operations by road and by air	Section 6.5, 9
13. Qualification of shipping containers	Section 6.8.1 to 6.8.4
14. Transport route profiling qualification	Section 6.8.3, 6.8.4
15. Temperature and humidity monitoring systems for transport operations	Section 6.5, 9
16. Environmental management of refrigerant gases and refrigeration equipment	Section 10.2

1.2 Target readership

The target readership for the model guidance, and for the technical supplements, includes regulators, logisticians and pharmaceutical professionals in industry, government and international agencies.

1.3 Document development and review process

The technical supplements have been written by specialist authors. All 16 supplements passed through the following editorial and public review process.

1. Each document was prepared over the course of several drafts in consultation with the series editor.
2. Acronyms and glossary definitions were harmonized throughout.
3. Public consultation drafts were posted on the WHO website in mid-2014. Review comments were received from a number of people and organizations.
4. Reviews were consolidated by the series editor and sent to the individual authors for initial comment.
5. Amended documents were prepared containing the consolidated comments categorized as “accepted”, “rejected” and “for discussion”. These new drafts were sent back to the individual authors for further comment.

6. The series editor prepared final drafts based on the authors' responses and these drafts were checked, reviewed and signed off.
7. On the basis of these final comments, clean versions were prepared for review by the Expert Committee on Specifications for Pharmaceutical Preparations and by the Expert Committee on Biological Standardization.

On the following pages, the contents pages of the 16 technical supplements are reproduced. The full texts will be made available in electronic form on the CD-ROM of *Quality assurance of pharmaceuticals* (2015 and updates) and on the website.²

² <https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/>.

Supplement 1

Selecting sites for storage facilities

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-trsno-961>

Contents

Acknowledgements

Abbreviations

Glossary

1. Introduction

- 1.1 Requirements
- 1.2 Objectives
- 1.3 Target readership

2. Guidance

- 2.1 Associated materials and equipment
- 2.2 Designing and costing the supply chain
- 2.3 Logistics network planning
- 2.4 Finding a potential site
 - 2.4.1 *Establish the size of the warehouse*
 - 2.4.2 *Narrow down the choices*
 - 2.4.3 *Choose a secure site*
 - 2.4.4 *Choose a future-proof site*
 - 2.4.5 *Ensure labour availability*
 - 2.4.6 *Assess flood risks*
 - 2.4.7 *Assess weather and climate-related risks*
 - 2.4.8 *Assess fire hazards*
 - 2.4.9 *Assess other natural hazards*
- 2.5 Detailed site investigation: identifying risks and opportunities
 - 2.5.1 *Ground conditions and pollution hazards*
 - 2.5.2 *Existing underground and overhead services*
 - 2.5.3 *Site survey*
 - 2.5.4 *Site clearance costs*
 - 2.5.5 *Building surveys*
 - 2.5.6 *Service connections to the site*
 - 2.5.7 *Low carbon energy potential*
 - 2.5.8 *Environmental impact assessment*

References

Revision history

Supplement 2

Design and procurement of storage facilities

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-a-trs-961>

Contents

Acknowledgements

Abbreviations

Glossary

1. Introduction

- 1.1 Requirements
- 1.2 Objectives
- 1.3 Target readership

2. Guidance

- 2.1 Associated materials and equipment
- 2.2 Design of pharmaceutical warehouses
 - 2.2.1 *Low-carbon design and environmental auditing*
 - 2.2.2 *Warehouse layouts*
 - 2.2.3 *Temperature-controlled storage areas*
 - 2.2.4 *Cold rooms and freezer rooms*
 - 2.2.5 *Order assembly and packing area*
 - 2.2.6 *Staging area*
 - 2.2.7 *Loading docks*
 - 2.2.8 *Other areas*
 - 2.2.9 *Temperature monitoring, mapping and qualification*
- 2.3 Design of dispensing facilities
 - 2.3.1 *Workflow*
 - 2.3.2 *Working environment and ergonomics*
 - 2.3.3 *Incoming stock*
 - 2.3.4 *Refrigerators*
 - 2.3.5 *Controlled drugs*
 - 2.3.6 *Waste and returns*
 - 2.3.7 *Location and arrangement of stock*
 - 2.3.8 *Separation of stock*
 - 2.3.9 *Patient areas*
 - 2.3.10 *Supervised consumption*

- 2.4 Building procurement
 - 2.4.1 *Preparing and agreeing the brief*
 - 2.4.2 *Appointing and working with the consultant team*
 - 2.4.3 *Design risk assessment*
 - 2.4.4 *Choosing a procurement route for new buildings*
 - 2.4.5 *Choosing a procurement route for building alterations or refurbishment*
 - 2.4.6 *The client's role in tendering*
 - 2.4.7 *The client's role during the construction stage*
 - 2.4.8 *Commissioning and handover*
- 2.5 Procuring cold rooms and freezer rooms

References

Annex 1

Briefing documents

- A1.1 Statement of need
- A1.2 Strategic brief
- A1.3 Project brief

Annex 2

Alternative contracts

- A2.1 Lump sum contract
- A2.2 Design and build
- A2.3 Design, build, finance and operate

Revision history

Supplement 3

Estimating the capacity of storage facilities

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-b-trs-961>

Contents

Acknowledgements

Abbreviations

Glossary

1. Introduction

- 1.1 Requirements
- 1.2 Objectives
- 1.3 Target readership

2. Guidance

- 2.1 Associated materials and equipment
- 2.2 Inventory management concepts
- 2.3 Collecting product data
 - 2.3.1 Vaccines
 - 2.3.2 General pharmaceuticals, including non-vaccine TTSPs
 - 2.3.3 Volume data and SKU types
- 2.4 Calculating maximum inventory volumes
 - 2.4.1 Vaccines and related supplies
 - 2.4.2 General pharmaceuticals and supplies, including non-vaccine TTSPs
- 2.5 Calculating net storage capacity requirements
 - 2.5.1 Classifying products by storage temperature and security category
 - 2.5.2 Load support systems
 - 2.5.3 The utilization factor concept
 - 2.5.4 Pallet bay calculation
 - 2.5.5 Shelving unit calculation
 - 2.5.6 Closed shelving units and safety cabinets
 - 2.5.7 Refrigerators and freezers
 - 2.5.8 Load optimization tools

References

Tools

Revision history

Supplement 4

Building security and fire protection

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-c-trs-961>

Contents

Acknowledgements

Abbreviations

Glossary

1. Introduction

- 1.1 Requirements
- 1.2 Objectives
- 1.3 Target audience
- 1.4 Associated materials and equipment

2. Guidance

- 2.1 Site security and emergency access
- 2.2 General building security
- 2.3 Controlled and hazardous substances areas
- 2.4 Fire detection systems
- 2.5 Fire suppression equipment
 - 2.5.1 *Smoke ventilation systems*
- 2.6 Compartmentation
 - 2.6.1 *Sprinkler systems*
- 2.7 Fire prevention, training and control procedures
 - 2.7.1 *Risk assessment*
 - 2.7.2 *Fire prevention*
 - 2.7.3 *Fire safety training*
 - 2.7.4 *Fire control procedures*

References

Annex 1

- SOP: fire safety housekeeping
 - A1.1 Policy and objectives
 - A1.1.1 *Policy*
 - A1.1.2 *Objectives*

- A1.2 Responsibility
- A1.3 Associated materials and equipment
- A1.4 Procedure
 - A1.4.1 Reducing ignition sources*
 - A1.4.2 Reducing fuel load*
 - A1.4.3 Maintenance of fire protection measures*
- A1.5 Related documents

Annex 2

SOP: routine inspection and maintenance

- A2.1 Policy and objectives
 - A2.1.1 Policy*
 - A2.1.2 Objectives*
- A2.2 Responsibility
- A2.3 Associated materials and equipment
- A2.4 Procedure
 - A2.4.1 Daily inspections*
 - A2.4.2 Weekly inspections*
 - A2.4.3 Monthly inspections*
 - A2.4.4 Three-monthly inspections*
 - A2.4.5 Six-monthly inspections*
 - A2.4.6 Yearly inspections*
- A2.5 Related documents

Annex 3

SOP: fire drills

- A3.1 Policy and objectives
 - A3.1.1 Policy*
 - A3.1.2 Objectives*
- A3.2 Responsibility
- A3.3 Associated materials and equipment
- A3.4 Procedure
 - A3.4.1 Conducting test evacuations*
- A3.5 Related documents

Revision history

Supplement 5

Maintenance of storage facilities

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-d-trs-961>

Contents

Acknowledgements

Abbreviations

Glossary

1. Introduction

- 1.1 Requirements
- 1.2 Objectives
- 1.3 Target readership

2. Guidance

- 2.1 Associated materials and equipment
- 2.2 What is maintenance and why is it important?
- 2.3 The building design and construction phase
 - 2.3.1 *The operation and maintenance manual*
 - 2.3.2 *The health and safety file*
- 2.4 Maintenance management
 - 2.4.1 *Establish an institutional or contractual framework*
 - 2.4.2 *Preventive maintenance and replacement: standards and schedules*
 - 2.4.3 *Establish a multiyear maintenance plan*
 - 2.4.4 *Planned periodic inspections*
 - 2.4.5 *Planned service inspections*
 - 2.4.6 *Curative maintenance*
 - 2.4.7 *Organizing and managing the work*
 - 2.4.8 *Inspecting and signing off the work*

References

Annex 1

Uniclass: building elements

Annex 2

Checklist for building weatherproofing

Revision history

Supplement 6

Temperature and humidity monitoring systems for fixed storage areas

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-e-trs-961>

Contents

Acknowledgements

Abbreviations

Glossary

1. Introduction

- 1.1 Requirements
 - 1.1.1 *Temperature monitoring systems*
 - 1.1.2 *Humidity monitoring systems*
 - 1.1.3 *Alarm systems*
- 1.2 Objectives
- 1.3 Target readership

2. Guidance

- 2.1 Associated materials and equipment
- 2.2 Related activities
- 2.3 Choosing a monitoring system
 - 2.3.1 *Prepare a user requirements specification*
 - 2.3.2 *Select the basic system type*
 - 2.3.3 *Match the system to the needs*
 - 2.3.4 *Automated continuous monitoring*
 - 2.3.5 *Data collection: wireless versus wired data transmission*
 - 2.3.6 *Specific requirements for wireless networks*
 - 2.3.7 *Web-based systems*
 - 2.3.8 *Alarm system*
 - 2.3.9 *User controls*
 - 2.3.10 *Adaptability and expandability*
 - 2.3.11 *Security and compliance*
- 2.4 Maintenance and support

- 2.5 System extent
 - 2.5.1 *Number of monitoring points*
 - 2.5.2 *Location of monitoring points*
- 2.6 Complementary services
- 2.7 Deploying the system
- 2.8 Post-installation setup and qualification activities

References

Annex 1

Example of form for monitoring system start-up

Revision history

Supplement 7

Qualification of temperature-controlled storage areas

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-f-trs-961>

Contents

Acknowledgements

Abbreviations

Glossary

1. Introduction

- 1.1 Requirements
- 1.2 Objectives
- 1.3 Target readership

2. Guidance

- 2.1 Associated materials and equipment
- 2.2 Introduction to qualification
 - 2.2.1 *Qualification applied to temperature-controlled storage*
 - 2.2.2 *Installation qualification*
 - 2.2.3 *Operational and performance qualification*
- 2.3 Qualification protocols
 - 2.3.1 *Approval page and change control history*
 - 2.3.2 *Acronyms and glossary*
 - 2.3.3 *Description and rationale*
 - 2.3.4 *Scope and objectives*
 - 2.3.5 *Key parameters*
 - 2.3.6 *Procedures*
 - 2.3.7 *Qualification report template*
 - 2.3.8 *Approval process*
- 2.4 Installation qualification
 - 2.4.1 *Identifying critical components*
 - 2.4.2 *Checking installed systems, subsystems and components*
 - 2.4.3 *Checking electrical systems and requirements*
 - 2.4.4 *Checking environmental conditions*
 - 2.4.5 *Checking spare parts*
 - 2.4.6 *Checking auxiliary equipment*

- 2.4.7 *Checking information needed for the preventive maintenance programme*
- 2.4.8 *Writing the IQ report*
- 2.5 Operational qualification
 - 2.5.1 *Checking installed systems, subsystems and components*
 - 2.5.2 *Calibration of controllers and sensors*
 - 2.5.3 *Standard operating procedures*
 - 2.5.4 *Control panel*
 - 2.5.5 *Alarm tests*
 - 2.5.6 *Temperature mapping – empty*
 - 2.5.7 *Power failure test*
 - 2.5.8 *Writing the OQ report*
- 2.6 Performance qualification
 - 2.6.1 *Checking installed systems, subsystems and components*
 - 2.6.2 *Temperature mapping – full*
 - 2.6.3 *Temperature recovery after door opening*
 - 2.6.4 *Writing the PQ report*
- 2.7 Specific requirements for small-scale equipment

References

Revision history

Annex 1

Form for reporting deviations and corrective action

Supplement 8

Temperature mapping of storage areas

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-g-trs-961>

Contents

Acknowledgements

Abbreviations

Glossary

1. Introduction

- 1.1 Requirements
- 1.2 Objectives
- 1.3 Target readership

2. Guidance

- 2.1 Associated materials and equipment
- 2.2 The mapping protocol
 - 2.2.1 *Approval page and change control history*
 - 2.2.2 *Acronyms and glossary*
 - 2.2.3 *Description and rationale*
 - 2.2.4 *Scope*
 - 2.2.5 *Objectives*
 - 2.2.6 *Methodology*
 - 2.2.7 *Mapping report template*
- 2.3 Conducting the mapping exercise
- 2.4 Analysing the data and preparing the mapping report
 - 2.4.1 *Preliminary analysis*
 - 2.4.2 *Minimum and maximum temperatures and hot and cold spots*
 - 2.4.3 *Mean temperatures*
 - 2.4.4 *Interpreting the results and making recommendations*
 - 2.4.5 *Report auditing*
- 2.5 Implementing the mapping report recommendations

References

Annex 1

Test data sheets

- A1.1 Test data sheet: temperature data logger locations
- A1.2 Test data sheet: temperature distribution
- A1.3 Test data sheet: temperature distribution

Revision history

Supplement 9

Maintenance of refrigeration equipment

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-h-trs-961>

Contents

Acknowledgements

Abbreviations

Glossary

1. Introduction

- 1.1 Requirements
- 1.2 Objectives
- 1.3 Target readership

2. Guidance

- 2.1 Associated materials and equipment
- 2.2 Active and passive transport containers
- 2.3 Refrigerators and freezers
- 2.4 Freezer rooms, cold rooms and controlled ambient stores
 - 2.4.1 *Maintenance overview*
 - 2.4.2 *Maintaining the cooling system*
 - 2.4.3 *Maintaining insulated panels and vapour control sealing*
 - 2.4.4 *Condensation control outside the cold store enclosure*
 - 2.4.5 *Frost-heave control*
 - 2.4.6 *Cold store panel insulation*
 - 2.4.7 *Insulation for refrigeration pipes and other penetrations*
 - 2.4.8 *Cold store maintenance schedule*
- 2.5 Refrigerated vehicles
 - 2.5.1 *Refrigerated vans*
 - 2.5.2 *Refrigerated rigid bodies*
 - 2.5.3 *Refrigerated semi-trailer*
- 2.6 Refrigerated containers
- 2.7 Maintenance management
- 2.8 Decommissioning
- 2.9 Staff training

References

Annex 1

Checking refrigerated vehicles

- A1.1 Checking insulation on a refrigerated vehicle
- A1.2 Checking cooling equipment on a refrigerated van
- A1.3 Checking cooling equipment on a rigid vehicle or semi-trailer

Revision history

Supplement 10

Checking the accuracy of temperature control and monitoring devices

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-i-trs-961>

Contents

Acknowledgements

Abbreviations

Glossary

1. Introduction

- 1.1 Requirements
- 1.2 Objectives
- 1.3 Target readership

2. Guidance

- 2.1 Associated materials and equipment
- 2.2 Procedure
 - 2.2.1 *Prerequisites*
 - 2.2.2 *Establishing the ice-point bath (excerpt from ASTM E563-11)*
 - 2.2.3 *Placing the device in the bath*
 - 2.2.4 *Carrying out the accuracy check, step by step*
 - 2.2.5 *Maintaining the bath temperature*
 - 2.2.6 *Actions to take following the test*

References

Annex 1

Generic temperature accuracy check form

Revision history

Supplement 11

Qualification of refrigerated road vehicles

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-j-trs-961>

Contents

Acknowledgements

Abbreviations

Glossary

1. Introduction

- 1.1 Requirements
- 1.2 Objectives
 - 1.2.1 *Verification*
 - 1.2.2 *Qualification*
- 1.3 Target readership

2. Guidance

- 2.1 Associated materials and equipment
- 2.2 Preliminary construction validation
 - 2.2.1 *Temperature-controlling equipment*
 - 2.2.2 *Thermal insulation*
 - 2.2.3 *Performance checks*
- 2.3 Field shipment test
 - 2.3.1 *Purpose*
 - 2.3.2 *Loading*
 - 2.3.3 *Temperature probe placement*
 - 2.3.4 *Test procedure*
 - 2.3.5 *Acceptance criteria*
- 2.4 Temperature-control failure test
 - 2.4.1 *Purpose*
 - 2.4.2 *Loading*
 - 2.4.3 *Temperature probe placement*
 - 2.4.4 *Test procedure*
 - 2.4.5 *Acceptance criteria*

2.5 Documentation

2.5.1 *Designation of the vehicle*

2.5.2 *Results of the qualification*

2.6 Vehicle qualification failure

2.7 Calibration

References

Annex 1

Placing EDLMs or temperature sensors

Revision history

Supplement 12

Temperature-controlled transport operations by road and by air Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-k-trs-961>

Contents

Acknowledgements

Abbreviations

Glossary

1. Introduction

- 1.1 Requirements
- 1.2 Objectives
- 1.3 Target readership

2. Guidance

- 2.1 Associated materials and equipment
- 2.2 Available shipping systems
 - 2.2.1 *Refrigerated vehicles – temperature-controlled*
 - 2.2.2 *Refrigerated vehicles – temperature-modified*
 - 2.2.3 *Passive shipping systems*
 - 2.2.4 *Active shipping systems for air transport*
- 2.3 Quality agreements
 - 2.3.1 *User requirements specification*
 - 2.3.2 *Service level agreements*
- 2.4 Identifying and controlling risk
- 2.5 Managing refrigerated road shipments
- 2.6 Managing passive container road shipments
- 2.7 Introduction to air transport
 - 2.7.1 *Types of air carrier*
 - 2.7.2 *Air transport labelling for TTSPPs*
- 2.8 Air transport processes
- 2.9 Managing air shipments

References

Annex 1

Packing a refrigerated vehicle

Revision history

Supplement 13

Qualification of shipping containers

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-l-trs-961>

Contents

Acknowledgements

Abbreviations

Glossary

1. Introduction

- 1.1 Requirements
- 1.2 Objectives
- 1.3 Target readership

2. Guidance

- 2.1 The three stages of qualification
 - 2.1.1 *Design qualification*
 - 2.1.2 *Operational qualification*
 - 2.1.3 *Performance qualification*
 - 2.1.4 *Requalification of reusable container systems*
- 2.2 Associated materials and equipment
 - 2.2.1 *Test equipment for design and operational qualifications*
 - 2.2.2 *Test equipment for performance qualification*
- 2.3 The performance qualification test protocol
 - 2.3.1 *Protocol title*
 - 2.3.2 *Protocol approvals*
 - 2.3.3 *Introduction*
 - 2.3.4 *Purpose*
 - 2.3.5 *Scope*
 - 2.3.6 *Acceptance criteria*
 - 2.3.7 *Responsibilities*
 - 2.3.8 *Test procedure*
 - 2.3.9 *Data analysis*
- 2.4 The performance qualification test
- 2.5 The performance qualification report

References

Revision history

Supplement 14

Transport route profiling qualification

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-m-trs-961>

Contents

Acknowledgements

Abbreviations

Glossary

1. Introduction

- 1.1 Requirements
- 1.2 Objectives
- 1.3 Target readership

2. Guidance

- 2.1 Associated materials and equipment
- 2.2 Study protocol
- 2.3 Carrying out the study
- 2.4 Data retrieval
- 2.5 Understanding temperature exposure: the degree-hour concept
- 2.6 Organizing, analysing and using the data
 - 2.6.1 *Method A for designing and testing packaging solutions*
 - 2.6.2 *Method B for passive containers with known performance characteristics*

References

Annex 1

Method B examples

- A1.1 Using the data
- A1.2 The warm climate case
 - A1.2.1 *Step 1: organize and analyse the route profile data*
 - A1.2.2 *Step 2: assess container suitability*
- A1.3 The cold climate case
 - A1.3.1 *Step 1: organize and analyse the route profile data*
 - A1.3.2 *Step 2: assess container suitability*

Revision history

Supplement 15

Temperature and humidity monitoring systems for transport operations

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-n-trs-961>

Contents

Acknowledgements

Abbreviations

Glossary

1. Introduction

- 1.1 Requirements
- 1.2 Objectives
- 1.3 Target readership

2. Guidance

- 2.1 Associated materials and equipment
- 2.2 Temperature and humidity monitoring devices
 - 2.2.1 *Device types*
 - 2.2.2 *Data collection, storage and retrieval*

References

Revision history

Supplement 16

Environmental management of refrigeration equipment

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-o-trs-961>

Contents

Acknowledgements

Abbreviations

Glossary

1. Introduction

- 1.1 Requirements
- 1.2 Objectives
- 1.3 Target readership

2. Guidance

- 2.1 Associated materials and equipment
- 2.2 Montreal Protocol
- 2.3 Selection of refrigerants and blowing agents
 - 2.3.1 *Use of chlorofluorocarbons*
 - 2.3.2 *Use of hydrochlorofluorocarbons*
 - 2.3.3 *Use of hydrofluorocarbons*
 - 2.3.4 *Use of hydrofluoro-olefin*
 - 2.3.5 *Use of hydrocarbons*
 - 2.3.6 *Ammonia and carbon dioxide*
 - 2.3.7 *Other cooling technologies*
- 2.4 Counterfeit refrigerants
- 2.5 Thermal insulation
- 2.6 CO₂ emissions
 - 2.6.1 *Kyoto Protocol*
 - 2.6.2 *CO₂ emissions from prime mover*
 - 2.6.3 *ODP and high GWP refrigerants*
- 2.7 Installation and maintenance
- 2.8 Decommissioning
- 2.9 Staff training

References

Annex 1

Montreal Protocol: non-Article 5 countries

Revision history

9. Good pharmacy practices

9.1 Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services

Annex 8, WHO Technical Report Series, 961, 2011

Background	1422
1. Introduction	1423
2. Underlying philosophy	1425
3. Definition of good pharmacy practice	1425
4. Requirements of good pharmacy practice	1426
5. Setting standards for good pharmacy practice	1428
6. Conclusions	1435

Background

Under the World Health Organization (WHO)'s Revised Drug Strategy adopted by the World Health Assembly in 1986, WHO organized two meetings on the role of the pharmacist, in Delhi, India in 1988 and in Tokyo, Japan in 1993. This was followed by the adoption, in May 1994, of the World Health Assembly Resolution WHA47.12 on the role of the pharmacist, in support of the WHO Revised Drug Strategy.

In 1992 the International Pharmaceutical Federation (FIP) developed standards for pharmacy services under the heading “Good pharmacy practice in community and hospital pharmacy settings”. The text on good pharmacy practice was also submitted to the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1994. Following the recommendations of the WHO Expert Committee and the endorsement of the FIP Council in 1997, the FIP/WHO joint document on good pharmacy practice (GPP) was published in 1999 in the thirty-fifth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 885).

Subsequently WHO organized two more meetings on the role of the pharmacist, in Vancouver, Canada in 1997 and in the Hague, Netherlands (Kingdom of the) in 1998. These meetings reinforced the need for pharmacy curricular reform and the added value of the pharmacist in self-care and self-medication.

In collaboration with WHO, the first edition of a practical handbook *Developing pharmacy practice — a focus on patient care* was launched in 2006. This handbook is designed to meet the changing needs of pharmacists, setting out a new paradigm for pharmacy practice and presenting a step-by- step approach to pharmaceutical care.

With the overall aim of improving standards and practice of distribution and use of medicines, using the FIP/WHO guidelines for GPP as the framework, FIP took the initiative to explore the possibilities for providing technical assistance to its Member Organizations in Cambodia, Moldova, Mongolia, Paraguay, Thailand, Uruguay and Viet Nam, in developing national standards for GPP in a pilot study from 2005 to 2007. In 2007 the “Bangkok declaration on good pharmacy practice in the community pharmacy settings” in the South- East Asia Region was adopted by the FIP South-East Asia Pharmaceutical Forum and set out the commitment of its Member Associations towards raising standards of pharmacy services and professional practice.

Since the adoption of the GPP guidelines in community and hospital settings, significant changes in practice, applied science and technology and pharmaceutical policy have occurred, including the relevance of more recent World Health Assembly resolutions: WHA54.11 (WHO Medicines Strategy), WHA54.13 (Strengthening health systems in developing countries), WHA55.14 (Ensuring accessibility of essential medicines), WHA55.18 (Quality of care: patient safety), WHA57.16 (Health promotion) and WHA60.16 (Rational use of medicines).

Furthermore, in 2007 FIP established an initiative to investigate the need to update the guidelines on GPP to reflect contemporary standards of practice and thinking.

An FIP working group on GPP first met on 15 October 2007 to identify key issues that needed to be considered in the revision of the guidelines.

In 2008 FIP organized an expert consultation in Basel, Switzerland during its 68th World Congress. Fifty participants attended the meeting, including the FIP Working Group (WG) on GPP, WHO staff from headquarters, representatives from the WHO Regional Office for the Eastern Mediterranean, country medicines advisers from Ghana, Nigeria and the United Republic of Tanzania, Presidents and Secretaries of the six FIP Regional Pharmaceutical Forums, FIP Member Organizations and several invited experts.

Following this consultation, the FIP WG on GPP undertook an extensive review of the existing national standards on GPP in at least 37 countries and established a time frame that would allow sufficient consultation with all of FIP's 120 national Member Associations, relevant experts and WHO. A proposal for this initiative was presented to the forty-third meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2008 and an updated report was provided to the Expert Committee at its forty-fourth meeting in October 2009.

1. Introduction

The health of the public is fundamental to the happiness and welfare of all people. Barriers to good health include poor access to quality medical products, lack of access to trained health professionals and care, an inadequate health workforce, unaffordable cost of care and poor standards of education of health-care professionals.

Medicines are an essential and critical part of health-care services in all cultures and societies. When accessed, medicines are often an essential component of many disease prevention programmes and virtually all disease treatment plans. The potential benefit of medicines is often not realized — there is a gap between the proven efficacy of medicines demonstrated in clinical trials and their actual effectiveness in practice. The reasons for this gap include problems with medicine selection and dosages, improper administration of medicines and lack of adherence by patients to prescribed treatment, medicine–medicine and medicine–food interactions, and adverse medicine events. Besides clinical problems associated with medicine-related problems, there are cost implications. It has been estimated that the cost of problems with the use of medicines is equal to or greater than the cost of the medicines themselves.

Medicines are also increasingly expensive and their cost is compromising the affordability of health care. Managing the costs of medicines is critical to making the best use of limited resources to maximize health care for as many people as possible.

Substandard, adulterated, unlicensed and spurious/falsely-labelled/falsified/counterfeit medicines are a growing problem that compromise health. There is a need for a system of assuring the integrity of the medicine supply chain to assure the value of medicines used for the prevention of disease and the treatment of patients.

Pharmacists¹ are specifically educated and trained health professionals who are charged by their national or other appropriate (e.g. state or provincial) authorities with the management of the distribution of medicines to consumers and to engage in appropriate efforts to assure their safe and efficacious use. There is also increasing recognition that providing consumers with medicines alone is not sufficient to achieve the treatment goals. To address these medication-related needs, pharmacists are accepting greater responsibility for the outcomes of medicines use and are evolving their practices to provide patients with enhanced medicines-use services.

As health-care professionals, pharmacists play an important role in improving access to health care and in closing the gap between the potential benefit of medicines and the actual value realized and should be part of any comprehensive health system. In addition, the increasingly complex and diverse nature of pharmacists' roles in the health-care system and public health demands a continuous maintenance of the competence of pharmacists as health-care professionals who have up-to-date skills and expertise.

National pharmacy professional associations need to work together with their governing bodies and other health-care professional associations to support pharmacists in their countries through provision of continuing professional development activities, including distance-learning programmes, and establishing national standards of pharmacy services and practice objectives.

These guidelines are intended to provide a description of ways in which pharmacists can improve access to health care, health promotion and the use of medicines on behalf of the patients they serve. The role of FIP is to provide leadership for national pharmacy professional organizations, which in turn provide the impetus for setting national standards.² The vital element is the commitment of the pharmacy profession worldwide to promoting excellence in practice for the benefit of those served. The public and other professions will judge the pharmacy profession on how its members translate that commitment into practice in all settings, especially community and hospital pharmacy settings.

It is the policy of FIP and WHO to provide guidance to national pharmacy professional organizations regarding the development of their national GPP guidelines. The conditions of practice vary widely from country to country and each national pharmacy professional organization is best able to decide what can be achieved and within what time-scale.

¹ Pharmacists are health-care professionals whose professional responsibilities and accountabilities include seeking to ensure that people derive maximum therapeutic benefit from their treatments with medicines. This requires them to keep abreast of developments in pharmacy practice and the pharmaceutical sciences, professional standards and requirements, the laws governing pharmacy and medicines and advances in knowledge and technology relating to use of medicines.

² Throughout this document, the term "national standards" includes laws, regulations, standards, ordinances or other requirements enacted or promulgated by an official body at any level of government, as well as guidelines, recommendations or other pronouncements of professional organizations of pharmacy.

2. Underlying philosophy

The mission of pharmacy practice is to contribute to health improvement and to help patients with health problems to make the best use of their medicines.

There are six components to this mission:

- being readily available to patients with or without an appointment;
- identifying and managing or triaging health-related problems;
- health promotion;
- assuring effectiveness of medicines;
- preventing harm from medicines; and
- making responsible use of limited health-care resources.

In the community setting, pharmacists should be acknowledged as health-care professionals whom patients can consult for health-related problems. Because health-care products and services are available from the pharmacist, some problems can be managed at this point of care. Problems that require additional diagnostic skill or treatments not available from a pharmacist can be referred to an appropriate health-care professional or site of care, such as a hospital. This should be done in good collaboration between the health-care providers.

To improve the use of medicines, pharmacists have responsibilities for many aspects of the process of medicines use, each of which is important to achieve good outcomes from treatment. This begins with assuring the integrity of the medicine supply chain, including detecting spurious/falsely-labelled/ falsified/counterfeit medicines, ensuring proper storage of medicines and quality preparation of medicines when needed. It also includes assuring the proper prescribing of medicines so that dose regimens and dosage forms are appropriate; instructions for use are clear; medicine–medicine and medicine–food interactions are prevented; known and predictable adverse medicine reactions, including allergies and other contraindications, are avoided; unnecessary treatments are minimized and the cost of medicines is considered.

Another important component of this mission is assisting patients and those administering medicines to understand the importance of taking medicines properly, including the correct timing of doses, foods or other medicines to avoid when taking a dose and what to expect after taking the medicine. Monitoring treatment to verify effectiveness and adverse medicine events is also an important part of the process of use of medicines.

3. Definition of good pharmacy practice

GPP is the practice of pharmacy that responds to the needs of the people who use the pharmacists' services to provide optimal, evidence-based care. To support this practice

it is essential that there be an established national framework of quality standards and guidelines.

4. Requirements of good pharmacy practice

- GPP requires that a pharmacist's first concern in all settings is the welfare of patients.
- GPP requires that the core of the pharmacy activity is to help patients make the best use of medicines. Fundamental functions include the supply of medication and other health-care products of assured quality, the provision of appropriate information and advice to the patient, administration of medication, when required, and the monitoring of the effects of medication use.
- GPP requires that an integral part of the pharmacist's contribution is the promotion of rational and economic prescribing, as well as dispensing.
- GPP requires that the objective of each element of pharmacy service is relevant to the patient, is clearly defined and is effectively communicated to all those involved. Multidisciplinary collaboration among health-care professionals is the key factor for successfully improving patient safety.

In satisfying these requirements, the following conditions are necessary:

- the well-being of patients should be the main philosophy underlying practice, even though it is accepted that ethical and economic factors are also important;
- pharmacists should have input into decisions about the use of medicines. A system should exist that enables pharmacists to report and to obtain feedback about adverse events, medicine-related problems, medication errors, misuse or medicine abuse, defects in product quality or detection of counterfeit products. This reporting may include information about medicine use supplied by patients or health professionals, either directly or through pharmacists;
- the relationship with other health professionals, particularly physicians, should be established as a therapeutic collaborative partnership that involves mutual trust and confidence in all matters relating to pharmacotherapy;
- the relationship between pharmacists should be one of colleagues seeking to improve pharmacy service, rather than acting as competitors;
- in reality, organizations, group practices and pharmacy managers should accept a share of responsibility for the definition, evaluation and improvement of quality;

- the pharmacist should be aware of essential medical and pharmaceutical information (i.e. diagnosis, laboratory test results and medical history) about each patient. Obtaining such information is made easier if the patient chooses to use only one pharmacy or if the patient's medication profile is available;
- the pharmacist needs evidence-based, unbiased, comprehensive, objective and current information about therapeutics, medicines and other health-care products in use, including potential environmental hazard caused by disposal of medicines' waste;
- pharmacists in each practice setting should accept personal responsibility for maintaining and assessing their own competence throughout their professional working lives. While self-monitoring is important, an element of assessment and monitoring by the national pharmacy professional organizations would also be relevant in ensuring that pharmacists maintain standards and comply with requirements for continuous professional development;
- educational programmes for entry into the profession should appropriately address both current and foreseeable changes in pharmacy practice; and
- national standards of GPP should be specified and should be adhered to by practitioners.

At the national or appropriate (e.g. state or provincial) level, it is necessary to establish:

- A legal framework that:
 - defines who can practice pharmacy;
 - defines the scope of pharmacy practice;
 - ensures the integrity of the supply chain and the quality of medicines.
- A workforce framework that:
 - ensures the competence of pharmacy staff through continuing professional development (CPD or continuing education (CE)) programmes;
 - defines the personnel resources needed to provide GPP.
- An economic framework that:
 - provides sufficient resources and incentives that are effectively used to ensure the activities undertaken in GPP.

5. Setting standards for good pharmacy practice

GPP includes standards that often exceed those laid down by national legislation. Furthermore, legislation seldom gives precise instructions about how the services should be produced to meet the requirements. Therefore, national pharmacy professional associations have a role in setting standards required for GPP, which includes a quality management framework and a strategic plan for developing services. It is also recognized that in developing national standards for GPP, attention must be paid to both the needs of the users of health-care services and the capacity of national health-care systems to support these services.

Just as pharmacy practice will vary among nations, it will also vary among practice locations. Therefore, standards should recognize the uniqueness of different pharmacy practice settings (e.g. community and hospital pharmacy). In addition, as medicines and needs change, the standards should acknowledge evolving practice settings and provide these developing services with guidance without negatively affecting the evolutionary nature of practice. At the same time, a baseline should be established for practice below which the activity cannot be considered “pharmacy practice” at all and, therefore, should not be condoned.

When establishing minimum standards on GPP, FIP emphasizes the importance of first defining the roles played by pharmacists, as expected by patients and society. Secondly, relevant functions for which pharmacists have direct responsibility and accountability need to be determined within each role. Thirdly, minimum national standards should then be established, based upon the need to demonstrate competency in a set of activities supporting each function and role.

The minimum national standards for each activity are based on processes that need to be relevant and defined appropriately according to the local needs of the pharmacy practice environment and national profession aspirations. All national pharmacy professional associations should also adapt these roles and functions in accordance to their own requirements. The activities listed below can be further defined and measured by setting indicators of good practice within a national context and can be weighted by actual practice-setting priorities.

It is recommended that national pharmacy professional associations consider the following roles, functions and activities for pharmacists, *where appropriate*:

Role 1: Prepare, obtain, store, secure, distribute, administer, dispense and dispose of medical products

- Function A: Prepare extemporaneous medicine preparations and medical products

Minimum national standards should be established for these activities.

- Pharmacists should ensure that medicine preparation areas are appropriately designed to permit ease of extemporaneous preparations

and are maintained in a manner that minimizes the potential for medication errors and assures the cleanliness and safety of medical products.

- Pharmacists should ensure that compounded medicines are consistently prepared to comply with written formulas and quality standards for raw materials, equipment and preparation processes, including sterility where appropriate.
- Function B: Obtain, store and secure medicine preparations and medical products

Minimum national standards should be established for these activities.

- Pharmacists who are responsible for procurement should ensure that the procurement process is transparent, professional and ethical so as to promote equity and access and to ensure accountability to relevant governing and legal entities.
 - Pharmacists who are responsible for procurement should ensure that procurement is supported by strong quality assurance principles to assure that substandard, adulterated, unlicensed and spurious/falsely-labelled/ falsified/counterfeit medicines are not procured or allowed into the system.
 - Pharmacists who are responsible for procurement should ensure that procurement is supported by a reliable information system which provides accurate, timely and accessible information.
 - Pharmacists should establish contingency plans for shortages of medicines and for purchases in emergencies.
 - Pharmacists should assure that proper storage conditions are provided for all medicines, especially for controlled substances, used in the pharmacy or health-care facility.
 - Function C: Distribute medicine preparations and medical products
- Minimum national standards should be established for these activities.*
- Pharmacists should ensure that all medical products, including medicine samples, are handled and distributed in a manner that assures reliability and safety of the medicine supply.
 - Pharmacists should establish an effective distribution system which includes a written procedure, to recall promptly and effectively
 - medical products known or suspected to be defective or spurious/ falsely-labelled/falsified/counterfeit, with a designated person(s) responsible for recalls.

- Pharmacists should develop with manufacturers, wholesalers and government agencies (where appropriate) an access plan for uninterrupted supply of essential medicines as part of a disaster or pandemic preparedness strategy.
- As part of a disaster or pandemic preparedness strategy, national medicines regulatory agencies may introduce new medicines which are authorized for marketing with limited safety data; pharmacists have a responsibility to be aware of the safety issues and to institute necessary mechanisms for monitoring occurrence of adverse events.

■ Function D: Administration of medicines, vaccines and other injectable medications

Minimum national standards should be established for these activities.

- Pharmacists should have a role in the preparation and administration of medicines, in establishing procedures in their work settings with respect to the administration, and in monitoring the outcomes of medication administration.
- Pharmacists should have an educator, facilitator and immunizer role, thus contributing to the prevention of diseases through participation in vaccination programmes, by ensuring vaccination coverage and by also ensuring vaccine safety.
- Pharmacists should participate in directly observed therapy (DOT) programmes in areas such as the management of drug addiction, HIV/ AIDS, tuberculosis and sexually transmitted diseases, where applicable.

■ Function E: Dispensing of medical products

Minimum national standards should be established for these activities.

- Pharmacists should ensure that appropriate facilities, trained personnel, standard dispensing practices and documentation procedures are in place in the pharmacy for the supply and dispensing of prescribed medicines and other health-care products.
- Pharmacists should assess and evaluate all paper or electronic prescriptions received, considering the therapeutic, social, economic and legal aspects of the prescribed indication(s) before supplying medical products to the patient. Where possible, generic substitution is recommended.
- Pharmacists should ensure patient confidentiality at the point of dispensing medical products and should provide advice to ensure that the patient receives and understands sufficient written and oral information to derive maximum benefit for the treatment.

- **Function F: Dispose of medicine preparations and medical products**

Minimum national standards should be established for these activities.

- Pharmacists should ensure that regular monitoring of the medicines inventory is conducted and should always include medicines samples in the process of periodic inspection for expiration dates and removal of outdated stock.
- Pharmacists should ensure that recalled medical products, including medicines samples, are immediately stored separately for subsequent disposal and prevented from being available for further dispensing or distribution.
- Pharmacists should establish a safe way of medicines waste disposal at the hospital and/or community pharmacy so that patients and the public can be encouraged to return their expired or unwanted medicines and medical devices. Alternatively, pharmacists should provide appropriate information to patients on how to safely dispose of expired or unwanted medicines.

Role 2: Provide effective medication therapy management³

- **Function A: Assess patient health status and needs**

Minimum national standards should be established for these activities.

- Pharmacists should ensure that health management, disease prevention and healthy lifestyle behaviour are incorporated into the patient assessment and care process.
- Pharmacists should acknowledge unique patient considerations such as education level, cultural beliefs, literacy, native language and physical and mental capacity in all individual patient assessments.

- **Function B: Manage patient medication therapy**

Minimum national standards should be established for these activities.

- Pharmacists should maintain access to an appropriate evidence base relating to the safe, rational and cost-effective use of medicines such as reference books on medicines, journals, national essential medicines lists and standard treatment guidelines.

³ Medication therapy management is a distinct service or group of services that optimize therapeutic outcomes for individual patients. Medication therapy management services are independent of, but can occur in conjunction with, the provision of a medication product.

- Pharmacists should ensure that medicine formulary system(s) (local, regional and/or national) are linked to standard treatment guidelines, protocols and treatment pathways based on the best available evidence.
 - Pharmacists should have a key role in educating prescribers on the access to and evidence for optimal and appropriate use of medicines including the required monitoring parameters and prescribing adjustments. Where appropriate, pharmacists should provide advice or recommendations to the prescriber on medicine therapy, including the selection of the appropriate medication or dosage.
 - Pharmacists should have access to, contribute to and use all necessary clinical and patient data to coordinate effective medication therapy management, especially when multiple health-care practitioners are involved in the patient's medication therapy, and intervene if necessary.
 - Pharmacists should establish a standard operating procedure for referrals to physicians, specialists or other health-care providers, where appropriate.
 - Pharmacists should provide continuity of care by transferring information on patients' medicines as patients move between sectors of care.
- Function C: Monitor patient progress and outcomes
Minimum national standards should be established for these activities.
 - Pharmacists should consider patient diagnosis and patient-specific needs when assessing patient response to medicine therapy and intervene if necessary.
 - Pharmacists should document necessary clinical and patient data to assess and monitor medication therapy and to track patients' therapeutic outcomes.
 - Pharmacists should perform point-of-care testing for patients in order to monitor and adjust therapy, when needed.
 - Function D: Provide information about medicines and health-related issues
Minimum national standards should be established for these activities.
 - Pharmacists should ensure that in every pharmacy there is a suitable place for discussing confidential information with the customers and patients.
 - Pharmacists should provide sufficient health, disease and medicine- specific information to patients for their participation

in their decision- making process regarding a comprehensive care management plan. This information should aim at supporting adherence to treatment and empowerment of the patient.

- Pharmacists should be proactive in reducing antimicrobial resistance by providing information about the appropriate use of antimicrobials to consumers and prescribers.

Role 3: Maintain and improve professional performance

- Function A: Plan and implement continuing professional development⁴ strategies to improve current and future performance

Minimum national standards should be established for these activities.

- Pharmacists should perceive continuing education as being lifelong and be able to demonstrate evidence of continuing education or continuing professional development to improve clinical knowledge, skills and performance.
- Pharmacists should take steps to update their knowledge and skills about complementary and alternative therapies such as traditional Chinese medicines, health supplements, acupuncture, homeopathy and naturopathy.
- Pharmacists should take steps to update their knowledge and be engaged in implementation of new technology and automation in pharmacy practice, where feasible.
- Pharmacists should take steps to become informed and update their knowledge on changes to information on medical products.

Role 4: Contribute to improve effectiveness of the health-care system and public health

- Function A: Disseminate evaluated information about medicines and various aspects of self-care

Minimum national standards should be established for these activities.

- Pharmacists should ensure that the information provided to patients, other health-care professionals and the public is evidence-based, objective, understandable, non-promotional, accurate and appropriate.

⁴ The concept of continuing professional development (CPD) can be defined as “the responsibility of individual pharmacists for systematic maintenance, development and broadening of knowledge, skills and attitudes, to ensure continuing competence as a professional, throughout their careers.”

- Pharmacists should develop and/or use educational materials for health management, health promotion and disease prevention programmes that are applicable to a wide range of patient populations, age groups and health literacy levels.
 - Pharmacists should educate patients on how to evaluate and use web-based or other forms of health-care information (including medicines information) and strongly encourage them to be advised by a pharmacist regarding the information they find, particularly if obtained from the Internet.
 - Pharmacists should assist patients and their care providers to obtain and critically analyse information to meet their individual needs.
- Function B: Engage in preventive care activities and services
Minimum national standards should be established for these activities.
 - Pharmacists should engage in preventive care activities that promote public health and prevent disease, i.e. in areas such as smoking cessation, infectious and sexually transmitted diseases.
 - Pharmacists should provide point-of-care testing, where applicable, and other health screening activities for patients at higher risk of disease.
- Function C: Comply with national professional obligations, guidelines and legislations
Minimum national standards should be established for these activities.
 - Pharmacists should take steps to ensure that they comply with the provisions of a national code of ethics for pharmacists.
- Function D: Advocate and support national policies that promote improved health outcomes
Minimum national standards should be established for these activities.
 - Pharmacists should contribute to public and professional groups to promote, evaluate and improve health in the community
 - Pharmacists should collaborate with other health-care professionals in their efforts to improve health outcomes.

6. Conclusions

There are four main roles where pharmacists' involvement or supervision is expected by society and the individuals they serve:

1. Prepare, obtain, store, secure, distribute, administer, dispense and dispose of medical products.
2. Provide effective medication therapy management.
3. Maintain and improve professional performance.
4. Contribute to improve effectiveness of the health-care system and public health.

These roles may vary for each individual pharmacist depending on their practice responsibilities.

Specific standards of GPP can be developed only within a national pharmacy professional organization framework.

This guidance is recommended as a set of professional goals to be met in the interest of the patients and other key stakeholders in the pharmaceutical sector. Responsibility for moving the project forward will rest with each national pharmacy professional association. Achieving specific standards of GPP for each nation within these recommendations may require considerable time and effort. As health professionals, pharmacists have a duty to begin the process without delay.

9.2 FIP–WHO technical guidelines: Points to consider in the provision by health-care professionals of children-specific preparations that are not available as authorized products

Annex 2, WHO Technical Report Series, 996, 2016

1. Introduction and scope	1438
1.1 Background	1438
1.2 Purpose	1439
1.3 Target audience and health-care settings	1439
2. Glossary	1439
3. Alternatives to compounding	1441
3.1 Sourcing of a commercially-available (marketed) or manufactured product if available	1441
3.2 Dose rounding	1442
3.3 Therapeutic alternatives	1442
3.4 Manipulation of dosage forms	1442
3.4.1 Tablet splitting	1442
3.4.2 Tablet/capsule dispersion for oral administration	1443
3.4.3 Crushing tablets/opening capsules and mixing powder with food or drink	1444
3.4.4 Giving the injectable form by the oral route	1445
3.4.5 Splitting suppositories	1445
3.4.6 Rectal administration	1445
3.4.7 General advice when changing the route of administration	1445
4. Compounding	1446
4.1 Good manufacturing practices aspects	1446
4.2 Some potential problems	1446
4.2.1 Oral liquids	1447
4.2.2 Microbial contamination	1448
4.3 Basic considerations	1449

5. Information, availability and access	1454
5.1 Standards of practice and guidelines	1454
5.2 Formularies and compendia	1454
5.3 Source and supply	1455
5.4 Networks and information services	1455
References	1455
Appendix 1 Examples of therapeutic alternatives to extemporaneous formulations	1457

1. Introduction and scope

1.1 Background

Paediatric patients should have access to authorized, age-appropriate preparations of medicines that can be administered safely and effectively. Nothing in this document should detract from this objective. However, it is recognized that such preparations are not always available and in such cases a safe and effective alternative must be sought.

In the context of paediatric pharmacy practice, and for the purpose of this document, compounding is the technique applied by pharmacists to produce medicines from active pharmaceutical ingredients (APIs) or using authorized medicines when no commercially available, authorized, age-appropriate or adequate dosage form exists. Unless stated explicitly in this document, the compounded medicine is assumed to be dispensed immediately after preparation and not kept in stock. Compounding does not apply to reconstitution of authorized medicines prior to dispensing. A clarification of the terminology of preparation of medicines for children has been proposed by Ernest et al. 2012 (1).

The risks and benefits of compounding and of the alternatives should be fully understood by practitioners. Practitioners who do not have appropriate knowledge should seek advice.

Compared to the use of authorized medicines there are significant risks associated with compounding; quality, safety and efficacy can rarely all be assured, and many errors have been reported in the preparation of such medicines. In some situations compounding of a medicine for a child may be the only option, which may be supported by evidence of quality and occasionally evidence of bioavailability by industry or other parties, such as academia. There may be alternatives to compounding, which should also be considered, for example, use of a commercially available therapeutic alternative or manipulation of authorized dosage forms.

This points-to-consider document is supported by a literature review of the evidence available (2). An annex to the report contains an update on the abstracts and papers published in 2010–2015.

This document is to be considered as a time-limited document that addresses current needs for advice in the search for an alternative to an authorized, age-appropriate dosage form. Wherever possible the guidance is informed by the relevant evidence. However, the evidence base is weak or non-existent in most situations. Consequently, the guidance is predominantly informed by best practice, based on sound scientific and therapeutic principles and expert consensus. Although the guidance takes the form of a working practical document it is important to invite comment and input from interested practitioners so that the guidance can be developed further in response to feedback. The document addresses mainly paediatric medicines for oral administration; comments and proposals concerning other routes of administration are invited as well.

1.2 Purpose

The purpose of the document is to:

- provide evidence-based or best practice advice about alternatives to compounding of medicines for paediatric patients;
- describe the main potential problems of compounding and educate practitioners on how to avoid them;
- provide brief advice on compounding;
- reduce the risk of providing children-specific preparations without informed knowledge.

The document will not reproduce guidance and standards that already exist (e.g. good manufacturing practices (GMP) standards for facilities and documentation). Where appropriate, reference is made to the relevant resources and publications.

1.3 Target audience and health-care settings

The document is intended for a wide audience of health-care stakeholders including:

- all practitioners involved in health care of the paediatric population but mainly pharmacists, physicians, paediatricians and nursing staff;
- national medicines regulatory authorities and professional bodies, e.g. national paediatric organizations and national pharmacy associations;
- general hospitals and health clinics;
- specialized paediatric hospitals and primary care clinics;
- the pharmaceutical industry, given its role in providing information.

Pharmaceutical manufacturers can often provide useful information on validated compounded formulas and other information relating to the manipulations and specific characteristics of formulations.

2. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

active pharmaceutical ingredient (API). Any substance or mixture of substances intended to be used in the manufacture or compounding of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

authorized dosage form. A pharmaceutical dosage form that has been authorized by the competent authority to be marketed for the treatment of specific indications.

beyond-use date. The date after which a compounded preparation should not be stored, transported or used; the date is determined from the date or time the preparation is compounded. It is also known as the *expiry date*.

compounding. Preparation under the supervision of a pharmacist following national legislation of an unlicensed medicine to meet the specific needs of a patient when no suitable authorized dosage form is available. This may involve preparation from the authorized dosage form or from the active pharmaceutical ingredient and usually involves addition of excipients to produce an acceptable product.

dispensing pharmacy. The pharmacy receiving the prescription for a patient and providing the pharmaceutical preparation to the patient. For compounded medicines, the dispensing pharmacy is not necessarily the compounding pharmacy.

dose rounding. Amending a dose that has been calculated accurately on the basis of body weight or surface area to correspond with an amount of the dosage form that is easy to measure and administer. Account of therapeutic index should be taken before rounding the dose.

excipient. A substance or compound, other than the active pharmaceutical ingredient and packaging materials, that is intended or designated to be used in the manufacture or compounding of a pharmaceutical product.

expiry date. The date after which a compounded preparation should not be stored, transported or used; the date is determined from the date or time the preparation is compounded. It is also known as *beyond-use date*.

good manufacturing practices. A system of practice and processes to assure the quality and safety of manufactured pharmaceutical products, specified in, for example, WHO guidelines.

labelling information. Information to the user provided on the container or package label or in the patient information leaflet.

manipulation of a dosage form. Authorized dosage forms may be manipulated (or modified), often at the point of administration, to provide the appropriate dose (e.g. by segmenting tablets) or to facilitate administration (e.g. by crushing a tablet and adding to food).

pharmaceutical dosage form. The physical form in which a medicine is presented; the name of a dosage form combines its physical form and the intended route of administration, e.g. a tablet (to be swallowed), oral suspension (liquid suspension of solid particles intended for oral intake and swallowing).

route of administration. The way in which a medicine is given to a patient, e.g. oral administration (administration via the oral route), rectal administration (administration to the rectum), parenteral administration (administration via the blood, muscular or subcutaneous routes).

summary of product characteristics. Summary of product characteristics approved by the competent authority. The information may alternatively be presented in the container or package label.

verification. A process of providing any type of adequate evidence, e.g. new (bio)analytical data, from the literature or by referencing to existing practices to support that the proposed modification will not change the pharmaceutical characteristics of the original preparation in a way that will negatively impact the safety and/or efficacy of the medicine.

3. Alternatives to compounding

Before deciding to compound, consider possible alternatives that will give the greatest assurance of clinical effectiveness and safety.

The main alternatives to compounding are described below.

3.1 Sourcing of a commercially-available (marketed) or manufactured product¹ if available

A marketed, authorized, age-appropriate finished pharmaceutical preparation should always be sourced when available. Where appropriate and in accordance with the national regulations, this could include:

- off-label use of a medicine authorized in the country where the medicine is to be dispensed;
- (off-label) use of an imported product authorized in the country of origin;
- use of a manufactured product made in authorized facilities in the country where the medicine is to be dispensed.

The logistics of supply, costs and access are obvious factors that might present obstacles, but practitioners should liaise with suppliers, importers and regulatory authorities to access these products if possible.

Importation of products may be expensive, and reputable suppliers should be used to avoid spurious/falsely-labelled/falsified/counterfeit (SFFC) medicines. Quality assurance systems should be in place, for example, to ensure that recall systems are available and that information is provided in the local language.

The use of compounded products for children should not be justified on the grounds that they are cheaper than marketed products. Other options, including local manufacture in accordance with GMP standards, should be investigated.

¹ This includes products prepared to GMP standards, for example, at an accredited hospital manufacturing unit.

3.2 Dose rounding

If the dose prescribed does not correspond to a dosage form that is commercially available, consider whether the dose can be suitably amended while maintaining safety and efficacy.

The therapeutic index of the medicine and patient characteristics need to be considered before making a decision.

Some medicine doses are calculated accurately on the basis of body weight, yet the therapeutic index is such that one dose can be used for a broad age and weight band. Consult the WHO Model formulary for children.²

3.3 Therapeutic alternatives

If a medicine is prescribed in a formulation that is not available, e.g. in an age-appropriate form, consider the possibility of using a commercially available medicine with a similar therapeutic action, which is available in a more suitable form. Examples are presented in Appendix 1.

3.4 Manipulation of dosage forms

In situations where the prescribed dose is different from what is marketed, or there are administration-related difficulties, the possibilities for manipulation of a dosage form as outlined below can be considered. Formularies or manufacturer's information, if available, and the labelling or the summary of product characteristics (SmPC) should be consulted.

A report with evidence-based guidelines on the manipulation of medicines to obtain the required dose for children was published by the Manipulation of Drugs Required in Children (MODRIC) research group in 2013 (3).

The practitioner should bear in mind that manipulation, such as tablet splitting, tablet/capsule dispersion, or tablet crushing and mixing with food or drink, may increase the potential for inaccurate dosing and may affect the efficacy, stability and bioavailability of the dosage form, in particular when mixed with food or drink. Excipients that are safe for adults may not necessarily be so for children.

When medicines are mixed with food or drink, including breast milk for very young children, an unpleasant tasting mixture may cause aversion in the child. In addition, the compatibility of the product with the food, drink or breast milk will need to be taken into account. Where a child shows signs of refusal or aversion other options should be considered.

3.4.1 Tablet splitting

Not all tablets should be split. In general, those with a sustained-release or enteric coating should not be split, but it may be possible to split tablets with a sustained-release

² Available from: <http://apps.who.int/medicinedocs/en/m/abstract/Js17151e/>.

matrix. Formularies or manufacturer's information, if available, and the product label or SmPC should be consulted.

Some tablets allow splitting, either by breaking, if scored, or by using a tablet cutter designed for the purpose. If the child is able to take solid dosage forms safely, a tablet segment can be given; otherwise it can be dispersed or mixed with food or drink as described below in section 3.4.3.

Tablets without a score line cannot, in general, be split into uniform segments meeting relevant uniformity requirements. Information about possible splitting of such tablets may however be provided in the SmPC or on the label. Tablet splitting was reviewed by Freeman et al. (2012) (4).

Consider on a case-by-case basis whether splitting of tablets might lead to toxicity or reduced effect as a result of inaccurate dosing or an effect on the release profile. This is especially important in situations where the API is potent or has a narrow therapeutic index, if there is a lack of appropriate information, or if an accurate dose cannot be assured.

Consideration should be given to splitting tablets with an appropriate commercial tablet splitter in the pharmacy. If possible, tablets with score lines and uniform distribution of the API should be sourced and information sought on the stability of segments. If carers are cutting segments, they should be given a suitable tablet splitter and receive adequate instruction on the method for preparing and storing tablet segments.

3.4.2 Tablet/capsule dispersion for oral administration

It may be possible to disperse immediate-release tablets or the contents of capsules in water or another liquid. If the tablet disperses, the tablet or a fraction of it can be dispersed in a small volume appropriate for the child concerned and the whole dose given when a suspension is formed, or mixed with a flavoured vehicle if required. To ensure that the whole dose is administered the measuring device should be rinsed and the resulting solution or suspension administered. It is necessary to consider the impact of dispersion and the risk of interactions with the vehicle on the bioavailability.

Conventional tablets do not disperse readily but some form a suspension within a short time. Soluble tablets and dispersible tablets disintegrate and dissolve or disperse within a short time in water at room temperature.

If the tablet disperses in a known volume of water to form a stable suspension, a fractional dose can be appropriately measured with a syringe. As extraction of soluble API from the tablet may be incomplete, the suspension should be shaken or stirred before measuring the dose and not filtered unless it has been established that the API is fully dissolved. Dose uniformity of the prepared suspension cannot be assured and the risk of overdosing or underdosing must be considered. This may depend on the volume of prepared suspension that is to be extracted for administration. Any such tablet (whether

a dispersible or conventional-release tablet) compounded to a dispersion or solution should be administered immediately after preparation and the remainder should be discarded.

When the dispersion is intended for tube feeding, parameters such as particle size, viscosity, dosing volume and compatibility of the oral preparation with the tube material should be considered. Dispersions may be too viscous or may contain large particles that can mean that administration by feeding tube is not feasible. Adsorption of API to the tube material results in inappropriate dosing; this concern is most relevant for lipophilic and low-dose potent APIs.

WHO is promoting the use of flexible solid oral dosage forms such as dispersible tablets (5). Custom-made dispersible tablets for paediatric dosing should be used wherever possible but it is still necessary to ensure that carers understand how they are to be administered.

3.4.3 Crushing tablets/opening capsules and mixing powder with food or drink

The practice of crushing tablets or opening capsules and adding the powder to a palatable drink or sprinkling it onto solid food has been reviewed (6). Although common, there may be little evidence to support the efficacy and safety of this practice since stability and bioavailability may be altered. With the exception of multiple-unit preparations, which can be opened and administered without affecting efficacy and safety, modified-release tablets and capsules cannot be crushed or opened without affecting bioavailability and/or stability, and this should therefore not be done. Insoluble tablet excipients are in suspension and may compromise product appearance, whereas soluble excipients may alter stability, for example, by changing the pH of the preparation.

In the case of potent APIs, consider the risks associated with handling of powdered material to parents or carers.

In general, the decision on whether to crush tablets should be based on bioavailability and acceptability studies. Information should be sought from manufacturers (e.g. the label or SmPC and website) and formularies whenever possible. The process is acceptable only if bioavailability is not affected by food or drink, and the product has to be used immediately to minimize stability problems.

It is difficult to ensure that a complete dose has been taken and the practice of nurses and carers handling powdered medicines may present health concerns. Tablet dispersion may be a simpler, more reliable and potentially safer method.

Liquid-filled capsules should generally not be opened since it is difficult to remove and measure the total contents.

3.4.4 Giving the injectable form by the oral route

Oral administration is possible for some injections. If the injectable form of the API is the same as the oral form (for example, labetalol hydrochloride, ondansetron hydrochloride) it can be assumed that the API will be absorbed enterally from the injectable formulation. However, as the API is in solution, more rapid absorption and higher peak levels may occur than would result from the slower absorption from a solid oral dosage form. When evaluating whether an injection is suitable for oral use, specialist advice, e.g. consultation with a medicines information centre in the region, should be sought because there are important factors which must be considered, e.g. first-pass effect, oral bioavailability, gastric acidity (e.g. effect on stability), pH effects (e.g. precipitation of soluble salts of weak acids) and palatability.

Injections may contain excipients that may have undesirable effects in some patients, e.g. propylene glycol and ethanol. The pH of some injections may be high or low and they should therefore not be given orally, or alternatively should be diluted before administration to avoid irritation. The taste of the injectable form may not be known and may not be acceptable. Advice should be sought from the manufacturer and from experts to assist in deciding whether the injectable form can be administered orally.

3.4.5 Splitting suppositories

There is little information available on the accuracy with which suppositories can be split. Splitting is usually associated with major problems with regard to accurate dosing and is therefore generally discouraged. Most commercially available suppositories are formulated as suspensions, which means that sedimentation of the solid API particles may occur during solidification of the suppository; therefore, if suppositories need to be split, this should be done lengthwise.

Therapeutic index and the consequences of over- or underdosing should be taken into account when determining whether it is safe to split suppositories. If possible, this should be done in the pharmacy.

3.4.6 Rectal administration

There may be opportunities to give oral or injectable dosage forms by rectal administration (7).

3.4.7 General advice when changing the route of administration

Whenever a change of the route of administration for an authorized medicine is considered, advice should be sought from formularies and the literature and even from specialists. In general, altering the route of administration results in a different pharmacokinetic profile introducing a high risk of dosing errors and may compromise safety and efficacy. Hence, this practice is generally discouraged.

4. Compounding

4.1 Good manufacturing practices aspects

The dispensing pharmacy receives the prescription for a patient and provides the pharmaceutical preparation to the patient. For compounded medicines the dispensing pharmacy is not necessarily the compounding pharmacy. Regardless of where the product is compounded the dispensing pharmacy is responsible for ensuring the safety and quality of the product.

When a batch of non-authorized medicine is prepared, including for stock, the preparing pharmacy or hospital unit should meet – depending on a risk assessment – the GMP or good pharmacopoeial practices (GPhP) requirements pertaining to personnel, premises and equipment, quality assurance system, documentation and product dossier. Further, an authorization by the competent authority to carry out operations may be needed, in accordance with the national legislation. In this respect, one should refer to the relevant international and national guidance and to other guidelines, including WHO guidelines on GMP (8, 9), the Pharmaceutical Inspection Co-operation Scheme (PIC/S) *GPP Guide to good practices for the preparation of medicinal products in healthcare establishments* (10) and corresponding national guidelines.

When compounding is a one-off event, the intended prescription should be prepared for an identified individual patient for immediate dispensing. In such cases requirements may be less strict. Nevertheless, certain requirements need to be met:

- the preparing pharmacy should have appropriate premises and equipment;
- the pharmacist and staff, or entitled persons, must have sufficient training and background for compounding;
- access to relevant literature (e.g. pharmacopoeias, formularies, handbooks and scientific journals) and the Internet must be available;
- general instructions for the preparation of each dosage form should be available;
- a record on each preparation should be retained showing the calculations, key processing and packaging steps, and also including the name of the person responsible for each step.

4.2 Some potential problems

In some situations, for example, if the method of preparation and the stability of an oral liquid are well documented, e.g. if compounding has been supported by evidence of quality, stability data and occasionally evidence of bioavailability by industry or other parties, such as academia, and all facilities and ingredients are available, it may be less

pressing to seek an alternative to compounding. On the other hand, if there are no stability data and, for example, the API forms a caking suspension in the only available excipients (e.g. a syrup), an alternative must be considered to ensure safe and effective treatment.

In any case, the decision on how to prepare and/or provide an unlicensed preparation should be based on an assessment of risks and benefits of the dosing strategy. On a case-by-case basis, potential benefits from their use should be weighed against all possible risks arising from preparation and administration of such medicines. Even in cases where the compounded preparation can be considered a verified formulation, the impact of compounding on bioavailability may not be known.

Formulation of a compounded medicine is associated with a number of potential problems that may impact on its safety and effectiveness. Awareness of the relative complexity of the formulation and of the things that can go wrong will help to avoid such problems. Guidance on compounding has been published (e.g. 11). A review of extemporaneous compounding is also available (12).

Consideration must be given to the properties of the API (e.g. aqueous solubility, pH effect on solubility, particle size, polymorphism) and stability of both API and the compounded formulation, i.e. chemical, physical and microbiological instability.

Care must also be taken in the selection of excipients and their safety in relation to the age of the child as well as any possible adverse effects of the “inactive” components of the preparation should be considered. The use of preservatives, ethanol and sugars must be carefully considered. Some guidance and literature references on the formulation can be found in *Development of paediatric medicines: points to consider in formulation* (5).

4.2.1 Oral liquids

Deterioration of an oral liquid may be a result of chemical, physical or microbiological instability which can lead to a subtherapeutic dose of the medicine, exposure to toxic degradation products or ingestion of unacceptable numbers of microorganisms. It is important for pharmacists, clinicians and nursing staff to be aware of potential problems caused by instability and microbial contamination to ensure that any medicine used is effective and safe.

APIs in compounded liquids may be susceptible to chemical reactions leading to degradation. Publications reporting the stability of compounded paediatric preparations include a review by Glass and Haywood 2013 (13). The most common reactions are *hydrolysis*, oxidation and reduction. Usually the reaction rate or type is influenced by pH. Other factors that may increase the rate of reaction include the presence of trace metals which catalyse the oxidation of captopril, methyldopa or exposure to light, which catalyses the oxidative degradation of 6-mercaptopurine. The rate of chemical degradation usually increases with temperature.

The API in the preparation may be totally or partially in solution or predominantly in the solid state as a suspension. APIs in solution are more susceptible to chemical degradation than APIs in the solid state (i.e. suspensions); thus suspensions of acetazolamide and chlorothiazide are more stable than solutions. However, it cannot be assumed that a compounded suspension is always more stable than a solution. In a suspension, an equilibrium exists between the API in the solid state and an API in solution, and even though the amount of API dissolved may be minimal, the conditions could be optimal for degradation. Furosemide is a notable example: it undergoes hydrolysis in acidic conditions where the solid state is predominant, but is much more stable at alkaline pH where it is totally in solution.

Preparations made from tablets contain excipients such as binders and disintegrating agents in addition to the API. These excipients may reduce chemical stability by changing the pH to a value at which more rapid degradation occurs. This probably explains why amiloride solution prepared from pure API is more stable than an oral liquid prepared from tablets.

Hygroscopicity and/or moisture-sensitivity of the API also play a key role in degradation. These characteristics of the API(s) should be understood before compounding from a tablet to a liquid form. A common example of such an API is tenofovir disoproxil fumarate.

Dispersions and suspensions of medicine with low therapeutic index require special consideration with regard to efficient resuspension to avoid medication error.

4.2.2 Microbial contamination

Microbial growth in an oral liquid may cause a foul odour and turbidity and adversely affect palatability and appearance. High titres of microorganisms may be hazardous to health especially in very young or immunocompromised patients. By-products of microbial metabolism may cause a change in the pH of the preparation and reduce the chemical stability or solubility of the API. Microbial contamination during preparation must be minimized by using clean equipment, water of adequate quality and by avoiding contaminated raw materials and containers. If sodium benzoate or benzoic acid are used as antimicrobial preservatives, the final pH must be less than 5 so that the active unionized form is predominant. Consequently the API must also be stable at this pH.

Many factors can reduce the effectiveness of the preservative, including use of contaminated materials, chemical degradation, binding of preservative to suspending agents or tablet excipients, incorrect storage or unhygienic use of the final product.

4.3 Basic considerations

- *Quality of API and excipients*

It is important to ensure that the API and the excipients meet pharmacopoeial standards with regard to both identity and purity. The choice of excipients should be restricted to those that have been used in authorized medicines intended for the same route of administration and at similar concentrations.

- *Consider use of an authorized dosage form as a starting point*

It may be safer and more effective to crush tablets or use the contents of hard capsules with an appropriate suspending vehicle than to prepare medicines from an API and excipients. There are many formulations available with a validated shelf life but sourcing of suspending agents may be difficult and/or expensive.

There might be instances when a pharmacist crushes a number of tablets or opens a number of capsules, dilutes the powder with a suitable excipient and doses the powder in ready-to-use single-dose sachets. Before doing so, consider the stability of the preparation, including stability with respect to humidity and exposure to air.

- *Consult literature and guidelines if available*

Use a validated formulation whenever possible (i.e. based on literature, stability studies and guidelines). Consult product information and the latest national and international guidelines and/or a specialist information centre if possible.

- *Potential medication error*

Medication errors in preparing compounded medicines occur often, and some have resulted in serious harm to patients or even in death. The potential for medication error must be recognized and steps taken to minimize the risk. As a minimum, this will include the use of a worksheet listing the formulation ingredients and the identity of the ingredients; quantities, calculations and measurements should be double-checked by trained personnel and signatures provided. The pharmacist responsible should check the final product and label against the signed worksheet, ingredients and prescription.

- *Exercise caution in extrapolating from other formulations*

Caution is required when extrapolating the formulation from a published study or formulary. Formulations made from APIs may be more stable than formulations made from solid dose forms and vice versa. Tablet and capsule excipients can increase or decrease the stability of the API in an oral

liquid preparation. The salt form of the API used in a published study could be different to the form locally available and this may affect its solubility, bioavailability and stability. Consult publications and pharmacopoeias, and seek specialist advice, if possible.

Similarly, the results of a published study using an API mixed with a commercial suspending base cannot generally be extrapolated to a situation where the same API is mixed with a simple base of syrup or glycerol.

Formulations for compounded medicines based on APIs and crushed tablets are not interchangeable.

- *Dose uniformity may be a problem – explain the importance of shaking prior to use*

If the API is poorly soluble in water, uniformity of dosing may be a problem and a suspending agent will be required. Always check that the finished preparation resuspends under in-use conditions and explain the importance of resuspension by shaking to patients or their carers.

As excipients and other formulation components can affect solubility, all compounded liquid formulations should be shaken prior to administration. Some of the API may not be in solution even if it is highly soluble in water. The only exception would be if the preparation is made from pure API and it can be assured that the entire API is in solution.

Suppositories have sometimes been melted and recast into smaller moulds. This option is associated with a risk of recrystallization and of affecting the distribution and solubility of the API, resulting in over- or underdosing. Further, re-melting may affect degradant levels. Re-melting is therefore generally discouraged.

- Exceptionally, when no published formulation is available

When no published formulation is available the pharmacist must assess the risks associated with the different options and use his or her knowledge and experience to formulate a product taking into account the need to:

- obtain information on the physicochemical properties of the API if available.

If possible, obtain basic physicochemical information about the API, especially its aqueous solubility at the expected pH of the final preparation. This allows a judgement to be made as to whether an API solution or suspension is formed at a particular dose-relevant concentration.

- test the physical characteristics before using the preparation to treat a patient.

FPPs of the same medicine may vary worldwide, especially with respect to the content of excipients. Such differences can influence the safety, efficacy and acceptability of the preparation. Basic performance tests should be done before the preparation is used in a patient, particularly on formulations prepared for the first time. Tests include ease of resuspension and pouring, degree of caking on storage, and observation of physical behaviour and characteristics.

- consider risk of microbial growth.

All compounded liquid formulations are highly susceptible to microbial growth. Oral liquids that are not adequately preserved will support rapid growth of bacteria and fungi especially at warm to hot temperatures and can pose hazards to patients especially those who are immunosuppressed. An antimicrobial preservative should be included if the final product is likely to be used beyond 2–3 days, even when it is stored under refrigeration.

The effects of the addition of the preservative on interactions between pH, stability and effectiveness of the preservative should be carefully taken into account.

Compounded liquids should be prepared under conditions that minimize the introduction of microbial contaminants.

- *Use appropriate final containers*

Final containers and closures should be clean and free from dust and other residues. Use of new containers is recommended. Containers that are reused should be thoroughly washed, rinsed with sterile or freshly boiled water and dried. Light-protective (e.g. dark plastic or amber glass) containers should generally be used.

Consider the use of a light-protective wrapping such as foil if a light-protective container is not available. When selecting the final container, consider the interactions between the container and the product, for example, the possibility of adsorption to plastic containers.

- *Dosing device*

For liquid preparations, the feasibility of appropriate dosing should be confirmed bearing in mind that not all dosing devices may allow delivery of the required volume. Most compounded liquids should be shaken prior to administration and this may introduce entrapped air in the liquid, which could cause problems with accurate measurement of small volumes.

- *Consider in-use storage*

In-use storage conditions may vary considerably from those in a published study or formulary recommendation. Always consider whether it will be possible to store and use the preparation under the optimal conditions described in the study; usually refrigeration, protection from light and minimal possibility of in-use contamination. If these conditions are not possible locally it can be assumed that the preparation will be less stable and more susceptible to microbial growth. Reduce the shelf life according to professional judgement. If possible, obtain expert advice.

- *Expiry date*

It is recommended that each compounded preparation be given an expiry date assigned in a conservative way and taking into account API-specific and general stability documentation and relevant literature when available.

When an authorized medicine is used as the source of the API, stability information can be obtained from the manufacturer. Otherwise, applicable information on stability, compatibility and degradation of ingredients, and use has to be sought in the literature.

Stability may be formulation-dependent and is likely to change with any manipulation of the product. Most studies base their expiry date recommendation on chemical stability but do not address possible physical or microbiological spoilage which may be significant during actual use of the product. Whereas compounded preparations will normally be freshly prepared, the storage and shelf life during use need to be considered, in particular if it becomes impractical to prepare the product immediately prior to dispensing each time it is needed.

The assignment of an expiry date serves to ensure suitability for use and will encourage regular fresh preparations. It also allows the practitioner to regularly review the patient's use of the preparation.

The following aspects should be considered when determining an expiry date:

- nature of the API and its degradation mechanisms;
- dosage form and its components;
- potential for microbial proliferation in the preparation;
- container in which the preparation is packaged;
- expected storage conditions; and
- the intended duration of therapy.

The in-use conditions, for example, access to a refrigerator for storage, should be taken into account when establishing the expiry date.

- *Give clear instructions to caregivers and patients*

The instructions given to caregivers and patients may include instructions on storage, resuspension, changes in taste, smell, appearance, adverse effects and other pharmaceutical advice.

Compounded dosage forms are sometimes added to a small amount of liquid (e.g. water or juice) or sprinkled onto small amounts of food. Consideration should be given to the effect of food on bioavailability and to the risk that only part of the dose will be swallowed. Provide parents and carers with appropriate information.

If an oral syringe or other measuring device is used it is important to check the technique to ensure that the correct dose is administered. Advise the use of clean measuring devices and explain how to avoid contaminating the preparation when preparing the dose.

- *Label information*

In addition to dosage instructions, include at least the following information, subject to national regulations for the labelling of medicines:

- if applicable, the name of the pharmaceutical preparation;
- the route of administration;
- the name(s) of the API(s) and excipients of known pharmacological action, and adverse effects, e.g. antimicrobial agents, antioxidants;
- if the preparation is a liquid, give the concentration(s) of the API(s), e.g. in mg/mL, and the amount or volume of the preparation in the container;
- if the preparation is a solid, give amount(s) of the API(s) in each dose and the number of doses in the container;
- reference or batch number (or date of preparation);
- expiry date (“do not use after ...”);
- any special storage conditions and handling precautions that may be necessary, e.g. “to be shaken before use”, “shelf life during use”;
- the pharmacy name and contact information;
- name of the patient.

Consider adding pictograms to supplement the label information, e.g. for “to be shaken well” and “store in the refrigerator”.

- *Document concerns and share information*

Practitioners are encouraged to maintain a dialogue with regulatory bodies and international agencies and networks about problems and concerns associated with the preparation and availability of age-appropriate medicines for children. The sharing of solutions to problems is also important.

5. Information, availability and access

A number of networks, websites and other resources are available which provide information on standards of practice, formulas for compounded preparations, manufacturers, suppliers of oral liquid formulations and responsive information services. These should be consulted by practitioners and regulators to enable them to provide the safest and most effective treatment options for children who require an age-appropriate formulation.

5.1 Standards of practice and guidelines

Some national, regional and international guidelines for extemporaneous formulations and medicines administration to children have been published. Consulting these documents may assist in forming local policies on practice and educational activities for practitioners.

5.2 Formularies and compendia

Formularies and compendia may be helpful in providing formulation advice and general advice on dosage manipulations. The information in these formularies may be difficult to transfer to a local situation where the base ingredients (e.g. commercial suspending bases, antimicrobial preservatives, pure API powder) are not readily available.

In addition to formularies and compendia, information can be sought in:

- the eMixt database (www.pharminfotech.co.nz), which provides comprehensive information for all settings and environments;
- *Handbook of extemporaneous preparations* (11), which contains formulations and associated stability summaries for oral liquid preparations;
- *Improving medicines for children*, by the Council of Canadian Academies, which contains a comprehensive review of paediatric medicines (14);
- The International Journal of Pharmaceutical Compounding, which is a general source of information. It is a subscription-only journal, but the contents can be searched on the journal's website (<http://www.ijpc.com>).

5.3 Source and supply

A database of sources and prices of medicines for children has been compiled by the United Nations Children's Fund (UNICEF) (15) and the UNICEF catalogue (<https://supply.unicef.org>) provides examples without being exhaustive.

Countries may also have their own database to use to find suppliers of age-appropriate formulations for paediatric use.

5.4 Networks and information services

- Local, national and international medicines information centres may respond to questions about formulation. One example is the WHO Paediatric medicines Regulatory Network (PmRN) (<https://www.who.int/teams/regulation-prequalification/regulation-and-safety/regulatory-convergence-networks/paediatric-regulators>). Partnerships and twinning arrangements between hospitals in poorly-resourced countries and developed countries can be explored and are often beneficial.
- Questions can be posted via the eMixt website (www.pharminfotech.co.nz).
- Sharing of information and advice on paediatric formulations should be explored whenever possible.
- International discussion lists can be useful for posting questions on formulations and their archives can be searched for previous questions and answers. Examples include eDrug and INDICES (accessed via www.asksource.info/resources/essentialdrugsorg).

References

1. Ernest TB, Craig J, Nunn A, Salunke S, Tuleu C, Breitzkreutz J, et al. Preparation of medicines for children – a hierarchy of classification. *Int Journal Pharm.* 2012;435(2): 124–30. doi: 10.1016/j.ijpharm.2012.05.070.
2. Nunn T, Hill S, Secretary, WHO Expert Committee on the Selection and Use of Essential Medicines. Report for WHO on findings of a review of existing guidance/advisory documents on how medicines should be administered to children, including general instructions on extemporaneous preparations and manipulation of adult dosage forms. Geneva: World Health Organization; 2011 (working document QAS/11.400 – available on request).
3. MODRIC. Manipulation of drugs for children – a guideline for health professionals. Liverpool: Alder Hey Children's NHS Trust.
4. Freeman MK, White W, Iranikhah M. Tablet splitting: a review of weight and content uniformity. *Consult Pharm.* 2012;27(5):341–52. doi: 10.4140/TCP.n.2012.341.
5. Development of paediatric medicines: points to consider in formulation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-sixth report. Geneva: World Health Organization; 2012: Annex 5 (WHO Technical Report Series, No. 970; https://iris.who.int/bitstream/handle/10665/75168/WHO_TRS_970.pdf?sequence=1&isAllowed=y).

6. Anon. Crushing tablets or opening capsules: many uncertainties, some established dangers. *Prescrire Int.* 2014; 23(152): 209–11, 213–14.
7. Smith S, Sharkey I, Campbell D. Guidelines for rectal administration of anticonvulsant medication in children. *Paediatr Perinatal Drug Ther.* 2001;4(4):140–7.
8. WHO good manufacturing practices: main principles for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986; https://iris.who.int/bitstream/handle/10665/112733/WHO_TRS_986_eng.pdf?sequence=1&isAllowed=y).
9. Good manufacturing practices for pharmaceutical products. In: Quality assurance of pharmaceuticals. WHO guidelines, related guidance and GXP training materials. Geneva: World Health Organization; 2015 CD-ROM.
10. Pharmaceutical Inspection Co-operation Scheme. PE 010-3 Guide to good practices for the preparation of medicinal products in healthcare establishments. PICS; 2014.
11. Jackson M, Lowey A. Handbook of extemporaneous preparation: A guide to pharmaceutical compounding. London: Pharmaceutical Press; 2010.
12. Patel VP, Desai TR, Chavda BG, Katira RM. Extemporaneous dosage form for oral liquids. *Pharmacophore.* 2011;2(2):86–103.
13. Glass BD, Haywood A. Liquid dosage forms extemporaneously prepared from commercially available products – Considering new evidence on stability. *J Pharm Sci.* 2006;9(3):398–426.
14. Council of Canadian Academies. Improving medicines for children in Canada. Ottawa: The Expert Panel on Therapeutic Products for Infants, Children, and Youth; 2014.
15. Sources and prices of selected medicines for children, including therapeutic food, dietary vitamin and mineral supplementation – 2nd edition. Geneva: UNICEF/WHO; 2010.

Further reading

- The International Pharmacopoeia, fifth edition; 2015. Available online and CD-ROM version).
- Kastango ES, Trissel LA, Bradshaw BD. An ounce of prevention: Controlling hazards in extemporaneous compounding practices. *Int. J Pharm. Compounding.* 2003;7(5):401–16.
- Pharmaceutical development for multisource (generic) pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-sixth report. Geneva: World Health Organization; 2012: Annex 3 (WHO Technical Report Series, No. 970; https://iris.who.int/bitstream/handle/10665/75168/WHO_TRS_970.pdf?sequence=1&isAllowed=y).
- Pharmaceutical Inspection Co-operation Scheme (<http://www.picscheme.org/>). In particular the following documents can be downloaded free of charge: PE 009-9 (Part I); PIC/S GMP guide (Part I: Basic requirements for medicinal products); PE 010-3 Guide to good practices for the preparation of medicinal products in healthcare establishments.
- Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children. Geneva: World Health Organization; 2008.
- The WHO Model formulary for children. Geneva: World Health Organization; 2010 (https://iris.who.int/bitstream/handle/10665/44309/9789241599320_eng.pdf?sequence=1).

Appendix 1

Examples of therapeutic alternatives to extemporaneous formulations

Required (available)	Possible alternative	Notes
diclofenac oral liquid (tablet)	naproxen oral suspension; ibuprofen oral liquid	The alternatives are available in some countries.
enalapril oral liquid (tablet)	captopril oral liquid (losartan oral suspension)	Captopril oral liquid is not available in all countries. Captopril has a shorter duration of action than enalapril. Enalapril tablets can be crushed and suspended in water immediately before use. Captopril tablets can be easily dispersed in water. Losartan may be appropriate for hypertension.
ibuprofen oral liquid (tablet)	paracetamol oral liquid	For pain and fever but not as an anti-inflammatory.
levamisole oral liquid (tablet)	albendazole chewable tablet; mebendazole oral liquid; pyrantel oral liquid	
lisinopril oral liquid (tablet)	ramipril oral liquid	
omeprazole oral liquid (capsule)	esomeprazole granules; lansoprazole orodispersible tablet	
praziquantel oral liquid (tablet)	niclosamide chewable tablet	Niclosamide can also be crushed and mixed with water to form a vanilla paste.
sertraline oral liquid (tablet)	fluoxetine oral liquid	
tinidazole oral liquid (tablet)	metronidazole oral liquid	Very few reasons why tinidazole should be preferred over metronidazole.
ciprofloxacin/ dexamethasone ear drops	ciprofloxacin/ hydrocortisone ear drops	

10. Post-market surveillance

10.1 Guidelines on the conduct of surveys of the quality of medicines

Annex 7, WHO Technical Report Series, 996, 2016

1. Introduction	1461
2. Glossary	1462
3. Objectives of the survey and initial planning	1462
4. Survey management and time frame	1466
5. Methodology	1468
5.1 Selection of areas to be sampled	1468
5.2 Selection of medicines to be surveyed	1469
5.3 Selection of sample collection sites	1470
5.3.1 Types of sample collection sites	1470
5.3.2 Sampling designs	1472
5.3.2.1 Convenience sampling	1472
5.3.2.2 Simple random sampling	1472
5.3.2.3 Stratified random sampling	1473
5.3.2.4 Lot quality assurance sampling	1473
5.3.2.5 Sentinel site monitoring	1474
5.4 Sampling plans	1475
5.4.1 Number of dosage units to be collected	1475
5.5 Sample collection	1477
5.5.1 Overt sampling versus mystery-shopper approach	1477
5.5.2 Instructions to sample collectors	1478
5.6 Storage and transportation of samples	1480
5.7 Testing	1481
5.7.1 Testing laboratory	1481
5.7.2 Tests to be conducted	1482
5.7.3 Test methods and specifications	1484
5.7.4 Receipt and testing of samples by a testing laboratory	1485
6. Data management and publication	1485

References	1486
Appendix 1 Example of a sample collection form	1488
Appendix 2 Content of the analytical test report/certificate of analysis	1490
Appendix 3 Outline of the content of a survey report	1492

1. Introduction

Good quality medicines are essential for efficient disease management. To ensure that good quality medicines are available to patients in their countries, national medicines regulatory authorities (NMRAs) can apply various regulatory instruments. These are:

- authorization/registration for marketing following the assessment of product documentation, inspection to ascertain manufacturers' compliance with the principles of good manufacturing practices (GMP) and approval of product information;
- post-marketing surveillance activities, including maintenance of products' authorization and/or registration through variations or renewals, regular inspections of manufacturers, wholesalers, distributors and retailers, quality control testing and pharmacovigilance;
- implementation of regulatory actions in the event of any quality problem being found.

Quality surveys may serve as a source of information about the quality of medicines available to patients and are an important part of regulatory systems in all countries, whether they are strong or weak. However, it has to be borne in mind that quality surveys that rely only on laboratory testing cannot offer complete assurance that medicines are safe and effective as formulated. Quality surveys can be organized by NMRAs, international organizations, procurement agents, nongovernmental organizations (NGOs) or academic and research groups.

If properly collected, interpreted and used relevant data are vital for the planning of effective interventions to improve the quality of medicines. Surveys give snapshots of the medicine quality situation; however, the accuracy, reliability and interpretation of the data obtained depend on the survey design, organization of sample collection and available resources. Medicine quality surveys are costly and limitations on resources may restrict the number of samples collected, parameters tested, techniques to be used for analysis or number of staff available to conduct the survey and analysis. Therefore it is important to optimize use of resources by focusing on those medicines and parameters that pose a higher risk to patients and apply risk analysis during planning of the survey. Also cooperation with partners, joint organization of surveys in several countries, and sharing testing capacities, experience and information can enhance the effectiveness of quality surveys.

These guidelines outline the steps to consider when preparing and conducting a survey of medicines quality. They provide recommendations and examples of various methodological approaches with a discussion of their advantages and disadvantages, and suggestions on preparation of reports on the results obtained from such surveys.

2. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

pharmaceutical outlet. Any point (licensed or unlicensed) of sale or provision of medicines for individual patients or other medicine providers.

sample collected in a quality survey. A product in a given presentation (identified by its name, content of active pharmaceutical ingredient(s) (API(s)), dosage form, strength, batch number, production date (if known), expiration date, collection date and name of manufacturer or labelled registration holder) collected at the specific sample collection site. It means that the same product characterized by the same name, content of APIs, dosage form, strength, batch, and from the same manufacturer collected in two different sites represents two samples. Each sample should consist of the number of dosage units (e.g. tablets, capsules, ampoules, vials or bottles) required by the sampling plan.

sampling plan. A plan that contains detailed identification of sites where samples will be collected, medicines to be sampled, minimum number of dosage units to be collected per sample, number of samples to be collected per medicine and total number of samples to be collected in the area for which the sampling plan is prepared. It also contains detailed instructions for sample collectors.

3. Objectives of the survey and initial planning

In general, quality surveys are organized to assess the quality of medicines provided to patients and generate the data that can help to formulate strategies and plans to ensure provision of good quality medicines. They may be organized to confirm that patients are receiving satisfactory medicines and give reassurance that the regulatory system is functional, or when there is a suspicion that patients are not receiving satisfactory medicines. Detailed objectives must be set at the start of planning since all the activities and requirements of the survey should be derived from its objectives. The objectives of a quality survey should reflect the reasons why the survey is being conducted and should be formulated in a way that enables identification of medicines for the survey, sites of sample collection, surveyed areas, regions or countries, and tests to be conducted. Clearly defined objectives are essential for setting the conditions for sampling and testing, which should be described in detail in the survey protocol.

There is a wide range of possible objectives, a few examples of which are given below:

- to evaluate the quality of selected medicines available in the market, in selected areas, regions or countries, at various levels of the distribution/supply chain with the aim of assessing the exposure of patients to poor-quality medicines and proposing appropriate actions;

- to evaluate the quality of specific medicines used in the treatment programme;
- to compare the quality of domestically produced and imported medicines in order to recommend appropriate regulatory actions and adjust pharmaceutical policy in the country concerned;
- to identify possible causes of inferior quality of specific products to which patients are exposed and to propose possible strategies and implementation plans to address the problems identified by the survey;
- to test the quality of selected medicines in order to support the NMRA in identification of manufacturers that are not in compliance with quality standards and regulatory measures;
- to find out if, within a selected category of medicines, any spurious/falsely labelled/falsified/counterfeit (SFFC) products have penetrated the market in selected areas, regions or countries, what the possible health impacts may be for patients, and to propose possible strategies and implementation plans to prevent harm to patients.

To ensure that a survey provides the necessary information it is essential, in addition to a primary objective, to set appropriate and relevant questions to be addressed in the survey. Some examples of such questions include:

- What proportion of sampled medicines fails quality testing?
- What proportions of sampled medicines fail quality testing at different levels of the regulated distribution chain and in the informal market?
- What proportions of medicines sampled from different geographical regions fail quality testing?
- What proportions of sampled domestically produced and imported medicines fail quality testing?
- Which specific quality tests do the selected medicines fail?
- Are any of the deficiencies critical, i.e. could they substantially affect treatment efficiency and/or cause harm to patients?
- Are there treatment failures related to a specific disease, which can be associated with low-quality medicines?
- What is the registration status of the sampled products and what proportions of registered and unregistered products fail quality testing?
- What are the supply chains by which poor-quality medicines are distributed and what are the market segments they serve?
- Are there any indicators of poor storage and distribution conditions that influence quality of sampled medicines?

- Are there poor-quality medicines in the selected area, e.g. at the border checkpoint?
- What is the proportion of poor-quality medicines being sold and/or the proportion of pharmaceutical outlets selling poor-quality medicines in a particular area?
- Does the proportion of poor-quality medicines or the proportion of pharmaceutical outlets selling poor-quality medicines exceed a predetermined level?
- Has there been a change in the quality of a medicine or medicine category, or in an area (in the case of repeated random surveys with consistent design)?

Setting reasonable objectives and an appropriate design for a survey needs initial planning. Some examples of questions that should be considered in the planning phase are given below.

- *What is already known about the quality and risk of inferior quality of the target medicines?*

The information may be available from the scientific literature, alerts on medicines quality, or a search of published studies (e.g. in PubMed or Google Scholar). When an NMRA is involved in the survey it is important to gather information from inspectors, assessors, laboratory and pharmacovigilance experts and to design the survey in cooperation with such a multidisciplinary team. Discussions with pharmacists and other health-care professionals may also help to prioritize surveys.

- *What is the distribution/supply system of the target medicines?*

Distribution/supply chains vary between countries and even within a country they may be different for different categories of medicines. In order to design the survey properly it is important to understand how the target medicines are supplied in the surveyed area and how they reach patients. Knowledge of the distribution/supply chain of the target medicines enables risk-based selection of the sampling sites that best serve the survey objectives. Complex supply chains pose a higher risk of quality deterioration and should be prioritized in market surveillance activities. Information on distribution/supply chains should be available to NMRAs, ministries of health, provincial health departments and health centres or other governmental organizations. In the public domain, some information can be found on the World Health Organization (WHO) Essential Medicines and Health Products Department website (<https://www.who.int/teams/health-product-policy-and-standards>). Several

international NGOs are mapping pharmaceutical outlets in various areas and publishing the information on their websites, e.g. Population Services International (PSI) (<http://www.psi.org/>) or, specifically for antimalarials, ACTWatch (<http://www.actwatch.info/>). If the survey is intended to focus on unlicensed outlets, an initial investigation may be necessary to identify and map the relevant locations.

- *What health-seeking behaviour is associated with the target medicines?*

For some surveys it may also be important to understand where different categories of patients tend to buy their medicines and what kind of product they buy. In many countries the medicines market is heavily segmented with different markets for people with different spending power and different ethnicity. For example, the wealthier people may go to pharmacies or private clinics, whereas the poorest go to grocery shops or street peddlers, and people in the middle-income category may go to hospitals. There will also be brands of the same product sold at different prices aimed at different market segments. If such information is needed, an initial pre-survey should be performed.

- *What is the overall volume of use of the target medicines?*

The higher the volumes of a particular medicine used the bigger the impact the inferior-quality medicine will have on patients. Therefore medicines with high consumption volumes should be prioritized in market surveillance activities. It may be difficult to obtain data on consumption volumes in some countries but estimates based on distribution volumes or information from various disease control programmes can be used.

- *What registered medicines are available in the surveyed area?*

It may be useful for the evaluation of survey results to have available lists of registered medicines in the surveyed countries. These lists can often be obtained from NMRAs or ministries of health and sometimes may be published on their websites. Additionally, most countries make available unregistered medicines under certain conditions, e.g. specific medicines may be used in public health programmes or donated.

- *What brands of the target medicines are available in the surveyed area or in the selected outlets?*

If the objective of the survey is to obtain an overall impression of the quality of medicines available on the market, samples produced by as many manufacturers as possible should be collected and it may be necessary to visit several sampling sites. Often, it is very difficult to know

in advance how many brands of a specific medicine (containing the same API in the same dosage form) are sold in a particular market or what their market share is. A pilot study asking for a product list at the selling points may help in collecting the data needed to better plan the survey.

For correct understanding and proper interpretation of the results and conclusions of the survey, its limitations should always be stated and explained.

4. Survey management and time frame

Ideally, the authorities (ministry of health and/or NMRA) of target countries should be involved and should agree with the survey plan before it is implemented. The responsibilities and tasks of the people who have key roles in the survey organization (e.g. principal survey coordinator and the local coordinators in individual areas or countries) should be identified at the beginning and should include those with the responsibility for monitoring the conduct of the survey, performing analysis, processing results and preparing the final report. Lines and means of communication should be agreed in advance.

The primary aim of a medicines quality survey is to reduce harm to patients and enforce medicines quality standards. Surveys are organized for market surveillance or to generate new scientific knowledge. Normally they do not require ethical approval; however, such approval may be needed for an epidemiological survey. As the requirements for ethical clearance vary between countries, the regulations on ethical approval in the target countries should be verified before planning a specific survey.

It is recommended that before sample collection starts, a meeting with local coordinators is organized to explain and discuss the project and the survey protocol, and to provide detailed instructions to ensure survey consistency. After data analysis and before publication of the report it is useful to hold a meeting with appropriate stakeholders to discuss the results, conclusions and actions needed.

Timing of sample collection is important since seasonal changes in environmental conditions may have an influence on the quality of the medicine collected. It is possible that falsified antimalarials are more common during the malaria season, or that access to outlets in rural areas may be impeded in the rainy season, for example as a result of floods or landslides.

Issues such as the use of the results and their public availability should be clearly understood by the responsible authorities and all parties involved in the survey from the beginning. Relevant regulatory measures in individual countries lie within the responsibility of the NMRA, when applicable in collaboration with the police or other enforcement bodies (with respect to falsified medicines or criminal negligence). Therefore, if an NMRA does not organize the survey directly, it should be provided with the results before their publication to be able to investigate in line with the regulatory

practice and legislation with the relevant manufacturer and, if appropriate, adopt necessary regulatory measures.

A publication plan including authorship of any papers to be submitted for peer-reviewed publication and a distribution list of those to whom the report will be disseminated should be agreed at the beginning of the survey. A policy should be adopted concerning public release of data that might be considered confidential. The default position should be to distribute the data as widely and openly as possible.

The survey protocol should include the plan of survey activities and the personnel responsible for the completion of the different steps within the estimated time frames (Table A7.1). It is important to plan the financial resources expected for the whole survey before it commences.

Table A7.1
Example plan of survey activities

Activity	Time frame	Responsible person
Selection of areas/regions/countries and medicines to be surveyed		
Preparation of survey protocol		
Agreement with authority/authorities in surveyed country/countries		
Seeking ethical clearance for an epidemiological survey		
Selection of testing laboratory/laboratories		
Finalization of testing protocol in agreement with testing laboratory/laboratories		
Meeting held with local coordinators from the target areas to discuss the survey protocol		
Preparation of detailed sampling plans		
Preparation and pilot test of data collection instructions and procedures, if needed		
Training and supervision of personnel collecting samples		

Table A7.1 *continued*

Activity	Time frame	Responsible person
Collection of samples and transport to testing laboratory/laboratories in a manner that assures sample chain of custody and maintaining samples in a state of control, to preclude compromising the samples during shipment or transfer to the laboratory		
Database of information on collected samples (including scanned pictures or photographs of the dosage form, label and package leaflet)		
Testing of samples		
Compilation of results		
Data analysis		
Report drafting		
Meeting with appropriate stakeholders to discuss the results and the actions needed		
Report finalization		
Distribution and publication of the results		

5. Methodology

All surveys should be conducted according to a predefined survey protocol. Inadequate instructions on the protocol or noncompliance with the protocol, e.g. insufficient sample size, incorrect sampling and/or testing, may lead to inaccurate results and policy recommendations. Careful consideration of the methodology and ethical issues should guide the survey preparation and the people involved should comply with the instructions and with appropriate ethical standards.

In principle, in addition to the background and explanation of the survey objectives and limitations, the survey protocol should contain information on the following.

5.1 Selection of areas to be sampled

A number of different geographical areas should be sampled unless the objectives expressly justify targeting only one area. Samples should be collected in various

locations, as situations in rural and suburban areas often differ. Depending on the survey objectives, the following variables may be considered when selecting areas to be surveyed:

- population density;
- incidence or prevalence of the disease for which the target medicines are indicated;
- level of risk of poor-quality medicines, e.g. the risk may be higher along trade routes across country borders, in areas where poor-quality medicines have been previously found, areas where formal health services are limited, and in areas where the NMRA has few or no resources to monitor the distribution of medicines;
- degree of urbanization;
- income level of the population in the target area;
- areas with complex distribution systems;
- areas with outlets selling predominantly unregistered and/or illegal medicines.

Sampling several countries according to the same survey protocol gives a broader picture of the quality of medicines in the region and enables comparisons between countries to be made.

Selection of the sampled areas should be explained and justified.

5.2 Selection of medicines to be surveyed

The category of medicines to be surveyed may be characterized in various ways, e.g. according to their content of APIs, therapeutic group classification, formulation, the specific programme under which they are supplied, or the manufacturer or distributor declared on the label. If collection of commonly used products is required, a pre-survey investigation of treatment-seeking behaviour may be necessary. Collaborating with other actors, such as national disease control programmes, may help to identify products commonly used.

Selection of medicines is driven by the survey objectives and public health considerations. The potential public health impact of poor-quality medicines should be a key guide for selection. To optimize use of available resources the survey should focus on medicines posing most risk to patients, e.g. where the therapeutic index is narrow, substandard quality could lead to a significant change in the health outcome, or certain categories may be particularly vulnerable to counterfeiting. To estimate risks posed by individual medicines an analysis should be performed. Aspects to consider may include:

- probability of occurrence of a quality problem, taking into account:
 - complexity of manufacture,
 - stability of the medicine – risk of quality deterioration under local conditions of storage, distribution and use,
 - compliance of manufacturers of the target medicines with GMP principles,
 - complexity of distribution chain for the target medicines and likelihood of non-compliance with good distribution practices (GDP) principles and approved storage conditions during distribution and storage;
- exposure of patients to the medicine and seriousness of potential health impairment, considering:
 - extent of exposed population – number of patients and length of treatment, and volumes used,
 - vulnerability of target population – susceptibility of treated population to the undesired effects of the medicine,
 - complexity of the dosage form in relation to the route of administration,
 - therapeutic properties and risk, such as safety margins and risk of side effects, risk of therapeutic failure, acute versus chronic exposure, and risk of development of resistance.

Instructions should be provided to sample collectors with regard to the dosage forms and strengths of the selected medicines to be collected. Unless the objectives of the survey require a focus on a particular brand or brands, instructions should be given to the collectors on how to select samples if several brands are available at the sample collection site.

The number of medicines that should be selected for the survey depends on available resources (both financial and human) and care should be taken to keep the survey manageable.

5.3 Selection of sample collection sites

5.3.1 Types of sample collection sites

Types of pharmaceutical outlets vary greatly both within and between countries and may be classified according to the countries' medicine legislation. To allow comparison between regions and/or countries, outlets can be classed as:

- public (government);
- formal (licensed), i.e. registered private for profit and private not for profit (nongovernmental organizations (NGOs));
- informal (unlicensed).

Another way to classify sample collection sites is according to their level in the supply chain:

- Level 1 – points of entry to the market, e.g. warehouses of importers or manufacturers, central medical stores, NGO central stores, procurement centres or other facilities supplied directly within various programmes, central wholesalers and/or distributors;
- Level 2 – wholesalers and/or distributors, pharmacies and other regulated retailers, dispensing facilities, hospitals, health centres, sub-health centres, district hospitals, clinics, polyclinics, cabinets, treatment centres, health posts and community health workers;
- Level 3 – informal outlets selling medicines outside the approved distribution system, e.g. kiosks, street vendors, grocery shops, drug stores and itinerant sellers;
- Level 4: virtual outlets, e.g. sales of medicines via the Internet.

Sampling should usually be performed in both the public and private sectors as well as in the “informal market”, i.e. both licensed and unlicensed outlets should be included. Types of sites for sample collection should be selected in the way that will best serve the survey objectives and the selection should be explained.

Quality of samples collected in the supply chain close to the point of sale to patients (Levels 2 and 3) may be influenced by distribution and storage conditions. However, these samples will be the closest in terms of quality to the medicines that patients actually take. When a medicine at Level 2 or 3 is found to be substandard, possibly due to degradation, subsequent sampling of that medicine at Level 1 may identify the source of the problem in the supply chain.

Samples collected at points of entry to the market (Level 1) should be less affected by the conditions they may encounter during in-country distribution, but are relatively distant from the actual quality of medicines that patients will have access to and take. Sampling at this point in the supply chain has the advantage of determining the quality of products as supplied by manufacturers and allowing quality issues to be detected before the products reach patients. Corrective actions may be more easily taken if the results are quickly available.

Once the types of sample collection sites have been selected, the areas, regions or countries to be sampled need to be mapped and the sites where samples will actually be collected during the survey should be identified (by address and facility type). Good local knowledge of the distribution and supply chain structure for the target medicines and information on where patients obtain medicines is needed. Cooperation with NMRAs and relevant disease control programmes in this respect is crucial. If the survey objectives require collection of samples offered by itinerant sellers, it may not be possible to map their “territory” and a pre-survey investigation, e.g. in households, may be needed. Another option would be to include a list of the outlets where itinerant vendors buy their medicines.

5.3.2 Sampling designs

Various designs can be used for selection of sample collection sites. The choice depends on the objectives of the survey, the risks and consequences of inherent decision errors and biases, and available resources.

5.3.2.1 Convenience sampling

Convenience sampling is a non-probability sampling technique based on the judgement of the survey organizer. The sites, however, should not be selected just because of their convenient accessibility and proximity. There should be defined rules guiding the selection so as to best reflect the survey objectives. Whenever convenience sampling is used, it is necessary to report how the sites were identified and which types and what proportion of the outlets the selection represents.

Convenience samples are simple and do not necessarily need complete lists of outlets in defined areas, which may be difficult to obtain especially for unlicensed or mobile outlets. However, they are inherently prone to biases that have to be considered when interpreting the survey outcomes. Such surveys are predominantly used for selection of sample collection sites, e.g. by NMRAs for market surveillance. To utilize resources in the most efficient way NMRAs focus on outlets where the risk of poor-quality medicines being found is high. When selecting such sites the risk analysis should take into account, for example, how medicines are distributed to the site, transport conditions, storage conditions and handling of products at the site, and experience of the NMRA with the distribution chain and sites.

The results of convenience sampling cannot be generalized to other areas, even within the same country, or reliably interpreted over time. However, such surveys may provide the evidence necessary to support regulatory actions or to signal a quality problem. If convenience sampling does indicate a medicine quality problem, further investigation or regulatory actions can be initiated. If a wider picture is needed, subsequent surveys using probability sampling can be designed. If convenience surveys do not reveal a problem one should bear in mind that this may be a false-negative result. It is important to explain the limitations of this technique in reports and scientific papers.

Despite its limitations, convenience sampling is most suitable for NMRAs to identify high-risk areas for further regulatory actions.

Examples of convenience sampling include some surveys conducted in Africa (1, 2) and South East Asia (3, 4).

5.3.2.2 Simple random sampling

Random sampling is a probability sampling technique that, if the sample size is sufficient, will give reliable estimates (with confidence intervals) of the prevalence of outlets selling poor-quality medicines. Formulas for calculation of sample size for random sampling can be found in the literature (5, 6). The disadvantages of random sampling are the

large sample sizes needed, the necessity for complete lists of the locations of the target outlets and the additional costs in terms of labour and time. In addition, it is important to recognize that a random survey will only produce reliable and useful information if the list of outlets and actual within-outlet sampling is consistent with the primary aims of the survey. For example, a random survey of the quality of a medicine in the private sector, when most patients obtain this medicine in the public sector would not be useful, nor would a random survey using overt shoppers for a medicine which the outlet staff know should not be sold to patients. Comparisons with subsequent estimates using this same sampling design should, however, be valid and will allow the evaluation of interventions.

5.3.2.3 Stratified random sampling

Stratified sampling is a probability sampling technique wherein the researcher divides the entire group of subjects to be investigated (e.g. outlets) into different subgroups (layers or strata), then randomly selects the final subjects proportionally from the different subgroups. Stratified sampling can be used to adjust for potential differences, e.g. sales volume, type of customers, or geographical, trade and socioeconomic variables (such as rural versus urban, private versus public outlets and one geographical area versus another) may be considered. Stratification requires adjustment of the sample size calculation. Sampling that is proportional to the number of outlets will be more efficient than simple random sampling. It is important that the randomization procedure is done using formal random number tables or statistical software. This technique has been used in a stratified random survey in Lao People's Democratic Republic (7). Other examples of random surveys come from Nigeria (8) and the United Republic of Tanzania (9).

5.3.2.4 Lot quality assurance sampling

An alternative approach to formal random sampling that is simpler and less expensive, and needs smaller sample sizes, is lot quality assurance sampling (LQAS). This technique can be used to determine whether the prevalence of outlets selling poor-quality medicines exceeds a certain threshold.

LQAS is designed to find out whether a lot of goods meets the desired specifications without having to inspect the entire lot. Thus, the sample size in LQAS is defined as the number of outlets or medicines ("goods") that are selected for each site or region ("lot") and the only outcome is that the site or region is "acceptable" or "unacceptable". Setting the level of risk taken by not inspecting each and every item enables the researcher to accept or reject an entire lot after inspecting a randomly selected sample of items. Therefore the sample size in LQAS is based on defined threshold values that classify good and bad outcomes and the probability of error that the researchers are willing to tolerate.

Acceptable probabilities of error must be specified, i.e. the risk of accepting a "bad" lot (consumer risk) and the risk of not accepting a "good" lot (provider risk). These

risks are commonly referred to as Type I (alpha) and Type II (beta) errors, respectively. The former is often set to 0.05. This means that if the null hypothesis (that the site has fewer outlets selling poor-quality medicines than the specified value) is true, there is a 5% chance that a site with an unacceptable proportion of outlets selling poor-quality medicines will be “accepted” or go undetected. In general, Type I risk is set lower than the Type II risk.

Once the threshold values and probabilities of error have been considered, a sample size and decision value can be obtained. The decision value is the number of outlets selling poor-quality medicines that need to be found before an area is considered unacceptable. LQAS still requires random sampling and preparation of complete lists of the locations of the outlets, and has the disadvantage that it does not estimate an exact prevalence. The advantage is that it requires relatively smaller sample sizes. Sampling can stop once the number of outlets selling poor-quality medicine is exceeded, greatly reducing sampling time and costs.

As LQAS will only provide a binary result, formal random sampling may be required to examine longitudinal changes in the prevalence of poor-quality medicines accurately. It can also be useful as a way to monitor the situation when the exact prevalence of poor-quality medicines is known.

There has been almost no discussion as to what proportion of outlets selling poor-quality medicines should be regarded as unacceptable. Ideally there should be zero-tolerance for outlets selling poor-quality medicines, as even a 1% prevalence of such medicines for potentially fatal diseases, such as malaria, tuberculosis and HIV, is disastrous for individual patients.

Examples of this approach are described in several publications (10, 11). Sampling procedures and tables for lot acceptance by parties who receive goods manufactured by others can be found in the international standards, e.g. ANSI/ASQ Z1.4 and Z1.9 or ISO 2859 and ISO 3951 series.¹

5.3.2.5 Sentinel site monitoring

Sentinel site monitoring involves following the quality of medicines in a particular locality over time. There are no common rules as to whether these sites should be chosen on the basis of potentially important variables such as rural versus urban and private versus public outlets, or as to sampling design (i.e. convenience or random samples or LQAS). The power of this methodology resides in allowing longitudinal changes to be followed in one place, but data from fixed sentinel site monitoring should be interpreted with caution. Sentinel site monitoring suffers from the disadvantage that shop owners

¹ <http://asq.org/knowledge-center/Z14.Z19/index.html>;
http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=39991;
http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=57490.

may soon realize that they are being sampled, change their behaviour accordingly and thus cease to be representative. Examples of this approach include the survey in the Mekong region (12).

5.4 Sampling plans

Sampling plans should be prepared for each area, region or country involved in the survey and should be in compliance with requirements identified in the survey protocol. They should specify the:

- individual sites where collectors should collect samples (by facility type and address, possibly including global positioning system (GPS) coordinates);
- medicines to be sampled (by APIs, dosage form, strength, and, if needed, also by package size);
- minimum number of dosage units to be collected per sample;
- number of samples to be collected per medicine;
- total number of samples to be collected in the relevant area, region or country.

Sampling plans should also contain detailed instructions for collectors. Examples of sampling plans for surveys organized by WHO can be found in the published survey reports.²

5.4.1 Number of dosage units to be collected

The number of dosage units that should be collected per sample depends on the survey objectives, surveyed medicines, tests to be conducted, testing methods to be employed and available resources. To protect the integrity of the samples and avoid quality deterioration before testing, dosage units should normally not be taken out of the original primary and secondary packaging, and only intact and unopened packages should be collected. Sampling plans usually define the minimum number of dosage units to be collected per sample. The appropriate number of packages is collected in relation to the available package size.

In surveys aiming to provide evidence to support regulatory actions, which are often organized by NMRAs or with their participation, pharmacopoeial tests performed in compliance with pharmacopoeial procedures are commonly used. In such surveys the principles of good practices for pharmaceutical quality control laboratories (13) should be followed and the number of dosage units per sample should allow:

² World Health Organization Prequalification of Medicines Programme. Quality Monitoring (<https://extranet.who.int/prequal/medicines/quality-monitoring>).

- the planned tests to be conducted;
- investigation and confirmatory testing of samples found to be out-of-specification (OOS);
- sufficient retention samples to be used in case of dispute.

To fulfil these requirements, suitably large numbers of dosage units per sample should be collected (e.g. 100 tablets, 40 injection solution ampoules or powder for injection vials, depending on the medicine and the requested tests), which may be difficult to obtain from some outlets. Requests for such large quantities of products may also suggest to the outlet owner that the buyer is not an ordinary shopper, in cases where the survey objectives require a mystery-shopper approach. The minimum number of dosage units of each selected medicine to be collected should be agreed with the testing laboratory. The advantage of surveys using pharmacopoeial procedures is the possibility to apply quality acceptance criteria as defined in pharmacopoeias. The disadvantage is that the rather time- and resource-intensive laboratory testing leads to fewer samples that can be included in the survey.

Other types of surveys include quality screening surveys using basic, simple tests, non-destructive techniques (such as Raman and infrared (IR) spectroscopy) or unofficial testing methods (i.e. non-pharmacopoeial or not approved by the NMRA during the registration process) to assess the identity of the API and estimate its content. Such surveys cannot be used as a basis for regulatory actions but may prompt further investigations with appropriate protocols. The advantage is that only a few dosage units need to be collected per sample, a higher number of samples can be collected and the mystery-shopper approach can be used, if needed. The disadvantage is that when testing only a few individual dosage units, the usual pharmacopoeial quality acceptance criteria are difficult to apply, e.g. when estimating the content of the API by testing only a few individual tablets, pharmacopoeial criteria for the assay cannot be used.

Testing of individual dosage units to assess the content of API raises the question of how many dosage units, within a specific medicine sample, need to be analysed. The variability of individual units can be very high, especially within a sample of poor-quality medicine. Various statistical approaches to representative medicine sampling, especially for forensic analysis purposes, have been described. These are published, e.g. by the United Nations (UN) Office on Drugs and Crime (14), Scientific Working Group for the Analysis of Seized Drugs (15), European Network of Forensic Sciences Institutes,³ and in other publications (16).

Sampling procedures to ensure that representative samples are taken by authorities, procurement agencies, manufacturers or customers, for acceptance of

³ Calculator for qualitative sampling of seized drugs (<https://enfsi.eu/about-enfsi/structure/working-groups/documents-page/documents/best-practice-manuals/>).

consignments, batch release testing, in-process controls, special controls, inspection for customs clearance, deterioration and adulteration, or for obtaining a retention sample are described in the WHO guidelines for sampling of pharmaceutical products and related materials (17).

5.5 Sample collection

5.5.1 Overt sampling versus mystery-shopper approach

The decision on who should collect samples will depend on the survey objectives, the regulatory status of the target medicines and what is known about the knowledge and attitude of the sellers (i.e. whether they know that the outlet is selling poor-quality medicines and understand the health, legal and ethical implications). If outlet staff are anxious to avoid poor-quality medicines and are informed about the survey objectives, overt sampling with feedback would allow more data to be collected on poor-quality medicines and their risk factors and lead to a direct improvement in the medicine supply. Overt sampling may be the only possible method in some circumstances, such as when collecting samples at locations where people are seen first by clinicians, or in the public sector.

However, many outlets in countries with weak medicines regulation sell expired or unregistered medicines, which may make outlet staff suspicious and anxious about investigations. If the seller knows or is concerned that his or her stock contains illegal or poor-quality medicines and that the buyer is potentially linked to the NMRA, this may influence which medicines are offered. An additional concern is that in many resource-poor countries the medicine market is heavily segmented with different markets for people with different spending power and ethnicity. Even within a single outlet there will often be several different brands of the same medicine at different prices aimed at different market segments. In such cases a covert, mystery-shopper approach may be appropriate (18). The identity and purpose of the buyer should not be generally known by the outlet being evaluated. Sampling should usually be performed by nationals of the country concerned although there may be some situations, such as suspicion that migrant workers may take inferior medicines, where this would not be applicable. It may not be safe for people living in the same wider community to act as purchasers. In contrast, in some remote rural locations, it would be difficult for someone who is not local to request medicines as this would cause suspicion. The safety of those acting as mystery shoppers should be considered, a risk assessment performed and instructions appropriate to local conditions need to be developed.

The mystery shopper mimics a “normal shopper” from the community in which the outlet is located and should dress, speak and behave appropriately for that community. Shoppers should use a standard scenario, e.g. pretending to be a visitor from another part of the country who needs some medicines for a specified disease, for a specific reason and for a stereotypical patient. Mystery shoppers should be prepared to explain the real purpose of their visit to protect themselves if their identity is revealed.

After leaving the survey site the mystery shopper should record details of each purchase. Price, name of the provider and/or outlet, and an estimation of temperature at the site should be documented as well as the conditions of the purchase, e.g. how many people were in the outlet, how long the purchase took, the nature of the interaction between the mystery shopper and outlet staff, whether it was easy to convince the provider to sell medicines, and any other information needed to meet the survey objectives. All medicines collected should be properly identified and stored, e.g. in a plastic bag labelled with the name of the outlet.

The mystery shopper should brief the local coordinator for the surveyed area upon his or her return from each outlet. The local coordinator should transcribe the reported interaction together with a translation if appropriate. Translations should use a meaning-based method, rather than a literal or interpretative approach. The original text with translation should be double-checked for accuracy by other members of the team and kept.

Examples of overt sampling include some surveys in Asia (19, 20) and an example using the mystery-shopper approach can be found in the report of a survey conducted in Lao People's Democratic Republic (7).

5.5.2 Instructions to sample collectors

The local coordinator for each area, region or country will arrange for training of collectors to familiarize them with the project, survey protocol, sampling plan and instructions for collection of samples. Staff from the NMRA and different national disease control programmes may provide a useful insight into the survey planning. Instructions and procedures for data collection should be well understood by the collectors (translated into the language of the collectors, pilot-tested and revised, if needed). The following principles should be stated in detailed instructions for collectors.

- The minimum number of dosage units per sample and number of batches to be collected from each collection site for each selected medicine as indicated in the sampling plan should be adhered to.
- The target medicines, their dosage forms, strengths and package sizes should be defined. As outlets may have more than one brand of a particular medicine available, instructions should be provided on how to decide which to choose if a selection has to be made. It should be taken into consideration that mystery shoppers requesting a very specific brand or product may alert sellers. However, such an approach may be required if evidence suggests that only one brand of an essential medicine is affected by falsification or substandard production. It may be useful to consider using a specific written prescription for a number of items including the target medicine. This can reduce the suspicion that might be raised by a verbal request. Using the written prescription format may also

enable the quality of dispensing, labelling directions and counselling to be studied.

- All units of one sample should have the same batch number.
- The medicine samples should not be taken out of the original primary and secondary packaging (although removal from large secondary packs is appropriate). Containers such as bottles and vials should not be opened. Where medicines are sold without package leaflets, or in unlabelled plastic bags coming from large-sized boxes (locally repacked), or as individual dosage forms, this should be recorded.
- Ideally, samples collected should have at least six months remaining before expiry to allow sufficient time for chemical analysis. However, the frequency of expired medicines is also an important outcome measure and any expired medicine found in the outlet should be recorded.
- The medicine labels and package leaflets should not be removed or damaged.
- Each sample should be recorded separately using the sample collection form (for an example see Appendix 1). Whenever the required information is not available this should be noted in the appropriate space on the sample collection form; any observed abnormalities should also be recorded.
- Each sample should be identified by a unique sample code, defined on the sample collection form and specified on all original packages belonging to the respective sample. It should be written legibly and should not obscure the basic product information. The sample collection form and all packages belonging to one sample should be kept together (e.g. blisters inserted in a dedicated zip-lock plastic bag or an envelope marked with the appropriate sample code and trade name of the product). For large surveys, barcode systems may be helpful to reduce errors.
- When overt sampling is used, manufacturer's batch certificates of analysis should be collected with the samples, if available, and kept with the sample collection form.
- Storage conditions at the site (temperature, humidity, access of light and any other observations) should be described in the sample collection form. When overt sampling is used collectors can measure the temperature if it is not controlled at the site. Mystery shoppers can estimate and record the temperature.
- Samples should be collected and kept under controlled conditions in line with the product label requirements. The cold chain has to be maintained, where required. Samples should be kept protected from light, excessive moisture or dryness. Safety measures against theft should be taken; medicine boxes should be kept in a locked area.

The period within which samples should be collected and the deadline for sending the last sample to the testing laboratory should be clearly indicated and adhered to.

Normally samples of collected medicines should be paid for by collectors. The cost of collected samples needs to be taken into account when determining the numbers of samples to be collected. In some countries, NMRA inspectors have legal power to collect samples from the market without reimbursement.

Collectors should be mindful of the stock of sampled products held in outlets, and of the potential difficulties of replenishing sampled medicines through the supply chain, so as not to jeopardize the availability of these medicines to patients. If there is a risk of product shortage after sampling, replacement of the sampled amount should be arranged immediately after the survey or, less desirably, collection of that particular product from that outlet should be omitted.

For surveys seeking to determine the proportion of poor-quality medicines sold to patients, data on product-specific sales volumes from the outlets may be necessary. These data can be collected after sampling, especially when the mystery-shopper approach is used, and sellers should be informed about the survey. This approach requires the support of the NMRA as data on sales volumes are better collected by inspectors or by officers of the authority.

5.6 Storage and transportation of samples

Storage and transportation of the samples to the testing laboratory should be done according to the requirements set out in paragraph 2.3 of *WHO Guidelines for sampling of pharmaceutical products and related materials* (17). Transportation should be as quick and direct as possible so as not to jeopardize the quality of the collected samples.

- The samples should be kept in their original packaging and stored under the conditions specified on the label; freezing should be avoided and, where required, the cold chain should be maintained.
- For transport, all samples should be packaged adequately and transported in such a way as to avoid breakage and contamination. Any residual space in the container should be filled with a suitable material.
- For temperature-sensitive medicines, temperature data loggers may be included within shipments to document maintenance of an appropriate temperature during prolonged transit.
- A covering letter, copies of sample collection forms and, if available, copies of the manufacturer's batch certificate of analysis should accompany the samples.
- Where collectors do not transport samples directly to the testing laboratory, samples, with the accompanying documents, should be sent by a courier

service. The documentation with each shipment should clearly indicate that the samples are being sent for laboratory testing purposes only, will not be used on humans or animals, have no commercial value and will not be placed on the market. If the country where the laboratory is located requires permission for importation of samples, the laboratory or NMRA of that country may be able to assist to avoid long clearance procedures. The staff of the testing laboratory should be informed of the shipment and provided with the tracking number assigned by the courier service to enable them to follow the shipment and arrange collection as soon as possible.

- Copies of sample collection forms and, if available, copies of manufacturer's batch certificates of analysis should also be sent to the principal survey coordinator or the person preparing the survey report.

5.7 Testing

5.7.1 Testing laboratory

It is important that only quality control laboratories with demonstrated capability to produce reliable test results are used in quality surveys. Therefore laboratories for testing should be carefully selected and should meet the following criteria:

- the laboratory works in compliance with WHO *Good practices for pharmaceutical quality control laboratories* (13), is preferably a WHO prequalified⁴ laboratory or is a laboratory where other evidence of equivalent working standards is available;
- the laboratory is capable and competent to perform the tests required by the testing protocol;
- the laboratory should have sufficient capacity and should agree to test the required number of samples within the specified period for the cost specified according to the available budget.

The choice of the testing laboratory or laboratories should be explained in the survey protocol, reports and publications. One or more laboratories may be used for testing the samples collected during the survey. If several laboratories are testing collected samples, samples should be divided in such a way that all samples containing the same APIs are assigned for testing to the same laboratory. Many countries do not have a fully functioning quality control laboratory and should consider making arrangements with a laboratory abroad. The appropriate arrangements with the laboratory have to be made in advance.

⁴ The list of WHO-prequalified laboratories can be found at <https://extranet.who.int/prequal/medicines/prequalified/quality-control-labs>.

Within the usual selection procedure and the resulting agreement the following should be clearly specified in addition to the usual elements of such agreements (such as deadlines and financial arrangements):

- medicines and numbers of samples to be tested, tests to be conducted and specifications to be used, according to the testing protocol. If more than one testing laboratory is selected, a specific testing protocol should be prepared for each laboratory;
- responsibilities of the laboratory during the survey as specified in section 5.7.4;
- confidentiality declaration made by the laboratory;
- acceptance of a possible audit of the laboratory, access to records and retained samples.

Following conclusion of the agreement(s), the principal survey coordinator should inform the local coordinators in the areas, regions or countries participating in the survey about the following:

- name and address of the laboratory or laboratories;
- the contact person(s) in the laboratory; and
- medicines assigned for testing to the particular laboratory.

The laboratory normally starts testing only when all the samples containing the same API in the same dosage form have been received. Therefore it is important to set and adhere to the deadline for sending samples to the testing laboratory.

5.7.2 Tests to be conducted

Laboratory testing of all collected samples should be performed according to the testing protocol, which is a part of the survey protocol, and should be agreed with the testing laboratory or laboratories. Depending on the survey objectives, target medicines and available resources, the tests to be done on samples collected in the survey may include:

- verifying the identity;
- performing complete pharmacopoeial or analogous testing;
- performing special or specific tests.

If testing is expected to provide a full picture of the quality of target medicines, it should be performed according to a pharmacopoeial or analogous monograph and the following tests are, in principle, included:

- appearance, visual inspection;
- identity;

- assay for APIs declared on the label;
- test for related substances;
- for solid dosage forms – dissolution or disintegration, uniformity of dosage units (by mass or content), fineness of dispersion, for dispersible tablets;
- for liquid dosage forms – pH value and volume in containers or extractable volume;
- for parenteral products – sterility and bacterial endotoxins tests.

Inclusion of tests for uniformity of content for single-dose dosage forms, or for sterility and bacterial endotoxins, which are costly and time consuming, and necessitate the collection of more dosage units, should be considered in relation to the target medicines and available resources. It is impossible to achieve 100% certainty about sterility of the product through testing only and inspections and enforcement of compliance with GMP principles may be more efficient tools for verification in some cases.

The packaging of each collected sample, labelling and package leaflets should be inspected visually for any signs of being an SFMC product. The World Health Professionals Association has published a checklist that may be used for this purpose (21). Laboratory analysis is not always successful in identifying falsified or substandard medicines and any suspicious product that is identified should be further examined in cooperation with the NMRA in the country of collection and the manufacturer declared on the label of the suspicious sample (for guidance on conducting such investigations see the WHO guidelines⁵).

Information on labels and in package leaflets can also be checked for quality and completeness of essential information, and compliance with requirements and approved product information in the country of collection can be verified. However, when more than one country is involved in the survey, it should be kept in mind that requirements for information to be provided on medicines labels and package leaflets may differ between countries.

Screening methods do not provide a full picture of the quality of medicines and may be more likely to underestimate non-compliant findings than laboratory testing methods (1). However, they do enable testing of a large number of samples in the field, e.g. to search for SFMC medicines. It is recommended that outcomes of screening are verified by laboratory testing, at least for a random selection of those samples that pass screening and for all those that fail.

⁵ Testing of “suspect” substandard/spurious/falsely-labelled/falsified/counterfeit medicines (QAS/15.634) (draft in preparation).

5.7.3 Test methods and specifications

Test methods and specifications should be selected in the way that will best serve the survey objectives. In general, when samples from different manufacturers are collected in a quality survey, all samples containing the same APIs in the same dosage form are tested using the same method and specification to enable comparison of samples from different manufacturers. This specification is then used to decide on compliance or non-compliance of tested samples for the purposes of the survey. It should be noted that individual manufacturers may use different specifications and different methods for testing of their products and those specifications and methods may be approved by regulatory authorities in the countries concerned. Non-compliance with the specification selected for the survey does not therefore necessarily imply non-compliance with the specifications approved in the country but it indicates to the respective NMRA the need to look at the product and conditions of regulatory approval more closely and discuss these with the manufacturer or registration holder.

Wherever appropriate, pharmacopoeial methods and specifications should be used. A national pharmacopoeia may be applicable if a survey is organized in one country. If several countries are involved, widely accepted pharmacopoeias (such as the *British Pharmacopoeia*, *European Pharmacopoeia*, *The International Pharmacopoeia* or the *United States Pharmacopoeia*) may be appropriate. In spite of efforts to harmonize pharmacopoeias there are still many differences between them. When a monograph for the particular medicine being tested is available in more than one pharmacopoeia the ability of the different methods and specifications to reveal quality problems should be considered and the monograph selected accordingly. Suitability of test methods for the intended use should be appropriately verified.

If no monograph for the target medicine exists in a pharmacopoeia or the existing monographs do not cover the desired tests, a validated method of the laboratory should be used.

When samples from one manufacturer only are tested in a survey, that manufacturer's methods and specifications can be used, if available to the testing laboratory. The performance of such methods under the conditions of the testing laboratory should be verified.

If samples suspected of being an SFFC product are tested, pharmacopoeial methods may not be sufficient and further examination should be conducted (for guidance on such investigations see WHO guidelines⁶).

Once the tests to be performed and the methods and specifications to be used have been selected, the testing protocol should be finalized. For each of the target medicines the protocol should contain the list of tests to be conducted, reference to

⁶ Testing of "suspect" substandard/spurious/falsely-labelled/falsified/counterfeit medicines (QAS/15.634) (draft in preparation).

methods to be used and specifications to be employed. Examples of testing protocols used for surveys organized by WHO can be found in the published survey reports.⁷

5.7.4 Receipt and testing of samples by a testing laboratory

When samples are received, the testing laboratory should:

- inspect each sample to ensure that the labelling is in conformity with the information provided in the sample collection form or test request; an electronic databank (e.g. scanned pictures or photographs of the medicines, e.g. of the tablets, packaging and package leaflet) is recommended;
- store the samples according to the conditions set out on the product labels, including compliance with any cold chain requirements;
- conduct quality testing in line with the testing protocol and in compliance with WHO *Good practices for pharmaceutical quality control laboratories* (13), including appropriate verification of test methods, investigation and documentation of each OOS result according to the laboratory standard operating procedure. If the OOS result is confirmed, it should be reported without delay to the principal survey coordinator who should receive both the results and the investigation report;
- prepare complete analytical test reports and certificates of analysis containing the information listed in Appendix 2. The principal survey coordinator should define the format of the outcome (e.g. separately for each sample or as a tabulated report);
- keep document(s) received with the samples, records of testing of each sample including all raw data, and retention samples according to the requirements defined by the principal survey coordinator (e.g. for at least six months if the sample complied with the specifications, or for at least one year or until the expiry date (whichever is longer) if it did not comply) and archive data according to the agreed conditions.

6. Data management and publication

To allow proper interpretation, the data obtained during collection and testing of samples should be summarized and appropriately organized in a database (using Excel sheets or software for epidemiological studies), linking each sample with all the data gathered and ensuring consistency and security. Suitable precautions should be taken to avoid errors. For analysis of large sets of data, statistical software may be used. If relevant,

⁷ For details of the various studies carried out using the protocol referred to, see: <http://apps.who.int/prequal/>

personal identification of individuals who participated in the survey (e.g. buyers and sellers) should be entered in the database using codes only.

The NMRAs of countries involved in the survey should be informed immediately about confirmed OOS results. NMRAs should carry out their investigations with the involvement of the relevant manufacturer, registration holder or other party (e.g. procurement organizations). It should be kept in mind that if the testing methods and specifications approved during the registration process differ from those used in the survey, it may be necessary to retest the product concerned using the approved manufacturer's method, where available. Appropriate measures should be taken to ensure the accuracy of the results.

Once survey results have been compiled, evaluated and summarized they should be shared with the NMRAs involved as they may provide information on medicine quality problems that will alert NMRAs and manufacturers. Before publication of the results, it is useful to hold a meeting with appropriate stakeholders to discuss the results and the actions needed. The WHO Rapid Alert System should be informed when results are considered to constitute a public health emergency.

A detailed survey report should be prepared that includes all test results on the collected samples together with their interpretation. An example outline for the survey report content is provided in Appendix 3. Recommendations for items to be addressed in the reports of medicines quality surveys can also be found in the published literature (22).

The report should be published as widely and openly as possible. The conclusions and wording should be prepared with caution so as not to cause embarrassment or panic. The risk that patients will stop taking genuine medicines and that the public will lose faith in medicines or the health-care system should be reduced by careful wording. Also any potential harm that might be caused to manufacturers, suppliers or outlets should be considered to avoid any legal actions.

References

1. Survey of the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa. Geneva: World Health Organization; 2011.
2. United States Pharmacopeia Drug Quality and Information Program. Survey of the quality of selected antimalarial medicines circulating in Madagascar, Senegal, and Uganda – November 2009. Rockville (MD): The United States Pharmacopeial Convention; 2010.
3. Newton P, Proux S, Green M, Smithuis F, Rozendaal J, Prakongpan S, et al. Fake artesunate in Southeast Asia. *Lancet*. 2001;357(9272):1948–50.
4. Dondorp AM, Newton PN, Mayxay M, Van Damme W, Smithuis FM, Yeung S, et al. Fake antimalarials in Southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials. *Trop Med Int Health*. 2004; 9(12):1241–6.
5. Cochran WG. Sampling techniques, second edition. New York: John Wiley and Sons; 1963.
6. Yamane T. Statistics: an introductory analysis, second edition. New York: Harper and Row; 1967.

7. Sengaloundeth S, Green MD, Fernández FM, Manolin O, Phommavong K, Insixiengmay V. A stratified random survey of the proportion of poor-quality oral artesunate sold at medicine outlets in the Lao PDR – implications for therapeutic failure and drug resistance. *Malar J.* 2009;8:172. doi: 10.1186/1475-2875-8-172.
8. Onwujekwe O, Kaur H, Dike N, Shu E, Uzochukwu B, Hanson K, et al. Quality of anti-malarial drugs provided by public and private healthcare providers in south-east Nigeria. *Malar J.* 2009;8:22. doi: 10.1186/1475-2875-8-22.
9. Kaur H, Goodman C, Thompson E, Thompson KA, Masanja I, Kachur SP, et al. A nationwide survey of the quality of antimalarials in retail outlets in Tanzania. *PLoS One.* 2008;3(10):e3403.
10. Khojah HMJ, Pallos H, Yoshida N, Akazawa M, Tsuboi H, Kazuko K. The quality of medicines in community pharmacies in Riyadh, Saudi Arabia. A lot quality assurance sampling (LQAS)-based survey. *Pharmacol Pharm.* 2013;4(7):511–9. doi: 10.4236/pp. 2013.47074.
11. Lemeshow S, Taber S. Lot quality assurance sampling: single- and double-sampling plans. *World Health Stat Q.* 1991;44(3):115–32.
12. Phanouvong S. Mekong Malaria Initiative. Antimalarial drug quality monitoring and evaluation. Indicators. Rockville (MD): United States Pharmacopeia Drug Quality and Information Program; 2004 (http://pdf.usaid.gov/pdf_docs/pnadh147.pdf, accessed 25 November 2015).
13. Good practices for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 1 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y).
14. United Nations Office on Drugs and Crime. Guidelines on representative drug sampling for use by national drug analysis laboratories. New York: United Nations; 2009 (http://www.unodc.org/documents/scientific/Drug_Sampling.pdf, accessed 25 November 2015).
15. Scientific working group for the analysis of seized drugs (SWGDRUG). Recommendations. United States Department of Justice Drug Enforcement Administration; 2011 (<http://www.swgdrug.org/Documents/SWGDRUG%20Recommendations%206.pdf>, accessed 25 November 2015).
16. Hoffman CG, Frank RS, Hinkley SW. Representative sampling of drug seizures in multiple containers. *ASTM International.* 1991;36(2).
17. WHO guidelines for sampling of pharmaceutical products and related materials. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-ninth report. Geneva: World Health Organization; 2005: Annex 4 (WHO Technical Report Series, No. 929; https://iris.who.int/bitstream/handle/10665/43157/WHO_TRS_929_eng.pdf?sequence=1&isAllowed=y).
18. Madden JM, Quick JD, Ross-Degnan D, Kafle KK. Undercover careseekers: Simulated clients in the study of health provider behavior in developing countries. *Soc Sci Med.* 1997;45(10):1465–82.
19. ACTwatch. Outlet survey. Kingdom of Cambodia. 2011 Survey Report. Washington (DC): Population Services International; 2011 (http://www.actwatch.info/sites/default/files/content/outlet-reports/ACTwatch%20Cambodia%20O5%20Endline_2011.pdf, accessed 25 November 2015).
20. Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union. Geneva: World Health Organization; 2011.
21. Be aware. Tool for visual inspection of medicines. Ferney Voltaire: World Health Professions Alliance (https://www.whpa.org/sites/default/files/2018-12/Toolkit_BeAware_Inspection.pdf).
22. Newton PN, Lee SJ, Goodman C, Fernández FM, Yeung S, Phanouvong S, et al. Guidelines for field surveys of the quality of medicines: A proposal. *PLoS Med.* 2009;6(3):0252–0257.

Appendix 1

Example of a sample collection form¹

SURVEY TITLE

Area/region/country: _____ Sample code: _____

(Area/region/country code/medicine abbreviation/
sequence number/sampling date dd/mm/yy)²

Name of location/place where sample was taken: _____

Address (with telephone, fax number and email address, GPS coordinates, if applicable):

Organization and names of people who collected the sample:

1. _____

2. _____

Product name of the sample: _____

Name of active pharmaceutical ingredient(s) (INN) with strength:

Dosage form (tablet, injection, powder for injection, etc.): _____

Package size, type and packaging material of the container: _____

Batch/lot number: _____

Date of manufacture: _____ Expiry date: _____

Regulatory status in the country, registration number if applicable: _____

Name and address of the manufacturer: _____

¹ The sample collection form should always be kept with the collected sample.

² *Area/region/country code*: e.g. for countries, the two-letter code is used for the Internet country top-level domains; *medicines abbreviations* to be established; sample code system can be extended to be appropriate for a collection system in a particular area, region or country.

Quantity collected (number of tablets/ampoules/vials and number of packages):

Initial first page:

Product name: _____ **Sample code:** _____

Date the batch was received at the location: _____

Storage and climatic conditions at sampling site:

Conditions controlled? Yes ☐ No ☐

Temperature and humidity in the place where the sample was stored at the time of sample collection: _____

Comments on suitability of premises where products are stored, abnormalities, remarks or observations that may be considered relevant, if any:

Date:

Signature of person(s) taking samples

Signature of representative of the facility
where sample was taken (*only for overt
sampling, optional*)

1. _____

2. _____

Note: Samples collected must remain in their original primary and secondary packaging, intact and unopened.

Appendix 2

Content of the analytical test report/certificate of analysis

- Name and address of the laboratory performing the sample testing
- Name and address of the originator of the request for testing
- Number/code of the analytical test report/certificate of analysis
- Sample reference number assigned by the laboratory and sample code assigned at the time of sampling (specified in the sample collection form and packages belonging to one sample)
- Date on which the sample was received
- Name of the area, region or country where the sample was collected
- Sample product name (trade name as it appears on the label), dosage form, APIs, strength, package size (e.g. number of tablets in one blister and number of blisters in the secondary packaging, volume in one ampoule and number of ampoules in secondary packaging)
- Description of the sample (describing both the product and the primary and secondary packaging, type and packaging material of primary container); if there is any sign of unsatisfactory handling during transportation, this should be mentioned
- Batch number of the sample, expiry date and, if available, date of manufacture
- Number of units received for the sample
- Name and full address of the manufacturer (as specified on the label or in the package leaflet)
- Reference to the specifications used for testing the sample, including the limits
- If a reference substance was used for quantitative determination, this substance should be specified (e.g. *The International Pharmacopoeia*, *British Pharmacopoeia* or *United States Pharmacopoeia* reference substance or working standard)
- Results of all the tests performed; for the evaluation and interpretation of results it is useful to request numerical results wherever possible, any observation made during testing, and the following details:
 - for content uniformity, all results for individual units,

- for dissolution test, results for all tablets tested,
 - for assay, results of each individual sample preparation (usually 3 sample preparations), the average and the relative standard deviation; in the case of an OOS result followed by retesting, also the investigation report and results of retesting
- Conclusion as to whether or not the sample complies with the specifications set for the survey
 - Date on which the test was completed
 - Signature of the head of the laboratory or authorized person

Appendix 3

Outline of the content of a survey report

Glossary and abbreviations

Executive summary

1. Introduction

- 1.1 Background
- 1.2 Objectives of the survey

2. Methodology

- 2.1 Survey period
- 2.2 Selection of medicines for sampling and testing
- 2.3 Selection of areas, regions or countries
- 2.4 Sampling design and selection of sample collection sites
- 2.5 Sample collection and transportation
- 2.6 Testing laboratories
- 2.7 Quality tests performed and test methods and specifications used
- 2.8 Definition of compliance of samples with standards

3. Results

- 3.1 Overview of samples collected
 - 3.1.1 Medicines
 - 3.1.2 Manufacturers and batches
 - 3.1.3 Sites of sample collection
 - 3.1.4 Storage and transportation conditions
- 3.2 Registration status of sampled products
- 3.3 Compliance with specifications
 - 3.3.1 Overall results
 - 3.3.2 Results of specific quality tests for individual products

4. Discussion

- 4.1 Testing methods and data quality
- 4.2 Limitations of methodology
- 4.3 Interpretation of the results
- 4.4 Recommendations

5. Conclusions

6. Other information (conflict of interests, funding)

References

Attachments – Detailed test results tabled for individual samples

10.2 WHO guidelines for sampling of pharmaceutical products and related materials

Annex 4, WHO Technical Report Series, 929, 2005

1. Introduction	1495
1.1 General considerations	1495
1.2 Glossary	1495
1.3 Purpose of sampling	1498
1.4 Classes and types of pharmaceutical products and related materials	1498
1.5 Sampling facilities	1499
1.6 Responsibilities for sampling	1499
1.7 Health and safety	1500
2. Sampling process	1501
2.1 Preparation for sampling	1501
2.2 Sampling operation and precautions	1501
2.3 Storage and retention	1503
3. Regulatory issues	1503
3.1 Pharmaceutical inspections	1504
3.2 Surveillance programmes	1504
4. Sampling on receipt (for acceptance)	1505
4.1 Starting materials	1505
4.2 Intermediates in the manufacturing process and bulk pharmaceutical products	1505
4.3 Finished products	1506
4.4 Packaging materials (primary and secondary)	1507
5. Sampling plans for starting materials, packaging materials and finished products	1507
5.1 Starting materials	1509
5.2 Packaging materials	1510
5.3 Finished products	1510
Bibliography	1510
Appendix 1 Types of sampling tools	1512
Appendix 2 Sample collection form ^a	1517
Appendix 3 Steps to be considered for inclusion in a standard operating procedure	1519

Appendix 4	Examples of types of containers used to store samples of starting materials and bulk products	1523
Appendix 5	Examples of use of sampling plans n , p and r	1525

1. Introduction

These guidelines are primarily intended for use by governmental organizations, such as drug regulatory authorities (including inspectorates), quality control laboratories and customs and police officials, but some of the general principles may also be appropriate for application by procurement agencies, manufacturers and customers.

These guidelines should be useful when surveying the national markets for the quality of drug products in accordance with national drug quality surveillance programmes for marketed products, whether registered for sale or compounded in pharmacies.

The choice of a sampling plan should always take into consideration the specific objectives of the sampling and the risks and consequences associated with inherent decision errors. The bibliography at the end of this Annex should be consulted when justifying a sampling plan for a given purpose.

1.1 General considerations

Sampling comprises the operations designed to select a portion of a pharmaceutical product (for definition, see glossary) for a defined purpose. The sampling procedure should be appropriate to the purpose of sampling, to the type of controls intended to be applied to the samples and to the material to be sampled. The procedure should be described in writing.

All operations related to sampling should be performed with care, using proper equipment and tools. Any contamination of the sample by dust or other foreign material is liable to jeopardize the validity of the subsequent analyses.

1.2 Glossary

The definitions given below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

Available sample

Whatever total quantity of sample materials is available.

Batch

A quantity of any drug produced during a given cycle of manufacture. If the manufacturing process is continuous, the batch originates in a defined period of time during which the manufacturing conditions are stable and have not been modified.

Combined sample

Sample resulting from combining all or parts of two or more samples of the material.

Consignment

The quantity of a bulk starting material, or of a drug product, made by one manufacturer or supplied by an agent, and supplied at one time in response to a particular request or

order. A consignment may comprise one or more lot-identified packages or containers and may include material belonging to more than one lot-identified batch.

Final sample

Sample ready for the application of the test procedure.

Homogeneity

A material is regarded as homogeneous when it is all of the same origin (e.g. from the same batch) and as non-homogeneous when it is of differing origins.

Original sample

Sample collected directly from the material.

Pharmaceutical product

Any material¹ or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

Prequalification

The activities undertaken in defining a product or service need, seeking expressions of interest from enterprises to supply the product or service, and examining the product or service offered against the specification, and the facility where the product or service is prepared against common standards of good manufacturing practice (GMP). The examination of the product or service and of the facility where it is manufactured is performed by trained and qualified inspectors against common standards. Once the product is approved, and the facility is approved for the delivery of the specified product or service, other procurement agencies are informed of the approval. Pre-qualification is required for all pharmaceutical products regardless of their composition and place of manufacture or registration, but the amount and type of information requested from the supplier for use in the assessment by the procurement agency may differ.

Production

All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

Random sample

Sample in which the different fractions of the material have an equal probability of being represented.

¹ "Material" is used in the document for "pharmaceutical products and related materials".

Representative sample

Sample obtained according to a sampling procedure designed to ensure that the different parts of a batch or the different properties of a non-uniform material are proportionately represented.

Retention sample

Sample collected as part of the original sampling process and reserved for future testing. The size of a retention sample should be sufficient to allow for at least two confirmatory analyses. In some cases statutory regulations may require one or more retention samples, each of which should be separately identified, packaged and sealed.

Sample

A portion of a material collected according to a defined sampling procedure. The size of any sample should be sufficient to allow all anticipated test procedures to be carried out, including all repetitions and retention samples. If the quantity of material available is not sufficient for the intended analyses and for the retention samples, the inspector should record that the sampled material is the available sample (see *Sampling record*) and the evaluation of the results should take account of the limitations that arise from the insufficient sample size.

Sampler

Person responsible for performing the sampling operations.

Sampling method

That part of the sampling procedure dealing with the method prescribed for withdrawing samples.

Sampling plan

Description of the location, number of units and/or quantity of material that should be collected, and associated acceptance criteria.

Sampling procedure

The complete sampling operations to be performed on a defined material for a specific purpose. A detailed written description of the sampling procedure is provided in the *sampling protocol*.

Sampling record

Written record of the sampling operations carried out on a particular material for a defined purpose. The sampling record should contain the batch number, date and place of sampling, reference to the sampling protocol used, a description of the containers and of the materials sampled, notes on possible abnormalities, together with any other relevant observations, and the name and signature of the inspector.

Sampling unit

Discrete part of a consignment such as an individual package, drum or container.

Selected sample

Sample obtained according to a sampling procedure designed to select a fraction of the material that is likely to have special properties. A selected sample that is likely to contain deteriorated, contaminated, adulterated or otherwise unacceptable material is known as an *extreme sample*.

Uniformity

A starting material may be considered uniform when samples drawn from different layers do not show significant differences in the quality control tests which would result in non-conformity with specifications. The following materials may be considered uniform unless there are signs to the contrary: organic and inorganic chemicals; purified natural products; various processed natural products such as fatty oils and essential oils; and plant extracts. The assumption of uniformity is strengthened by homogeneity, i.e. when the consignment is derived from a single batch.

1.3 Purpose of sampling

Sampling may be required for different purposes, such as pre-qualification; acceptance of consignments; batch release testing; in-process control; special controls; inspection for customs clearance, deterioration or adulteration; or for obtaining a retention sample.

The tests to be applied to the sample may include:

- verifying the identity;
- performing complete pharmacopoeial or analogous testing; and
- performing special or specific tests.

1.4 Classes and types of pharmaceutical products and related materials

The materials to be sampled may belong to the following classes:

- starting materials for use in the manufacture of finished pharmaceutical products;
- intermediates in the manufacturing process (e.g. bulk granule);
- pharmaceutical products (in-process as well as before and after packaging);
- primary and secondary packaging materials; and
- cleaning and sanitizing agents, compressed gases and other processing agents.

1.5 Sampling facilities

Sampling facilities should be designed to:

- prevent contamination of the opened container, the materials and the operator;
- prevent cross-contamination by other materials, products and the environment; and
- protect the individual who samples (sampler) during the sampling procedure.

Where possible, sampling should be performed in an area or booth designed for and dedicated to this purpose, although this will not be possible where samples are required to be taken from a production line (e.g. in-process control samples). The area in which the sample was taken should be recorded in the sampling record and a sequential log should be kept of all materials sampled in each area.

Sampling from large containers of starting material or bulk products can present difficulties. Whenever possible, this work should be carried out in a separate, closed cubicle within the warehouse, to reduce the risk of contamination (e.g. by dust) of either the sample or the materials remaining in the container, or of cross-contamination.

Some materials should be sampled in special or dedicated environments (e.g. when sampling articles for which contamination with dirt or particles from the environment should be avoided, such as aerosol valves, hormones and penicillins).

Generally, taking the original sales pack as a sample from outlets such as pharmacies or hospitals does not present problems. However, the inspector should ensure that the quantity of sample taken is sufficient for the intended analyses and for the retention samples, and that all units sampled are derived from the same batch and preferably from the same location.

1.6 Responsibilities for sampling

Those responsible for sampling procedures include:

- *governmental organizations*, such as drug control authorities (including inspectorates); quality control laboratories; customs and police authorities responsible for the clearance of drug products held in quarantine after manufacture or importation, and for the detection of pharmaceutical products that have deteriorated or have been contaminated, adulterated or counterfeited;
- *customers* such as governmental or nongovernmental agencies involved in the acquisition of drug products; and
- *manufacturers* in the context of good manufacturing practices (GMP).

The samplers need to be adequately trained in the practical aspects of sampling, qualified to perform the sampling operation, and should have sufficient knowledge of pharmaceutical substances to allow them to execute the work effectively and safely. Given that the sampling technique itself can introduce bias, it is important that personnel carrying out the sampling should be suitably trained in the techniques and procedures used. The training should be documented in the individual's training records. Sampling records should clearly indicate the date of sampling, the sampled container and the identity of the person who sampled the batch.

A conscientious approach, with meticulous attention to detail and cleanliness, is essential. The sampler should remain alert to any signs of contamination, deterioration or tampering. Any suspicious signs should be recorded in detail in the sampling record.

If a governmental agency needs to sample a sterile or bulk pharmaceutical product at the manufacturing site, it may be best to have the manufacturer's personnel collect the sample, using their own procedures. The regulatory inspector would observe the procedure in such a way as not to increase the chance of contamination (e.g. for sterile pharmaceutical products, the inspector would observe through a glass window outside the aseptic sampling area) and to preclude the possibility of the inspector inadvertently contaminating the remaining bulk pharmaceutical product through poor procedures, for example.

1.7 Health and safety

It is the responsibility of the sampler to read the relevant health and safety information (e.g. the safety data sheet for a pharmaceutical product and related materials) before sampling the material. The information should include necessary safety precautions and requirements for both the operator and the environment.

The sampler should wear appropriate protective clothing for the task. If specific safety precautions are required, such as the use of respiratory equipment, the sampler should be properly trained in its use.

The sampler should have safe access to and egress from the place where the sample is taken, and the places where the samples are taken for storage. The sample storage areas should have adequate light and ventilation and should be arranged to satisfy the requirements for safety as well as any special ones arising from the characteristics of the material being sampled.

Care should be taken to guard against collapse of stacked containers or solids in bulk.

2. Sampling process

2.1 Preparation for sampling

For the sampling of products, the responsible person should have at his or her disposal all the tools needed to open the containers (e.g. packages, barrels and others). Tools may include knives, pliers, saws, hammers, wrenches, implements to remove dust (preferably a vacuum cleaner), and material to reclose the packages (such as sealing tape), as well as self-adhesive labels to indicate that some of the contents have been removed from a package or container. Containers due to be sampled should be cleaned prior to sampling if necessary.

Sampling of uniform starting materials does not require complicated tools. A variety of pipettes fitted with suction bulbs, cups or beakers, dippers and funnels are needed for liquids of low viscosity. The use of glass should be avoided. A suitable inert rod can be used for highly viscous liquid, and spatulas or scoops are needed for powdered and granular solids. Sterile pharmaceutical products should be sampled under aseptic conditions, and only when deemed absolutely essential, to avoid the risk of loss of sterility.

The tools for sampling non-uniform materials are more complicated and more difficult to clean. For example, a sampling tube with a shutter at the lower end may be used to sample liquids in drums or other large containers and a slotted tube with a pointed end may be used to sample solids. It is important to follow the manufacturer's instructions for the use of sampling devices.

All sampling tools and implements should be made of inert materials and kept scrupulously clean. After use or before reuse, they should be thoroughly washed, rinsed with water or suitable solvent, and dried. They should be stored in clean conditions. Adequate washing facilities should be provided in, or in close proximity to, the sampling area, otherwise samplers will need to bring separate clean sets of implements for sampling each product. The cleaning procedure used for all sampling tools and implements should be documented and recorded. The adequacy of the cleaning procedure for the material from which the sampling tool is made should be demonstrated. The use of disposable sampling materials has distinct advantages.

Examples of sampling tools suitable for each type of material are given in Appendix 1.

2.2 Sampling operation and precautions

There should be a written procedure describing the sampling operation. This should include details of the health and safety aspects of sampling. It should ensure that representative samples are taken in sufficient quantity for testing in accordance with specifications. Closures and labels should preferably be such that unauthorized opening can be detected. Samples should never be returned to the bulk.

The sampling process should be appropriately supervised and documented (see Appendix 2 for an example of a sample collection form).

The sampling procedure should be such that non-uniformity of the material can be detected. During the sampling procedure, attention should be paid to any signs of nonconformity of the material.

Signs of non-uniformity include differences in shape, size or colour of particles in crystalline, granular or powdered solid substances; moist crusts on hygroscopic substances; deposits of solid pharmaceutical product in liquid or semi-liquid products; and stratification of liquid products. Such changes, some of which may be readily reversible, can occur during prolonged storage or exposure to extreme temperatures during transportation. Homogeneous portions of the material or bulk such as those mentioned above should be sampled and tested separately from the rest of the material that has a normal appearance.

Pooling of the samples from the different portions should be avoided, because this can mask contamination, low potency or other quality problems.

Labelling of samples should provide appropriate details, including the batch number and, if known, the container number from which the sample was taken, the amount taken and for what purpose. Labels should be applied at the time of sampling. The container used to store the sample should also be properly labelled with appropriate details such as sample type, name of material, identification code, batch/lot number, code, quantity, date of sampling, storage conditions, handling precautions and container number.

For finished drug products, the sampling procedure should take account of the official and non-official tests required for the individual dosage form (e.g. tablets or parenteral preparations). Non-official tests could include testing for adulteration and counterfeiting.

The sampling procedure should also take account of past experience with the pharmaceutical product or related material and with the supplier, and of the number of sampling units in the consignment.

Examples of steps for sampling are given in Appendix 3.

When a container is sampled outside the control of the consignee of the product, the following precautions should be taken. If the tamper-proof seal is broken to obtain a sample, then the consignee of the product should be informed and the container resealed with an appropriate tamper-proof seal, and the consignee of the product informed of its type and its identification. If a bag has been punctured to take a sample, then the sampling hole should be appropriately closed and identified as a sampling hole made by an authorized sampler. Sampled containers should be identified, as they may no longer contain the quantity of product stated on the label. In accordance with national legislation there may be exceptions, e.g. during ongoing investigations of cases related to counterfeit pharmaceutical products.

2.3 Storage and retention

The container used to store a sample should not interact with the sampled material nor allow contamination. It should also protect the sample from light, air and moisture, as required by the storage directions for the pharmaceutical product or related material sampled. As a general rule the container should be sealed and preferably tamper-evident.

Samples of loose materials, whether solid or liquid, should be placed in one or more clean containers. Liquid samples should be transported in suitable bottles closed by screw tops with inert liners that provide a good vapour-proof (moisture-proof) seal for the contents. Suitable screw-top jars in exceptional cases only should be used for solid or semi-solid pharmaceutical products. The container should be inert. Light-sensitive materials should be protected by using amber glass containers or by wrapping colourless glass containers in foil or dark-coloured paper. Headspace should be kept to a minimum to minimize any possible degradation. Any special procedures, for example, nitrogen gassing, should be discussed with the consignee of the material and carried out as appropriate.

Solid dosage forms such as tablets or granules should be protected during transit, either by totally filling the container with the product or by filling any residual space with a suitable material. All containers should be sealed and labelled, and all samples should be packaged adequately and transported in such a way as to avoid breakage and contamination during transport.

For all containers that come apart (e.g. screw-capped jars or metal tins with separate lids) precautions should be taken to avoid any mix-up when they are opened for examination, such as by labelling all parts of each container whenever possible.

If one sample is divided into several sample containers, they should be transported in a suitably sealed box, which should be labelled with the identity of the product, the consignment from which the sample was drawn, the size of the sample, the date and place of sampling, and the name of the inspector.

Security and adequate storage conditions should be ensured for the rooms in which samples are stored. Samples should be stored in accordance with the storage conditions as specified for the respective active pharmaceutical ingredient (API), excipient or drug product. Packaging materials similar to those in which the bulk is supplied should be used for long-term storage.

Examples of types of containers used to store samples of starting materials and bulk products are given in Appendix 4.

3. Regulatory issues

When sampling for regulatory purposes, additional samples for regulatory testing and verification purposes should be provided (e.g. for duplicate testing and parallel testing by different regulatory laboratories and by the consignee of the product). The

consignee of the product should be informed that samples have been taken, and should the consignee wish to conduct his/her own testing of the sample taken for regulatory purposes, regulatory authorities should provide a sample to the consignee of the goods.

Sampling of products for prequalification purposes may follow similar procedures.

3.1 Pharmaceutical inspections

Pharmaceutical inspectors may take samples from retail or hospital pharmacies (including samples of preparations manufactured in bulk on the premises), or from industry and wholesalers for a variety of reasons, such as:

- routine monitoring and control;
- following the suspicion or discovery of products that show signs of possible deterioration, contamination, adulteration or counterfeiting; and
- when a particular product is suspected of being either ineffective or responsible for adverse clinical reactions.

For deteriorated dosage forms, the sample should consist of one or more retail containers of the product that shows visual signs of deterioration.

When a complaint has been received about a drug product, the sample should include the original container and, if possible, one or more unopened containers containing the same product and bearing the same batch number. There should be good communication between the regulatory authority and the consignee of the goods concerning the findings and any necessary corrective action.

3.2 Surveillance programmes

National drug regulatory authorities are responsible for monitoring the quality of all drug products marketed in their country and as defined by legislation. The extent to which routine surveillance should be undertaken, as opposed to assessment of suspect products, will depend upon factors such as:

- the capacity of the national quality control laboratory;
- the extent to which the quality of the product has been assessed prior to registration;
- the extent to which the requirements for GMP are implemented; and
- the number of products that are imported from abroad.

A systematic programme of drug quality surveillance should be in place which may include sampling of marketed products, whether registered for sale or compounded in pharmacies, as deemed necessary. Each product should be assessed regularly (e.g.

every 2–3 years) for inclusion in the surveillance programme, but particular attention should be accorded to products that are of prime importance to public health programmes or that are potentially dangerous, unstable or difficult to formulate properly.

The responsible laboratory should draw up the sampling programme, if necessary under the guidance of the drug regulatory authority, on a yearly or half-yearly basis. This programme should not only list the products to be sampled during a given period, but should also specify the sampling procedures and the size of the samples to be collected, taking into account the need for retention samples. The programme should state to what extent each brand of a given product will be sampled and which local authority or inspector will be responsible for each sampling operation. It should indicate to which laboratory (if more than one exists) each sample should be sent. Such a programme enables the facilities of each laboratory to be used to best advantage.

4. Sampling on receipt (for acceptance)

4.1 Starting materials

Testing of starting materials should be undertaken using samples collected in accordance with an appropriate procedure.

If the material of a consignment can be regarded as uniform, the sample can be taken from any part of the consignment. If, however, the material is not physically uniform, special sampling tools may be required to withdraw a cross-sectional portion of the material. Alternatively, where applicable, a validated procedure can be followed to restore the uniformity of the material before sampling, based on information concerning the subsequent handling and manufacturing steps. For example, a stratified liquid may be stirred or a solid deposit in a liquid may be dissolved by gentle warming and stirring. Such interventions should not be attempted without adequate knowledge of the properties of the contents and appropriate discussions with the consignee of the goods.

All partially processed natural products, both animal, herbal (dried plants and their parts) and mineral, should be treated as intrinsically non-uniform. Special procedures requiring considerable practice are needed to prepare representative samples from such consignments, including coning and quartering and the treatment of fines. Details of appropriate procedures may be found in the relevant International Organization for Standardization (ISO) documents (see Bibliography). These procedures are not further described in these guidelines.

4.2 Intermediates in the manufacturing process and bulk pharmaceutical products

Pharmaceutical intermediates and products supplied in bulk may need to be examined. These include liquids and semi-solid pharmaceutical products, powdered solids or granulates transported in large containers and intended either for further processing

or for direct packaging into final market containers, and unit dosage forms (tablets, capsules) supplied in bulk which are intended for repackaging into smaller containers.

There is a risk of segregation of bulk materials during transportation and this should be taken into account when drawing up the sampling plan.

Products of this kind may be assumed to be uniform where the transportation process has been validated, provided that they:

- are labelled with the name of the manufacturer and a single batch number;
- have been produced in accordance with GMP; and
- are supplied with a certificate, issued in the country of origin, according to the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce.

In these circumstances the collection of a single sample, sufficient for the intended analyses, is adequate.

4.3 Finished products

The quality of finished pharmaceutical products frequently needs to be verified at the time of their importation or purchase. The necessary sampling should be performed using an appropriate method and with regard to the presumed uniformity. A single consignment of a product from a single manufacturer and labelled with a single batch number may be assumed to be uniform.

The minimum size of the samples will be determined by the requirements of the analytical procedure that will be used to test the product. Tests of unit dosage forms for uniformity of weight, volume or content can require a considerable number of units, as can tests for sterility. Depending upon the type of material, the size of the consignment and the way in which the material is packed, a unit to be sampled may be regarded as the transport container, e.g. 20 packs shrink-wrapped or boxed together, rather than an individual container. The required number of unit dosage forms is then withdrawn from any individual container in the selected transit container.

Sampling and testing may be adjusted according to experience with the specific source (e.g. manufacturer or supplier) of the product. If the consignment consists of one very large batch, or if little experience has been obtained with the product to be sampled, it may be prudent to carry out two independent analyses. Two independent final samples should then be taken from different sampling units. Conversely, when a consignment is composed of two or three batches from the same manufacturer, a single sample taken from each batch may suffice, provided that favourable documented experience has previously been gained with the product and the manufacturer, and that there is evidence from the expiry date, or other information, that the batches were produced at approximately the same time.

Note: When sampling finished products, packaging materials may be retained for testing.

4.4 Packaging materials (primary and secondary)

There is a potential for mixing up printed packaging materials during the sampling operations and, therefore, only one material should be handled at a time. Also, samples of packaging materials should never be returned to the consignment.

Adequate protection (e.g. collapsible metal tubes) and identification should be provided for the sample to avoid mixing or damage.

Primary packaging materials should be adequately protected during the sampling operation to avoid environmental contamination. The final use of the packaging should be taken into consideration and appropriate sampling protection afforded (e.g. in the sampling of parenteral ampoules). There are several reasons why a consignment of packaging materials may not necessarily be considered homogenous; for example:

- Materials were manufactured on different days or machines.
- Materials were manufactured on one machine, but on different stations (e.g. 16 printing dye stations or 12 moulding stations).
- Packaging was manufactured with different source materials (e.g. polyethylene from two different sources).
- A change of quality occurred during the process (e.g. container-wall thickness, colour variation, text legibility or change of printing plate).

It is, therefore, important at least to take random samples (e.g. from across the consignment), and to consider focused sampling, taking into account some of the above points.

5. Sampling plans for starting materials, packaging materials and finished products

As stated in the introduction, these guidelines are intended primarily for drug regulatory authorities and procurement agencies. The following sampling plans are, therefore, not necessarily appropriate for manufacturers, although the guiding principles may be useful. The choice of the sampling plan should always take into consideration the specific objectives of the sampling and the risks and consequences associated with inherent decision errors. It should be noted that sampling plans are not recommended for sampling of starting materials for identification tests (see *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, Updated edition. Good manufacturing practices and inspection*. Geneva, World Health Organization, 2004; and *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report*. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929, Annex 2).

Ideally each sampling unit should be examined to ensure that it is intact and also checked for possible damage to the container. The contents should be inspected for uniformity and appropriately tested for identity. Uniformity should be tested on selected layer samples at different points in the material without previous intermixing. However, in cases when this ideal procedure is not possible or justified by the purpose of sampling, a number of sampling units should be randomly selected for sampling. It is not prudent to open all containers of products, which are liable to deteriorate under the influence of moisture or oxygen when held in a transit warehouse. However, materials in damaged containers or those found to be non-uniform should either be rejected or individually sampled for a complete quality control. Unlabelled sampling units should be rejected.

Table 1
Values of n , p or r for the N sampling units^a

Value of n , p or r	Values of N		
	n plan	p plan	r plan
2	up to 3	up to 25	up to 2
3	4–6	26–56	3–4
4	7–13	57–100	5–7
5	14–20	101–156	8–11
6	21–30	157–225	12–16
7	31–42		17–22
8	43–56		23–28
9	57–72		29–36
10	73–90		37–44

^a An example of how these plans work is given in Appendix 5.

For random sampling, whenever possible each sampling unit should be consecutively numbered and the required number of random sampling units selected using tables of random numbers.

The number of units to be sampled depends on different assumptions and three possible plans are shown in Table 1. For more comprehensive, statistically-based sampling schemes, see Bibliography.

It is important to recognize that the “ n -plan” is not statistically based and should be used only as a guiding principle.

5.1 Starting materials

When sampling starting materials proper consideration has to be given to deciding on a sampling plan. The following are examples of sampling plans that could be used.

5.1.1 *The n plan*

The “ n plan” should be used with great caution and only when the material to be sampled is considered uniform and is supplied from a recognized source. Samples can be withdrawn from any part of the container (usually from the top layer). The n plan is based on the formula $n = 1 + \sqrt{N}$, where N is the number of sampling units in the consignment. The value of n is obtained by simple rounding. A minimum number of containers needs to be sampled, e.g. if N is less than or equal to 4, then every container is sampled. According to this plan, original samples are taken from n sampling units selected at random and these are subsequently placed in separate sample containers. The control laboratory inspects the appearance of the material and tests the identity of each original sample according to the relevant specification. If the results are concordant, the original samples are combined into a final, composite sample from which an analytical sample is prepared, the remainder being kept as a retention sample.

Note: The n plan is not recommended for use by control laboratories of manufacturers who are required to analyse and release or reject each received consignment of the starting materials used to produce a drug product.

5.1.2 *The p plan*

The “ p plan” may be used when the material is uniform, is received from a recognized source and the main purpose is to test for identity. The p plan is based on the formula $p = 0.4 \sqrt{N}$, where N is the number of sampling units. The figures for p are obtained by rounding up to the next highest integer. According to this plan, samples are taken from each of the N sampling units of the consignment and placed in separate sample containers. These original samples are transferred to the control laboratory, visually inspected and tested for identity (a simplified method may be used). If the results are concordant, p final samples are formed by appropriate pooling of the original samples.

5.1.3 *The r plan*

The “ r plan” may be used when the material is suspected to be non-uniform and/or is received from a source that is not well known. The r plan may also be used for herbal medicinal products used as starting materials. This plan is based on the formula $r = 1.5\sqrt{N}$, where N is the number of sampling units. The figures for r are obtained by rounding up to the next highest integer.

Samples are taken from each of the N sampling units of the consignment and placed in separate sample containers. These original samples are transferred to the control laboratory and tested for identity. If the results are concordant, r samples are randomly selected and individually subjected to testing. If these results are concordant, the r samples are combined for the retention sample.

5.2 Packaging materials

Sampling plans for packaging materials should be based on defined sampling standards, for example, British Standard BS 6001-1, ISO 2859 or ANSI/ASQCZ1.4-1993.

The objective is to ensure that there is a low probability of accepting material that does not comply with the predefined acceptance level.

5.3 Finished products

As for packaging materials, sampling plans for finished products should be based on defined sampling standards such as BS 6001-1, ISO 2859 or ANSI/ASQCZ 1.4-1993.

In some cases it may be sufficient to limit examination of finished goods to visual inspection only. If physical and chemical testing is required, however, the sampling units should consist of whole packs. Individual packs should not be broken open for the purposes of sampling.

An example of the steps to be considered when sampling finished products is given in Appendix 3, based on the sampling plans given in ISO 2859-1.

Bibliography

- Good practices for national pharmaceutical control laboratories. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 3.
- Guidelines on packaging for pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 9.
- **Koratochvil B, Taylor JK.** Sampling for chemical analysis. *Analytical Chemistry*, 1981, 53:925A.
- **Oakland JS.** Management tools in the manufacture of chemicals: statistical quality control. *Chemistry and Industry*, 1981, 16:562–567.
- **Gy P.** *Sampling of particulate materials — theory and practice*, 2nd edition. New York, Elsevier, 1979.
- **Sommer K.** *Sampling of powders and bulk materials.* Heidelberg, Springer-Verlag, 1986.
- *Acceptance sampling plans and procedures for the inspection of bulk materials.* Geneva, International Organization for Standardization, 2000. ISO 10725.
- *Sampling procedures for inspection by attributes. Procedures for assessment of stated quality levels. British Standard BS 6001-5:2000.* Geneva, International Organization for Standardization, 1999. ISO 2859-4.

- *Sampling procedures for inspection by variables. Specification for single sampling plans indexed by acceptable quality level (AQL) for lot-by-lot inspection. British Standard BS 6002-1.* Geneva, International Organization for Standardization, 1993. ISO 3951:1989.
- *Sampling procedures for inspection by attributes. Sampling schemes indexed by acceptance quality limit for lot-by-lot inspection. British Standard BS 6001-1.* Geneva, International Organization for Standardization, 1999. ISO 2859-1.
- American National Standards Institute/American Society for Quality. *Sampling procedures and tables for inspection by attributes.* Washington, DC, American Society for Quality, 1993. ANSI/ASQCZ1.4-1993.
- *Methods for sampling chemical products. Introduction and general principles.* British Standard BS 5309-1. London, British Standards Publishing, 1976.
- *Methods for sampling chemical products. Sampling of liquids.* British Standard BS 5309-3. London, British Standards Publishing, 1976.
- *Methods for sampling chemical products. Sampling of solids.* British Standard BS 5309-4. London, British Standards Publishing, 1976.

Appendix 1

Types of sampling tools

Scoops

Small containers of solid materials may be adequately sampled using a spatula or scoop. The samples are then blended to provide a representative sample of that container. Figure 1 shows the recommended designs of scoops, which should preferably be rounded.

Figure 1
Sampling scoops for solids



If the scoop used is too small for the sizes of particle being sampled, large particles will roll off and testing bias may be introduced. On the other hand, if the scoop is too big, an unnecessarily large sample will be obtained for a given number of increments.

A scoopful of sample should be taken in a single movement and transferred to the sample container. Avoid tapping the scoop to remove pharmaceutical product as this is likely to cause segregation of the sample.

Dip tubes

Dip tubes should be used for sampling liquid and topical products and should be made of an inert material, such as polypropylene or stainless steel. A typical dip tube is shown in Figure 2.

Figure 2
Typical dip tube



Weighted containers

For taking samples from large tanks and storage vessels, a container in a weighted carrier can be used. The container is designed such that it can be opened at the required depth. Marks on the cord used for lowering the container can be used to determine when the correct sampling depth has been reached. A typical weighted container is shown in Figure 3.

Thieves

Sample thieves should be used when taking samples from deep containers of solids. Typical thieves are shown in Figure 4.

The plug thief typically consists of a hollow tube with an inner rod that has a tip on the end to allow the thief to enter the powder bed in the closed position (see Figure 4.i). The geometry of this tip can influence the sample taken; pointed tips distort the powder bed less than blunt-tipped probes, thereby reducing sampling error. Some thieves have a locking device that allows the sample volume to be set to the required sample weight, thereby reducing the weight variation in the sample population.

Figure 3
Typical weighted container

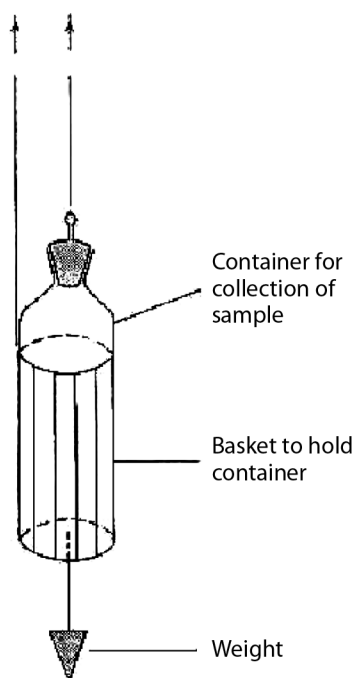
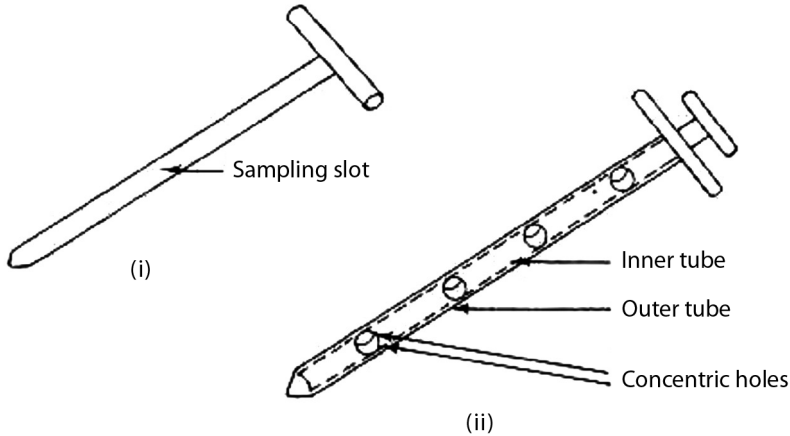


Figure 4
Typical sample thieves



A chamber thief generally consists of two concentric tubes (see Figure 4.ii); the inner tube is solid except for the chambers in which the sample is collected. The outer tube is hollow with openings that can be aligned with the chambers in the inner tube. A well-designed thief will have a sharp end to minimize disruption to the powder bed. When it is inserted into a static powder blend a thief will distort the bed by carrying pharmaceutical product from the upper layers of the blend to the lower layers. The magnitude of this distortion can depend on whether the thief is inserted into the blend with a smooth, jerky or twisting action. Therefore, the correct sampling procedure should be defined and staff trained in using the appropriate technique. Thieves are also sometimes referred to as “double-tube spears”.

The angle at which the thief enters the powder bed can also influence sampling error. If a thief is inserted into the powder bed vertically, it can extract samples of different particle size from those that would be obtained using the same thief inserted at an acute angle. In addition the orientation of a chamber thief in relation to the powder bed (i.e. whether the chamber is at the top, the bottom or in the middle of the thief) may also influence the sampling error.

The material from which the thief is constructed, e.g. stainless steel or polypropylene, may also have an effect on sampling error due to static effects.

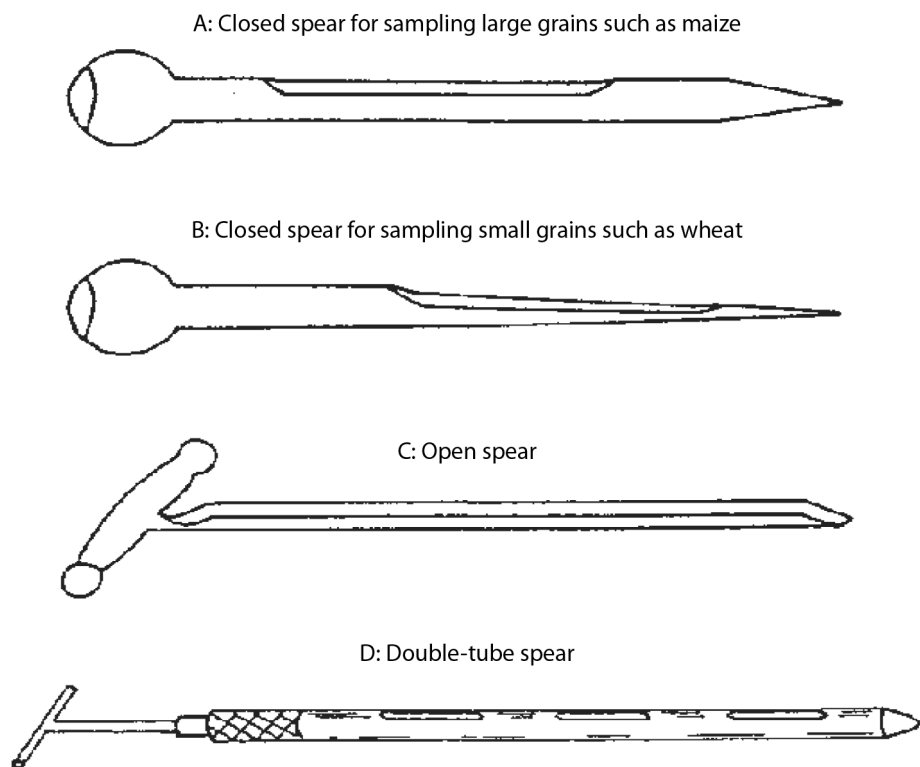
Sampling error can also be affected by bed depth, as the static pressure of the bulk blend forces the material into the sample chamber(s). This pressure is far greater at the bottom of a large container than it is in the middle or at the top. It is quite possible that the same thief could extract samples of different particle size from the top or bottom of a static powder blend.

Simple bag-sampling spears

Simple bag-sampling spears are the most commonly used instruments for taking samples from bags, because they are relatively cheap, simple and quick. Sampling spears generally have a maximum external diameter of about 12 mm, but can be up to 25 mm in diameter. To obtain a good cross-sectional sample, the spear should be 40–45 cm in length. The tapered type of sampling spear penetrates bags easily. Typical spears are shown in Figure 5.

Figure 5

Typical sampling spears



Appendix 2

Sample collection form^a

Serial number: _____

Name of location/place where sample was taken:

Address (with telephone and fax number, if applicable):

Date of sampling: _____

Names of people who took samples:

1. _____
2. _____

Product name of the sample: _____

Name of (active) starting material (INN, generic or scientific name) with dosage strength: _____

Dosage form (tablet, capsule, etc.): _____

Batch/lot number: _____

Date of manufacture: _____ Expiry date: _____

Registration or licence number (if applicable): _____

Name of the manufacturer: _____

Number of sample unit taken (tablet, capsule, etc.: at least 20 but not more than 30 units):

^a This sample collection form should always be kept with the sample collected. Proper sampling procedures should be followed.

Brief physical/visual description of sample:

Signature of person(s) taking samples

1. _____

2. _____

Signature of representative of the
establishment where sample(s) was
taken (optional)

Appendix 3

Steps to be considered for inclusion in a standard operating procedure

The steps for inclusion in a standard operating procedure described below are derived on a purely theoretical basis and are presented for information purposes only.

Bulk liquid products

The steps to be considered when sampling bulk liquid products are as follows.

1. Read and understand the precautions to be observed for the safe handling of the material.
2. Gather together the required sampling equipment (sampling tube or weighted sampling can, sample bottles and labels) and check that all the required items are clean.
3. Locate the batch.
4. Examine the container(s) for signs of contamination of the batch. Record any faults.
5. Examine the labels for obvious differences and signs of changes including obliterations and mislabelling. Record any faults.
6. Investigate and clarify the sources of and reasons for any faults before proceeding.
7. Choose a liquid-sampling tube of size and orifice suitable for the viscosity of the liquid being sampled.
8. Sample the liquid, suspension or emulsion (well stirred, if appropriate) by slowly pushing the open sampling tube vertically down- wards through the liquid so that material is collected from each layer.
9. Seal the tube, withdraw it from the bulk liquid, and allow liquid adhering to the outside of the tube to drain. Transfer all the contents of the tube to a clean, labelled sample bottle.
10. Repeat steps 8 and 9 until sufficient samples for analytical and retention purposes have been obtained.
11. Seal the sample bottle.
12. Reseal the container from which the samples were taken and label as “sampled”.
13. Clean and dry the sampling tube, observing the relevant safety precautions.

14. Sample other required containers in the same manner following steps 8–12 above.
15. Clean the sampling tube using the recommended cleaning procedure.
16. Deliver the analytical samples to the laboratory and the reserve samples to the retention sample store. Report any aspects of the sampling that should be brought to the attention of the analyst or the inspector.
17. Check supplier certificate versus the specifications, if applicable.

Powdered starting material

The steps to be considered in sampling a powdered starting material are as follows.

1. Read and understand the precautions to be observed for the safe handling of the material.
2. Gather together the required sampling equipment (sampling spear, sample bottles and labels) and check that all items are clean.
3. Locate the consignment and count the number of containers. Record this number.
4. Examine all the containers for obvious differences and signs of damage. Record any faults.
5. Examine all the labels for obvious differences and signs of changes, including obliterations and mislabelling. Record any faults.
6. Segregate any damaged containers and those with suspected spoiled contents for separate examination. These should then be *referred* or *rejected* and dealt with accordingly.
7. Segregate any containers with different batch numbers and treat these separately.
8. Number the remaining containers.
9. Choose the appropriate sampling plan (n , p or r).
10. Choose the containers to be sampled in accordance with the requirements of the chosen plan (by the use of random number tables, by drawing lots or by the use of a random number generator if applicable).
11. Open the containers one at a time and inspect the contents. Record any differences.
12. Choose a suitable, clean sampling spear and plunge this (gates closed) into the powder so that the point of the spear reaches the bottom of the container.
13. Open the gates to allow the powder to enter the spear cavities, then reclose them.

14. Withdraw the spear from the container and transfer the spear contents to a labelled sample bottle.
15. Repeat steps 12–14 until sufficient material has been collected for analytical and retention requirements.
16. Seal the sample bottle.
17. Reseal the container from which the samples were withdrawn and label as “sampled”.
18. Wipe clean the sampling spear if required, observing the safety precautions, before sampling the other chosen containers.
19. Repeat steps 12–18 for each chosen container.
20. Clean the sampling spear using the recommended cleaning procedure.
21. Deliver the analytical samples to the laboratory and the reserve samples to the retention sample store. Report any aspects of the sampling that should be brought to the attention of the analyst or inspector.
22. Check the supplier certificate versus the specifications, if applicable.

Packaging materials

The steps to be considered in sampling packaging materials are as follows.

1. Check the consignment against any associated documentation.
2. Check transit containers for the following and report any deviations as necessary:
 - 2.1 correct identification;
 - 2.2 integrity of seal, if appropriate; and
 - 2.3 absence of physical damage.
3. Obtain the required sample from the required number of containers, bearing in mind the special considerations for sampling packaging materials noted in section 4.4 of this Annex.
4. Place the sample units into identified appropriate sample containers.
5. Identify the consignment containers that have been sampled.
6. Note any special situations found during the sampling process (e.g. rogue items or component damage). Report any such observations as necessary.
7. Remove all sampled material pallets or containers from the sampling area together with all documentation.
8. Check supplier certificate against the specifications, if applicable.

Finished products

The following steps should be considered when sampling finished products.

1. Determine the number of pallets per batch in the consignment.
2. Work out as per ISO 2859–1 table level II, the number of pallets to be checked visually.
 - 2.1 Check condition of pallet and packaging for integrity of outer packaging material.
 - 2.2 Check outside of goods on the pallets for general cleanliness.
 - 2.3 Check that the overall labelling of the pallets matches the packing list.
 - 2.4 Count, categorize and record the number of defects.
3. Count the total number of transport packs on the number of pallets present and verify the total against the packing list.
4. From the number of pallets work out the number of transport packs to be sampled using the ISO table.
 - 4.1 Check condition of boxes for integrity of packaging material.
 - 4.2 Check for cleanliness of boxes.
 - 4.3 Check the labelling of the boxes for damage.
 - 4.4 Check the boxes for overall damage.
 - 4.5 Check the labels for spelling mistakes.
 - 4.6 Check the labels for manufacturing and expiry dates.
 - 4.7 Count, categorize and record the number of defects.
5. From the number of boxes selected work out the number of unit packs to be examined visually using the ISO table.
 - 5.1 Check condition of the containers for integrity of packaging material.
 - 5.2 Check for cleanliness of containers.
 - 5.3 Check condition of containers for shape and colour.
 - 5.4 Check the labelling of containers for damage.
 - 5.5 Check the containers for overall damage.
 - 5.6 Check the labels for spelling mistakes.
 - 5.7 Check the labels for manufacturing and expiry dates.
 - 5.8 Count, categorize and record the number of defects.
6. From the number of containers selected, determine the number of containers to be taken for physical and chemical testing and for retention.
7. Check the supplier certificate against the specifications, if applicable.

Appendix 4

Examples of types of containers used to store samples of starting materials and bulk products

Figure 1
Bag for storage of samples

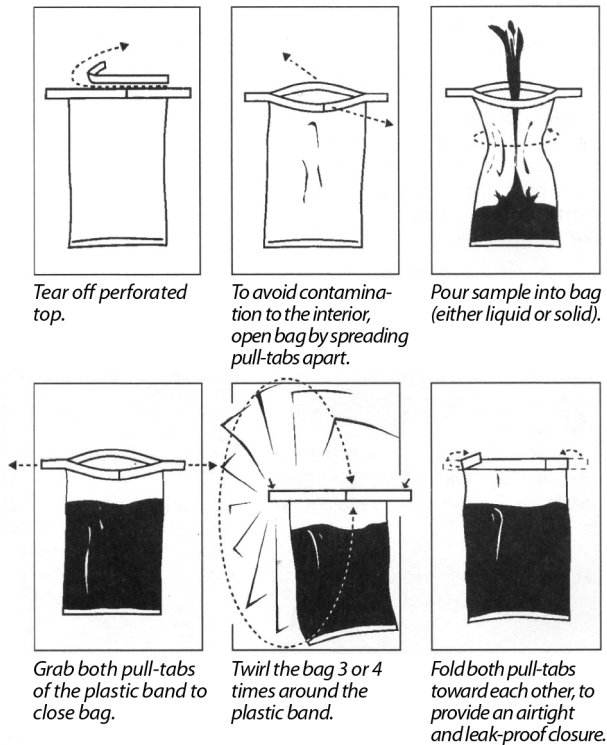
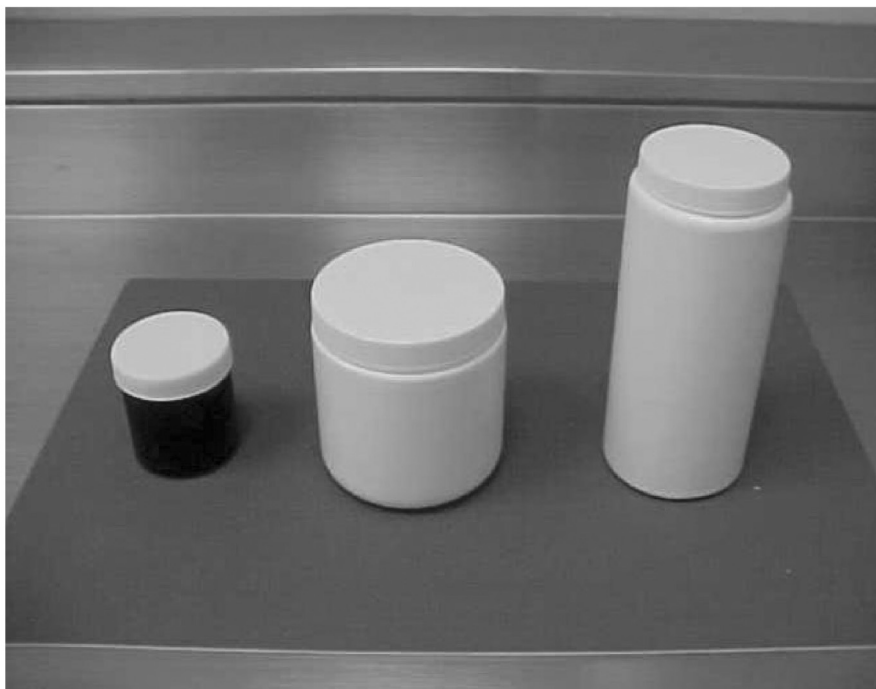


Figure 2
Screw-top containers



Appendix 5

Examples of use of sampling plans n , p and r

Consider a consignment of 40 containers of a starting material.

n Plan

Assuming a uniform material from a recognized source where there is a high degree of confidence in the source

Using the n plan, samples would be taken from seven containers selected at random. The appearance and identity of each of these seven samples is checked. If the results are concordant, the seven samples are combined to produce a single, composite sample from which an analytical sample is prepared for full testing.

p Plan

Assuming a uniform material from a recognized source with the main purpose of checking the identity

Using the p plan, samples would be taken from each container. The appearance and identity of each of these samples is checked. If the results are concordant, the samples are appropriately combined to form three final, composite samples to be used for retention (or full testing if required).

r Plan

Assuming the material is non-uniform and/or from a source that is not well-known

Using the r plan, samples would be taken from each container. The appearance and identity of each of these samples is checked. If the results are concordant, 10 samples are selected at random and individually subjected to full testing.

10.3 Considerations for requesting analysis of medicines samples

Annex 3, WHO Technical Report Series, 1010, 2018

An earlier version of this guidance was published as *Considerations for requesting analysis of drug samples* in 2002.¹

Medicines quality control testing independent of manufacturers is an important tool of medicines regulation. However, it demands considerable resources and the need for analysis should therefore always be thoroughly considered. Independent quality control testing should be performed if it adds value to the evaluation performed, when viewed from a public health perspective, and it should not cause unnecessary delays in access to medicines.

- Testing should focus on medicines most likely to pose a risk to patients, for example, medicines:
- produced by manufacturers for which poor evidence of compliance with the principles of good manufacturing practices (GMP) (1) is available, or where the origin is uncertain;
- suspected of being falsified;
- suspected of being substandard because of incorrect distribution or storage conditions, or their instability;
- suspected of causing adverse reactions due to a quality defect;
- for which analytical testing results are needed as evidence in litigation (requires the implementation of a rigorous chain of custody – see World Health Organization (WHO) guidelines) (2).

The risk of poor quality should be assessed before deciding to request analysis of a particular product. For example, if the manufacturing site has been found to comply with GMP principles, the manufacturer is under regular supervision of an authority applying international standards, and there is no specific reason for testing of the product (such as a quality complaint or a suspicion of quality deterioration during distribution or storage), the manufacturer's batch certificate may be relied upon to indicate the quality of the product. Such a certificate should be issued in accordance with the criteria applicable to the WHO Model Certificate of good manufacturing practices (3) or WHO Certification Scheme (4).

¹ This guidance was previously published as Annex 4 in the WHO Technical Report Series, No. 902, 2002.

Independent post-production testing may be performed by regulators for different reasons and in various regulatory phases of the medicine's life. The following should be borne in mind when considering testing approaches:

- pre-registration testing of samples submitted for registration
 - As the sample is selected by the manufacturer, it may not provide a true picture of product quality. Testing at this stage may be useful to assess functionality of analytical methods in local conditions in certain rare cases when data reviewers have some doubts.
- Official batch release of some biological products by the national medicines regulatory authority (NMRA)
 - This is usually requested to fulfil national regulations for specified products and described in guidelines.
- Pre-marketing testing of all or of selected batches
 - Often samples of imported medicines are collected at points of entry into a country. It would be reasonable to subject them to screening and select for testing only those that show physical signs of instability or deterioration (5), other indications of inferior quality, or those whose origin is suspicious. Routine testing of each imported batch is not considered reasonable as the quality of medicines should in principle be assured through the registration process. Batch-to-batch testing may be worthwhile in specific situations, for example, when proper registration assessment and verification of compliance with good practices in production and/or product development is not feasible. Again the risk of poor quality should be assessed before deciding on the testing of a particular product.
- Post-marketing testing as risk-based sampling and surveillance/monitoring projects
 - The advantage of this approach is the selection of samples that are in the distribution chain and are intended for administration to patients. Detailed advice is provided in WHO *Guidelines on the conduct of surveys of the quality of medicines* (6).

1. Selection of tests and specifications

Tests to be performed and applicable specifications depend on the reasons for testing a particular sample. Full-scale testing is expensive and it may be reasonable to limit the tests chosen to those that can provide the answers sought. However, tests should always

be considered in terms of logical combinations: for example, a dissolution test or a test for impurities without assay/potency, would not provide sufficient information.

Selection of specifications (methods and limits) for testing again depends on the reasons for testing a particular sample. If the compliance of a product with registered specifications is to be verified, specifications approved by the NMRA as part of the registration process should be used.

If products containing the same active pharmaceutical ingredients in the same dosage form produced by different manufacturers are to be compared, pharmacopoeial specifications should be used. However, noncompliance with pharmacopoeial specifications may not necessarily imply noncompliance of the test product with the registered specifications. Also, in spite of efforts to harmonize pharmacopoeias, there are still many differences between them. When a monograph for a particular medicine is available in more than one pharmacopoeia the ability of the respective specifications to reveal quality problems should be considered and the monograph selected accordingly. In particular, when impurities are evaluated, the suitability of the pharmacopoeial monograph tests for the detection of impurities should be evaluated, especially if the product is from a new source, which may cause it to have a different impurity profile.

If samples suspected of being falsified are to be tested, manufacturers' or pharmacopoeial methods may not be sufficient and further examination should be conducted (for guidance on such investigation see WHO guidelines (2)).

If necessary, advice on selection of tests and specifications should be sought from an experienced laboratory.

2. Selection of laboratory and communication before samples are submitted

Once it has been decided to test a medicine, a laboratory, which produces reliable testing results and is capable of and competent to perform the tests required, should be selected. This can be a local national laboratory or a contracted laboratory in the same or in another country.

In general, to demonstrate that testing results are reliable, a laboratory should work in compliance with internationally recognized standards such as *WHO good practices for pharmaceutical quality control laboratories* (7) or ISO 17025 (8). Compliance with the relevant standard should be verified, for example, the laboratory should be WHO-prequalified,² or ISO 17025 accredited by an internationally recognized accreditation body. Assurance that the laboratory works in a reliable manner can also be obtained by organizing an audit by competent auditors or using the audit report from an independent third party, if available.

² The list of WHO-prequalified laboratories can be found at <https://extranet.who.int/prequal/medicines/prequalified/quality-control-labs>.

Before submitting samples to a laboratory, an understanding of its capability to carry out the requested tests and an agreement on performance of the analysis should be reached. The following information, as a minimum, should be provided to the laboratory:

- the reason(s) for the request and the purpose of the analysis;
- the composition of the product(s) (using International Nonproprietary Names (INNs), where possible), concentration or strength and pharmaceutical dosage form;
- a reference to specifications, including (if needed) analytical methods that should be used;
- the expiry date(s) of the sample(s), required storage conditions and duration of the storage of retention samples;
- the number of samples of each product to be tested;
- the date by which testing results are expected;
- the proposed mode of payment for the analysis;
- the preferred language and format of the report containing the results, and the method to be used to transmit the results.

The laboratory that has been contacted should indicate, as quickly as possible, whether or not it is able and willing to undertake the analysis. Any laboratory has the right to decline a request for analysis without furnishing any explanation.

If the laboratory agrees to undertake the analysis, the following should be communicated to the requesting party and mutually agreed:

- the size of the sample (minimum number of dosage units) required for each product (if possible, the number should be sufficient for conducting the tests; investigation and confirmatory testing for those found to be out of specification; and retention of samples to be used in case of dispute);
- any additional tests that may be required or recommended;
- the cost and the mode of payment;
- a tentative estimate of how long the analysis will take.

It is recommended that an appropriate arrangement between the requesting party and the laboratory that will perform the tests should be formalized. The arrangement should, in addition to the points above, settle issues such as liability, confidentiality, acceptance of a possible audit of the laboratory, deadlines, retention period for samples and records, and access to records and retained samples. The arrangement should also specify when the testing results need to be communicated rapidly (such as when defects that can endanger patients' health are identified). The responsibilities of the two parties should be defined.

An example of an analysis request form is shown in Appendix 1.

3. Submission of samples

Upon reaching agreement with a laboratory, the sample(s) should be dispatched by the requesting party. If samples are not delivered to the laboratory directly by the requesting party, they should be transported using a courier service to avoid any delays and deterioration of the quality. Unless there are special circumstances, the sample(s) must be kept in the original packaging and suitably packaged and labelled to avoid breakage and contamination during transport (9). Freezing should be avoided during air transport and, where required, the cold chain should be maintained. When transporting temperature-sensitive medicines, temperature data loggers may be included within shipments to document that appropriate temperatures have been maintained during prolonged transit.

When sending samples to another country, delays in customs clearance should be prevented. The accompanying documents should state that the samples are being sent for laboratory testing purposes only, will not be used on humans or animals, have no commercial value and will not be placed on the market. In the case of products that are subject to legal controls on exportation, appropriate arrangements must be made by the requesting party to ensure due compliance with customs requirements. The laboratory may be able to advise on further precautions. If the country where the laboratory is located requires permission for importation of samples, the laboratory may assist in applying for permission, to avoid long clearance procedures. The laboratory should be informed of the dispatch of the shipment, including the tracking number as provided by the courier service, to enable it to follow the shipment and arrange for prompt collection.

If the product to be tested contains a controlled substance (a substance regulated under the international drug control conventions³) the requirements of the relevant national legislation (for example, secure storage, documentation, etc.), are to be implemented.

As soon as the sample has been received by the laboratory, the requesting party should be notified of the delivery and condition of the sample. This information can assist any investigations at a later stage.

4. Analytical results

All analyses undertaken by a laboratory should be performed in accordance with the specifications mentioned in the request for analysis, or as subsequently agreed, and conducted in compliance with *WHO good practices for pharmaceutical quality control*

³ http://www.incb.org/incb/en/narcotic-drugs/1961_Convention.html;
https://www.incb.org/incb/en/psychotropics/1971_convention.html;
http://www.incb.org/incb/en/precursors/precursors/legislation_and_control/legislation_and_control.html.

laboratories (7). All individual results (all test data), with acceptance criteria should be reported (7). The results should be compiled in the agreed language in the form of an analytical test report or certificates of analysis in line with WHO guidelines (7, 10) and transmitted by the agreed method.

References

1. WHO good manufacturing practices for pharmaceutical products. Geneva, World Health Organization, <https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/guidelines>, accessed 30 October 2017).
2. WHO guidance on testing of “suspect” falsified medicines In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. Geneva: World Health Organization; 2018: Annex 5 (WHO Technical Report Series, No. 1010; <https://iris.who.int/bitstream/handle/10665/272452/9789241210195-eng.pdf?sequence=1&isAllowed=y>).
3. WHO Model Certificate of good manufacturing practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-seventh report. Geneva: World Health Organization; 2003: Annex 5 (WHO Technical Report Series, No. 908; https://iris.who.int/bitstream/handle/10665/42613/WHO_TRS_908.pdf?sequence=1&isAllowed=y).
4. Guidelines for implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-fourth report. Geneva: World Health Organization; 1996: Annex 10 (WHO Technical Report Series, No. 863; https://iris.who.int/bitstream/handle/10665/41849/WHO_TRS_863_%28p1-p98%29.pdf?sequence=1&isAllowed=y).
5. The International Pharmacopoeia, sixth edition. Quality specifications for pharmaceutical substances and dosage forms together with supporting general methods for analysis. Geneva: World Health Organization; 2016 (<https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/international-pharmacopoeia>).
6. Guidelines on the conduct of surveys of the quality of medicines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 7 (WHO Technical Report Series, No. 996; <https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>).
7. Good practices for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 1 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y).
8. General requirements for the competence of testing and calibration laboratories. Geneva: International Organization for Standardization; 2005 (ISO/IEC 17025).
9. WHO guidelines for sampling of pharmaceutical products and related materials. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-ninth report. Geneva: World Health Organization; 2005: Annex 4 (WHO Technical Report Series, No. 929; https://iris.who.int/bitstream/handle/10665/43157/WHO_TRS_929_eng.pdf?sequence=1&isAllowed=y).
10. Model certificate of analysis. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. Geneva: World Health Organization; 2018: Annex 4 (WHO Technical Report Series, No. 1010; <https://iris.who.int/bitstream/handle/10665/272452/9789241210195-eng.pdf?sequence=1&isAllowed=y>).

Appendix 1

Example of an analysis request form

Requesting party	
Name, address	
Contact person: name, phone no., email	
Product to be tested ^a	
Name, dosage form	
INN(s), strength	
Package size, type and material of the container	
Name and address of the manufacturer	
Number of samples to be tested	
Batch number/s	
Date/s of manufacture	
Date/s of expiry	
Required storage conditions	
Sample/s source	
Sample size: number of dosage units/packages per sample ^b	
Testing	
Reason/s for the request and purpose of the analysis	
Reference to specifications (pharmacopoeial monograph or methods and specifications attached to the request)	

Table *continued*

Tests requested – tick ✓ requested tests				
Identity		Specific optical rotation		
Assay		Melting range/point		
Related substances/impurities		Conductivity		
Dissolution		Refractive index		
Disintegration		Microbial enumeration tests		
Friability		Tests for specified microorganisms		
Fineness of dispersion		Sterility		
Uniformity of dosage units		Bacterial endotoxins		
Water content		Other tests (please specify):		
pH value				
Relative density				
Viscosity				
Date by which testing results are expected				
Period for which retention samples should be kept				
Preferred language and format for reporting results				
Method to be used for transmission of the results				

^a Section to be repeated for each product tested.^b To be agreed with the laboratory.

Signature of the person representing the requesting party
Name, function

Date

10.4 WHO guidance on testing of “suspect” falsified medicines

Annex 5, WHO Technical Report Series, 1010, 2018

1. Introduction	1536
1.1 “Suspect” medicines	1536
1.2 Responsibility of regulatory authorities	1536
1.3 The role of the World Health Organization	1537
2. Scope	1537
3. Glossary	1537
4. Detection of suspect falsified products	1539
4.1 Entry points for detection	1539
4.2 Detection methods	1539
4.3 Selection of analytical techniques	1540
5. Sampling and documentation	1541
5.1 Sampling	1541
5.2 Documentation of information on suspect falsified medical products	1541
5.3 Chain of custody considerations	1542
6. Regulatory actions upon detection of suspect falsified medical products	1544
6.1 Risk assessment	1544
6.2 Questions to be answered by analytical testing	1544
6.3 Communication	1545
7. Confirmatory analytical testing	1545
7.1 Laboratory capacity	1546
7.2 Standard operating procedure	1547
7.3 Testing plan and test procedures	1547
7.4 Interpretation and reporting of results	1548
8. Reporting and regulatory action on confirmed falsified medical products	1548
9. Archiving of samples and reports	1549
References	1549
Appendix 1 Examples of analytical techniques that may be used for package identification, screening and testing of suspect falsified medical products	1551
Appendix 2 Example of an information collection form	1555

Appendix 3	Example of the content of a standard operating procedure for testing suspect falsified tablets	1561
Appendix 4	Examples of flowcharts for testing of suspect falsified medicines	1566

1. Introduction

1.1 “Suspect” medicines

“Suspect” medicines can be divided into three main categories of products as follows:¹

(a) substandard medicines

Also called “out of specification”, these are authorized medicines that fail to meet either their quality standards or their specifications, or both.²

(b) unregistered/unlicensed medicines

Medicines that have not undergone evaluation and/or approval by the national regulatory authority (NRA) for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.

These medicines may or may not have obtained the relevant authorization from the NRA of their geographical origin.

(c) falsified medicines

Medicines that deliberately/fraudulently misrepresent their identity, composition or source.

Any consideration related to intellectual property rights does not fall within this definition.

Such deliberate/fraudulent misrepresentation refers to any substitution, adulteration, reproduction of an authorized medicine or the manufacture of a medicine that is not an authorized product.

This document deals specifically with products that are suspected to belong to the third category, i.e. “falsified” medical products.

1.2 Responsibility of regulatory authorities

NRAs should establish rules and instruments that control the production, distribution and commercialization of medical products in order to ensure their quality through rigorous regulatory oversight, including postmarketing surveillance, in line with national legislation and regulations on pharmaceutical products. Rigorous regulatory oversight of medical products throughout their life cycle is necessary to recognize and remove unauthorized and/or falsified products and to protect the supply chain against infiltration of such products.

¹ Based on World Health Assembly (WHA) A70/23 and WHA70(21) for “medical products”.

² When the authorized manufacturer deliberately fails to meet these quality standards or specifications due to misrepresentation of identity, composition or source, then the product should be considered “falsified”.

Falsified medical products can originate from inside or outside the legal supply chain. It is important that NRAs secure the supply chain and raise awareness among health workers and patients of risks associated with medicines from illegal sources.

A legal definition of falsified medicines and specific legal provisions to penalize acts related to falsification of medicines will empower NRAs to take actions against this problem. In implementing and enforcing legal provisions on falsified medicines, NRAs should collaborate with customs, police, legislature, industry experts, judiciary, prosecutors and enforcement agencies at the national and international level as appropriate.

1.3 The role of the World Health Organization

The World Health Organization (WHO), through its Expert Committee on Specifications for Pharmaceutical Preparations, sets technical standards on quality assurance of pharmaceutical products, including guidance on registration, good manufacturing practices (GMP), good distribution practices (GDP) and quality control (QC) testing of medicines, and on other topics that are relevant to the regulatory oversight of medicines.

A survey conducted among regulatory authorities of WHO Member States (1) indicated the need for specific technical guidance on laboratory testing of suspect falsified products. The present document was developed in response to the survey findings and complements the Committee's guidelines on sampling and market surveillance (2).

The Member State Mechanism on substandard and falsified medical products, created in 2012, makes recommendations to support regulatory authorities to prevent, detect and respond to activities and behaviours that result in falsified medical products (3). This document is intended to complement the Member State Mechanism's recommendations in accordance with the sixty-seventh World Health Assembly resolution WHA67.20 on Regulatory system strengthening for medical products (4).

2. Scope

This document provides technical guidance on laboratory testing of samples of suspect deliberately falsified medical products detected on the markets of WHO Member States and related aspects of sampling and reporting. This guidance should be read in conjunction with the guidelines on sampling and market surveillance (2).

3. Glossary

The definitions given below apply specifically to the terms used in this document. They may have different meanings in other contexts.

authorized product. A product in compliance with national and regional regulations and legislation. National or regional regulatory authorities can, according to

national or regional regulations and legislation, permit the marketing or distribution of medical products with or without registration and/or licence.

chain of custody. A chronological and continuous record of the seizure and custody of the suspect product and the subsequent transfer of a sample of the suspect product to the laboratory as well as the handling of the sample within the laboratory.

falsified product. For the purposes of this document, a product that has been deliberately and/or fraudulently misrepresented as to its identity, composition or source, and which therefore requires testing beyond the routine quality control testing. Such deliberate/fraudulent misrepresentation refers to any substitution, adulteration, reproduction of an authorized product or the manufacture of a product that is not an authorized product.

“Identity” shall refer to the name, labelling or packaging or to documents that support the authenticity of an authorized product. “Composition” shall refer to any ingredient or component of the product in accordance with applicable specifications authorized/recognized by the NRA. “Source” shall refer to the identification, including name and address, of the marketing authorization holder, manufacturer, importer, exporter, distributor or retailer, as applicable.³

forensic. Related to analysis for law enforcement purposes.

marketing authorization (product licence, registration certificate). A legal document issued by the competent medicines regulatory authority that authorizes the marketing or free distribution of a pharmaceutical product in the respective country after evaluation for safety, efficacy and quality. In terms of quality it establishes inter alia the detailed composition and formulation of the pharmaceutical product and the quality requirements for the product and its ingredients. It also includes details of packaging, labelling, storage conditions, shelf life and approved conditions of use.

medical product⁴ refers to medicines, vaccines and in vitro diagnostics (and in the future may include medical devices).

quality control. Embraces all measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other pharmaceutical characteristics.

³ Member State mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit medical products. Report by the Director-General; 2017 (A70/23; http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_23-en.pdf, accessed 27 February 2018).

⁴ Working Group of the Member State Mechanism (http://apps.who.int/gb/sf/pdf_files/A_SSFFC_WG2_2-en.pdf).

quality management. A wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use.

screening technologies. The qualitative and/or semiquantitative technologies that can rapidly acquire the information or analytical data for preliminary identification of suspect medical products in the field.

standard operating procedure. An authorized written procedure giving instructions for performing standardized operations both general and specific.

4. Detection of suspect falsified products

4.1 Entry points for detection

Regulatory authorities are responsible, in collaboration with relevant national and international stakeholders, for establishing mechanisms to detect falsified products circulating in their territories and for removing them from the market.⁵

Suspect falsified products can be detected using a range of approaches, including routine inspections performed by national or regional authorities and enforcement agencies, targeted risk-based surveys (1), investigation of complaints, follow-up of reports on any suspicious observations in the supply chain (for example, inconsistent documentation or unexpected stock levels), discrepancy during verification and investigation of unexpected adverse events reported to have occurred with a specific product. It is important to evaluate any information on suspect falsified products reported by customs, medicines inspectorates and other authorities, procurement agencies, wholesalers and importers, pharmacies, health-care institutions, patients and other stakeholders.

4.2 Detection methods⁶

Falsified medical products may be identified by their packaging characteristics and/or by identity verification, physical and chemical testing. This may require confirmation, where appropriate, by the stated manufacturer, that the product was not manufactured by them (for example, written confirmation that packaging and other elements do not correspond to the genuine manufacturer's records).

⁵ See also reference (3), Paragraph II.1. Quality monitoring and control.

⁶ Further guidance on screening technologies is provided by the Working Group of the WHO Member State Mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit medical products (3) through its prioritized activities 2014–2015, specifically Activity C, aiming to establish and convene a working group comprising Member States' experts to assess and report on: (a) existing "track and trace" technologies in use by Member States; and (b) existing field detection devices in use or available to Member States.

When available, the packaging and patient information leaflets of suspect falsified medicines should always be examined visually and compared with samples or photographic images of genuine registered products if available.⁷ Product protection features may also be utilized to screen and/or authenticate suspect packaging components. Attention should be paid to any irregularities or inconsistencies, such as spelling mistakes, unusual batch numbers, unusual printing of batch number and shelf life, verification of serialization data when appropriate, unexpected or modified manufacturing or expiry dates, signs of repacking, for example, to circumvent inspection activities, or instructions in a language that does not match the area of their distribution. Microscopy and other analytical techniques (including but not limited to optical techniques) may be utilized for package examination. The purpose of these technologies is to rapidly provide evidence that the sample comes from a falsified product.

An extensive list of analytical techniques that can be used to screen the market for falsified products is provided in Appendix 1. More detailed descriptions of available technologies can be found in published literature and online guidance (5, 6, 7).

The result of a screening test is only indicative (preliminary or presumptive adverse analytical result) and other analytical techniques must be applied to confirm unequivocally that a falsified medical product has been detected.

Some of the methods shown in Appendix 1 rely on a comparison with suitable reference materials or data available in a library or a reference database. Sharing of reference values and screening results through access-controlled information technology interfaces can provide strong support for the application of rapid screening technologies.

4.3 Selection of analytical techniques

Appendix 1 provides an overview of the analytical techniques available at the time these guidelines were developed. The choice of analytical technology to be applied should be based on the information required. The regulatory authority should obtain advice about available analytical techniques including, for example, from the manufacturer and the analytical testing laboratory, before deciding which analytical technique to use, taking into account:

- the expected benefits of each technology (scientifically based), given its applicability and performance characteristics;

⁷ The manufacturer or marketing authorization holder should inform the relevant NRA of any changes to the artwork or packaging of its registered products. Details of analysis/observation of authentication features displayed on the product packaging, or embedded within the product itself, should also be included in the registration dossier. This will help the NRA to assess the authenticity of a given suspect product when conducting visual inspections.

- opportunities for efficient use within existing postmarketing surveillance activities, such as inspections for compliance with licensing requirements, GMP or GDP;
- the availability of adequately trained local operators and cost of training;
- the expected cost of equipment, including its periodic calibration and qualification;
- recurring costs and availability of consumables, reference materials, libraries and maintenance;
- any other factors that may influence the use of analytical techniques in the national context.

5. Sampling and documentation

5.1 Sampling

Sampling of suspect falsified products is typically performed by inspectors or enforcement officers (such as police or customs officers) or other competent personnel, for example, laboratory personnel. Suspect medical products can also be detected during the complaint process. Care should be taken to ensure that the sample taken or seized is representative of the suspect medical product. A sufficient number of dosage units should be taken to enable thorough analytical testing. Guidance and advice should be sought from a suitably qualified analytical testing laboratory (1). However, if the requisite amount is not available all units should be collected.

5.2 Documentation of information on suspect falsified medical products

An information collection form, which is to be completed by the inspector or enforcement officer, should be comprehensive and include, but not be limited to:

- the point of detection in the supply chain (manufacturer, wholesaler, pharmacy, hospital or patient);
- the quantity of suspect product found;
- a visual description of its packaging;
- product name as marketed (if any);
- name of active substance (if known);
- the dosage units;
- the batch number;
- photographs;

- any signs of irregularities;
- the supply history of the product including the name, address of parties involved, date of transfer, etc.;
- a description of the circumstances leading to its detection (for example, adverse effects and any other relevant information).

This document should accompany the sample from the time it is taken until it is delivered to the testing laboratory. An example of an information collection form is presented in Appendix 2.

5.3 Chain of custody considerations⁸

From the time of collection or seizure of the suspect falsified medical product until its ultimate fate is decided, a rigorous chain of custody should be maintained to ensure that the integrity of the sample and its accompanying documentation is preserved. Secure packing, labelling, appropriate transport and storage conditions for the sample must be provided and documented. In addition, adequate security arrangements must be in place to prevent any theft, tampering, substitution or unauthorized disclosure of information.

The chain of custody of a sample consists of two parts. The first starts at the location where the suspect falsified medical product was seized or purchased by the inspector, or when a suspect falsified medical product has been detected by a manufacturer or any other stakeholder and includes all stages of the process of delivering the sample to the analytical testing laboratory. The second part relates to the laboratory, where all transfers of the sample must be recorded so that the analytical report generated by the laboratory can be unequivocally linked to the source of the sample.

The inspectors or enforcement officers should document details of the suspect falsified product including (but not limited to):

- location of detection (name or title and address);
- at what point in the supply chain detection occurred (manufacturer, wholesaler, pharmacy, hospital, patient, etc.);
- pharmaceutical product type, pharmaceutical dosage form (tablet, capsule, injection, etc.);
- quantity and/or volume;
- date and time of seizure or purchase;
- names and signatures of the inspector or enforcement officer and the owner of the suspect falsified medicine at the location;

⁸ See also reference (3), Paragraph IV.1.1.30.

- the amount collected;
- description of packaging;
- location to which the sample is sent;
- other relevant information (international nonproprietary name (INN), brand name, batch number, shelf life, dosage, strength, etc.).

The inspector or enforcement officer is responsible for securing the sample appropriately and arranging transport to the testing laboratory. Whenever possible, samples that cannot be transported immediately are to be stored according to the storage conditions defined by the manufacturer, in a secure place. Otherwise, whenever possible, samples are to be stored in a secure, cool environment.

The inspector or enforcement officer should include a copy of the appropriate documentation (see section 5.2) in each transport bag or container holding the samples, to ensure that the laboratory can verify the contents upon delivery.

Samples may be taken directly to the analytical testing laboratory by the inspector or enforcement officer or handed over to a qualified and approved courier for transportation.

If an approved courier company is used to transport the samples, this should be documented in the chain of custody of the samples and the inspector or enforcement officer should record the waybill and tracking numbers of the shipment. The recipient of the sample should be informed of the expected delivery date and the storage and transportation conditions.

Within the laboratory, samples are considered to be in custody when they are:

- in the physical possession of authorized staff;
- visible to authorized staff after being in his/her physical possession;
- stored in a secure location.

The laboratory chain of custody should be reflected in all the documentation generated by the laboratory, which may include logbooks, worksheets, photographs and analytical reports where the custody of the samples during analysis and storage is recorded with the signature of the staff member concerned and the date and time of the action(s). The laboratory chain of custody shall be a continuous record of authorized staff with custody of the samples at all stages of the process from receipt to disposal. At each stage, the authorized staff involved must sign and date the entry for the action performed (for details see WHO *Guidance on good data and record management practices* (8)).

It is essential to ensure traceability throughout the process – from the seizure or purchase of the suspect falsified medical product to the conclusion of the investigation.

6. Regulatory actions upon detection of suspect falsified medical products

6.1 Risk assessment

When a suspect falsified medical product has been found, the relevant NRA is to be informed (for details see section 8). The NRA should then perform a risk assessment to determine what further action is required to protect public health.⁹ This assessment should be done in communication and collaboration with the marketing authorization, licence or registration holder, and if applicable with the manufacturer of the genuine product, and an analytical testing laboratory with experience in testing suspect falsified medical products. WHO and other regulatory authorities should also be informed as appropriate.

Further action may include confirmatory laboratory testing of the suspect samples.

6.2 Questions to be answered by analytical testing

If laboratory analysis is to be conducted, NRAs should send the samples to a laboratory with adequate capacity to perform the testing as described in this document. If no such laboratory is available in the country concerned, the NRA should identify a competent and suitably equipped laboratory in its region or elsewhere that can advise on designing a testing plan and/or perform some or all of the testing. The manufacturer of the genuine product may also be requested to provide information or methods (including reference substances and a sample of the genuine product), which may be used for the testing of suspect samples and/or may be requested to analyse the samples.

Upon receipt of a suspect falsified medical product, the regulatory authority, enforcement agencies and other relevant stakeholders need to clarify the purpose and aims of testing. Some examples of questions that laboratories may be requested to answer (with the assistance of the regulatory authority, enforcement agencies and other relevant stakeholders) are listed below.

- Does the sampled product fall under the national legislation for pharmaceutical products?
- Does the sample meet specifications defined as part of the stated product's marketing authorization?
- What specific substances should the testing be designed to detect? (Examples include specific unexpected active ingredients or groups of active ingredients, specific impurities and any substances that are consistent with reported adverse effects.)

⁹ See reference (3), Section III. Assessment of alerts, reports and notifications received.

- What additional parameters should be tested to assess the health impact of the ingredients? (Examples include content, dissolution or disintegration properties and sterility.)
- Is there a forensic relationship between different falsified products? If yes, in what aspects?
- Are there any market authorization specifications and methods of analysis available for the suspect samples? *Note:* Check if there is a product monograph in *The International Pharmacopoeia*, or any national or regional pharmacopoeia.

What are the expected excipients (if any) in the suspect samples?

Note: As it is often not possible to answer that question, the testing should be arranged in such a way that there is no (negative) interference of the excipients in the identification and quantification of the substance that is expected to be contained in the sample.

6.3 Communication

Care should be taken by the NRA to convey clear and appropriate messages when communicating information about suspect or confirmed falsified medical products to the stakeholders. Dissemination of information should be well planned, to reach all relevant stakeholders while ensuring confidentiality as appropriate. NRAs should keep a record of the date, recipients and content of information disseminated. WHO and other regulatory authorities should also be informed as appropriate.

Patients who might be affected by falsified medical products should be advised to consult their health professional. Health professionals and procurement agencies, wholesalers and importers should be instructed on the action(s) to be taken to enable a continued supply and treatment while ensuring patient safety. In all communications the manufacturer whose name is printed on the packaging of the products should be described as the “*Stated* manufacturer”, making it clear that the falsified medical product may not have originated from the stated manufacturer. Miscommunication can amount to falsely accusing the legitimate manufacturer of falsifying a product, which would be grounds for legal action by that manufacturer.

7. Confirmatory analytical testing

NRAs should refer samples to a laboratory with adequate capacity to perform the testing as described in this document. The manufacturer of the genuine product may also be requested to provide information or methods (including reference substances and a sample of the genuine product) that may be used for the testing of suspect samples or may provide technical support. Any information and/or materials provided by the

marketing authorization holder to a government laboratory in support of an investigation of a suspect falsified medical product must be handled as confidential. Where necessary, material transfer agreements or confidentiality agreements are to be invoked.

7.1 Laboratory capacity

Best practices for QC laboratories and the minimum requirements for equipment are described in WHO guidance (6). That guidance focuses on QC laboratories using compendial or manufacturers' methods, as described in dossiers submitted for marketing authorization, to ensure compliance with the requirements of compendial monographs or manufacturer's specifications. However, these methods are designed to detect problems that may arise during the approved manufacturing process and subsequent storage and distribution and may not necessarily be appropriate to detect all possible issues that could arise with medical products that have been deliberately falsified. Methods used to authenticate suspect medical products must be suitable for their intended use.

Laboratories, normally national medicines testing laboratories, that test suspect falsified medical products should preferably be ISO/IEC 17025 accredited by a recognized accreditation body (affiliated, for example, to the International Laboratory Accreditation Cooperation, etc.) to perform the appropriate analytical procedures that are listed in their scope of accreditation. Alternatively, a WHO-prequalified laboratory with the capability to test suspect falsified medical products, an appropriate array of analytical techniques and sufficient expertise, may be chosen. Furthermore, the laboratories should be able to perform, interpret and document the testing according to rigorous procedures to ensure that the results can withstand legal scrutiny.

Beyond the requirements of good practices, described in general WHO guidance (6) and ISO/IEC 17025, some additional skills and capacity, as outlined below, are required for the analytical testing of suspect falsified medical products.

7.1.1 Expertise

- **Critical thinking.** Laboratory staff should have the ability to critically appraise all that is known about each case of a suspect falsified product and not simply rely on pre-existing standard testing procedures. This skill can be strengthened through discussions with peers on specific cases and by learning from senior experts in the field.
- **Experience.** Laboratories should have access to staff with experience in designing and implementing science-based, tailor-made testing plans for suspect falsified medical products. Where this is not the case, they should cooperate with other institutions and/or refer the testing request to an institution where the required experience is available.

- **Knowledge.** Laboratory staff should have up-to-date scientific expertise enabling them to fully understand the scientific methods used in testing falsified medical products, to apply them correctly and to interpret the results adequately.

7.1.2 Equipment

Laboratories should ensure that technical equipment for testing of suspect falsified medical products about which they have adequate knowledge and experience is appropriately qualified and maintained in good condition. Investments should be planned so as to enable the basic functioning of the laboratory for all its intended purposes and to maximize the benefits of any additional specialized equipment purchased. The cost of the equipment should be considered together with that of accessory products such as consumables, reagents, standards, databases and libraries, as well as the costs of and access to installation, maintenance and training. Sharing of equipment in accordance with regional cooperation agreements can be considered to minimize the costs while maximizing the benefits.

Laboratories also need secure and adequate storage facilities for the suspect falsified samples, when not being tested, to ensure the chain of custody.

7.2 Standard operating procedure

Laboratories should develop, implement and maintain a standard operating procedure (SOP) for testing of suspect falsified medical products. Such an SOP cannot define each step in the testing, since this will be determined on a case-by-case basis. Rather, it should ensure that the laboratory follows good practice and internal quality management systems in planning, implementing and documenting its actions with regard to each request for testing. *WHO guidelines for sampling of pharmaceutical products and related materials* (7) and *Good practices for pharmaceutical quality control laboratories* (6) should be followed, as applicable.

Measures should be taken to minimize bias. Sampling should be separate from testing. Staff performing each analysis on the testing plan should be blinded to the results of the other analyses as far as possible.

The laboratory should ensure full traceability of samples and results as described in relevant WHO guidelines (1, 6, 7), and should follow rigorous procedures to preserve the integrity of samples and documentation, with a chain of custody that will stand up to scrutiny in case of legal action.

An example of an SOP for testing of suspect falsified products is provided in Appendix 3.

7.3 Testing plan and test procedures

All the available information about the samples should be provided to the laboratory in the form of a request for analysis that clearly indicates what is expected from

experimental testing. The inspector or enforcement officer who collected the sample should inform the laboratory as comprehensively as possible and necessary for efficient running of the testing.

A suitable analytical testing programme should be prepared to detect the suspect substances. An initial study should then be undertaken, keeping in mind the number of sampling units available, to determine the substances to expect in the sample and parameters to be tested, and to design a science-based testing plan identifying the most efficient combination of methods to provide the required answers.

A wide range of methods may be considered for inclusion in the testing plan, which includes simple visual checks as well as the technologies listed in Appendix 1, and other forensic analyses that may assist in determining likely sources of suspect falsified medical products. Each technique should be appraised to determine its most appropriate use in order to achieve the best possible performance in the given context.

More detail on combining technologies to identify falsified medical products can be found in the literature (e.g. (5)). Various examples of flowcharts describing how to proceed with testing are reproduced in Appendix 4 for illustrative purposes (with the kind permission of the authors, the European Network of Official Medicines Control Laboratories).

7.4 Interpretation and reporting of results

General good practices in interpreting laboratory testing results are described in WHO guidance (6). Specific points to document for testing of suspect falsified medical products include:

- reasons for selecting the particular methods used in the testing plan;
- measures taken to avoid bias in analysis and reporting;
- traceability of the measurements, with links to all physical material and to the original sample on which the test was done;
- limitations of the selected methods as used in the testing plan, together with an estimate of the measurement of uncertainty of a quantitative result, if performed, and the conclusions.

8. Reporting and regulatory action on confirmed falsified medical products

A legal framework for reporting of falsified products should be in place at national level (9).

The confirmed testing results should be reported to the regulatory authority of the country where the falsified product was found. It is the responsibility of the NRA, under the given circumstances, to decide how the findings should be translated into

appropriate action in accordance with national legislation and in cooperation with enforcement agencies and other stakeholders.¹⁰ The marketing authorization holder should be kept informed of the results of testing. Other regulatory authorities should be informed as appropriate. A report should be submitted to the WHO Global Surveillance and Monitoring system for Substandard and Falsified Medical Products (10).

9. Archiving of samples and reports

The testing laboratory should store the samples appropriately and archive the related documentation in separate secure locations for future reference as required by legislation, documenting that the integrity of samples and results have been preserved.¹¹

References

1. Combating unsafe medical products: outcomes of a survey on testing of suspect medicines. WHO Drug Info. 2014;28:317–23.
2. Guidelines on the conduct of survey of quality of medicines. In: WHO Expert Committee on Specifications on Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 7 (WHO Technical Report Series, No. 996; <https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>).
3. Report of the third meeting of the Member State Mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit medical products, Geneva, 29–31 October 2014. Annex. In: Sixty-Eighth World Health Assembly. Provisional agenda item 17.3 (Document A68/33. Substandard/spurious/falsely-labelled/ falsified/counterfeit medical products. Report by the Director-General) (<http://www.who.int/gb/ssffc/>, accessed 13 October 2016).
4. Resolution WHA67.20. Regulatory system strengthening for medical products. In: Sixty-seventh World Health Assembly, Geneva, 16–24 May 2011. Resolutions and decisions, annexes. Geneva: World Health Organization; 2014:41–5 (http://apps.who.int/gb/ebwha/pdf_files/WHA67-REC1/A67_2014_REC1-en.pdf, accessed 13 October 2016).
5. Institute of Research Against Counterfeit medicines (IRACM). [Compilation of analytical assays, covert or coded features, techniques, traceability and tracking technologies to detect counterfeit medicines].
6. WHO Good practices for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications on Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 1 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y).
7. WHO guidelines for sampling of pharmaceutical products and related materials. In: WHO Expert Committee on Specifications on Pharmaceutical Preparations: thirty-ninth report. Geneva: World Health Organization; 2005: Annex 4 (WHO Technical Report Series, No. 929; https://iris.who.int/bitstream/handle/10665/43157/WHO_TRS_929_eng.pdf?sequence=1&isAllowed=y).

¹⁰ <https://www.who.int/teams/regulation-prequalification/incidents-and-SF>.

¹¹ See also reference (3), Paragraph IV.1.1. 30.

8. WHO Guidance on good data and record management practices, In: WHO Expert Committee on Specifications on Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 5 (WHO Technical Report Series, No. 996; <https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>).
9. Guidance on developing a national plan for preventing, detecting and responding to actions, activities and behaviours that result in substandard/spurious/false-labelled/falsified/counterfeit (SSFFC) medical products, Member State Mechanism on substandard/spurious/false-labelled/falsified/ counterfeit medical products, Report by the Director-General. Geneva: World Health Organization; 2017 (WHA 70.23, Appendix 1; http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_23-en.pdf).
10. WHO project for the surveillance and monitoring of SSFFC medical products. WHO Drug Info. 2013;27:97–100.

Appendix 1

Examples of analytical techniques that may be used for package identification, screening and testing of suspect falsified medical products

The list in Table 1 provides examples of analytical techniques that may be considered. These include compendial methods as well as specific advanced techniques. Each technique should be appraised to determine its most appropriate use in order to achieve the best possible performance in the given context. Laboratories may decide to outsource some of the analyses necessitating specific advanced techniques to other suitably qualified laboratories.

Note: The list should not be considered to be complete or exhaustive. It is intended to provide illustrative examples of commonly available technologies. Moreover, not all techniques are required for a laboratory that undertakes such testing.

Table 1
Illustrative examples of commonly available techniques

Main use	Technique	Full name	Remark
Identification	ATR/FTIR spectroscopy	Attenuated total reflectance/Fourier transform infrared spectroscopy	–
Identification	Melting point	–	–
Identification	XRPD	X-ray powder diffractometry	–
Identity	RI	Refractive index	–
Identification assay	Spectrophotometry (colorimetry)	–	–
Identification assay impurities	TLC	Thin-layer chromatography	–
Assay identification impurities	GC/FID	Gas chromatography with flame ionization detection	–

Table 1 *continued*

Main use	Technique	Full name	Remark
Forensics identification assay impurities	GC/MS	Gas chromatography with mass spectrometric detection	–
Assay identification impurities	LC/UV	Liquid chromatography with ultraviolet detection	–
Residual solvents impurities	HS-GC/FID	Headspace gas chromatography with flame ionization detection	–
Forensics residual solvents impurities	HS-GC/MS	Headspace gas chromatography with mass spectrometric detection	–
Inorganic impurities	ICP/OES	Inductively coupled plasma with optical emission spectroscopy	–
Inorganic impurities	ICP/MS	Inductively coupled plasma with mass spectrometric detection	–
Elemental and chemical analysis	XRF	X-ray fluorescence	–
Finished pharmaceutical product testing	Dissolution testing	–	Indication on bioavailability of the active pharmaceutical ingredient (API)
Finished pharmaceutical product testing	Disintegration testing	–	Indication of bioavailability of API
Specific testing	Sterility	–	–
Specific testing	BET	Bacterial endotoxins test	–

Table 1 *continued*

Main use	Technique	Full name	Remark
Specific testing	Osmolarity and osmolality	–	Characterization of injections and infusions
Finished pharmaceutical product testing forensics	Light microscopy	–	Particle characterization (size distribution, size, particulate impurities)
Identification	Raman spectroscopy	–	Characterization of material
Forensics	Photo scan/overlay	–	Documentation, comparison (e.g. packaging, leaflets)
Forensic	FTIR/Raman imaging spectroscopy	–	Characterization of material composition (distribution, particulate impurities)
Forensics	TEM	Transmission electron microscopy	Characterization of material morphology (tablet, particles)
Forensics	SEM-EDX	Scanning electron microscopy with energy dispersive X-ray spectroscopy	Characterization of material (surface, distribution in mixtures, particulate impurities)
Forensics; identification of impurities	LC-HRMS	Liquid chromatography with high resolution mass spectrometric detection	Characterization of unknowns down to trace levels
Forensics; identification assay impurities	LC/MS	Liquid chromatography with mass spectrometric detection	–

Table 1 *continued*

Main use	Technique	Full name	Remark
Forensics; impurities	TDS-GC/MS	Thermodesorption gas chromatography with mass spectrometric detection	Qualitative analysis of volatiles and semi-volatiles in solid samples (direct analysis/ without sample preparation)
Forensics	LC/ELSD	Liquid chromatography with evaporative light scattering detection	–
Forensics; identification assay impurities	NMR, qNMR	Nuclear magnetic resonance, quantitative nuclear magnetic resonance	Characterization of unknown compounds and mixtures – qualitative and quantitative

Appendix 2

Example of an information collection form

RECEIPT OF SUSPECT FALSIFIED PRODUCT		
Date on which the suspect product was received:		
Suspect product received by:		
Signature of the inspector/ enforcement officer and that of the owner of the product collected or seized		
Suspect product:		
Supply history of the product		
Source of the suspect product:		
Contact details of source of suspect product:	Name and surname:	
	Physical address:	
	Email:	
	Telephone number(s):	
	Other:	

INFORMATION ON SUSPECT FALSIFIED PRODUCT			
1. Suspect product name(s):			
2. Type of product (select the most appropriate box):			
Innovator product	☐	Generic product	☐
Vaccine	☐	Blood product	☐
Other biological product	☐		
Diagnostic	☐	Herbal medicine	☐
Traditional medicine	☐	Other, please specify	☐
Additional comments (if applicable):			
3. API(s) present in the product and declared strengths:			
4. Description of the dosage form:			
5. Description of product packaging (primary and secondary):			

Table *continued*

INFORMATION ON SUSPECT FALSIFIED PRODUCT			
6. Does the packaging contain any holographic security features or short message service (SMS) verifiable coding?			
	Yes ☐	No ☐	
Provide description (if applicable):			
7. Is there a patient information leaflet available with the product?		Yes	No
		☐	☐
8. Batch number/lot number (if available):			
9. Date of manufacture (if available):			
10. Expiry date (if available):			
11. Does this product fall under the national legislation for pharmaceutical products?			
	Yes ☐	No ☐	
12. Market authorization holder (if applicable):			
13. Manufacturer(s) details as given on the suspect product packaging:			
14. Quantity of suspect product received:			

Table continued

INFORMATION ON SUSPECT FALSIFIED PRODUCT		
15. Does the suspect product meet specifications defined as part of the stated product’s marketing authorization?	Yes ☐	No ☐
Provide full data content by scanning the code (if applicable):		
Additional information:		
16. Any other information applicable:		

TESTING REQUIREMENTS

1. Has the product been subjected to any preliminary testing?

Yes

☐

No

☐

If "Yes" provide a summary of results

2. What specific substances should the testing be designed to detect?

3. What tests or parameters should be considered to assess the product?

4. Is this sample physically and/or chemically similar to other samples (either specified or in general)?

5. Are the market authorization specifications available?

Yes

☐

No

☐

6. Are official testing methods available?

Yes

☐

No

☐

Description of methods available:

7. Any specific testing requests:

IMPACT ON PUBLIC HEALTH				
Have any adverse reactions been reported?	Yes	☐	No	☐
If "Yes" provide more information:				
Estimated number of patients adversely affected?				
Estimated number of patients at risk?				
Any other related information:				

Appendix 3

Example of the content of a standard operating procedure for testing suspect falsified tablets

1. Purpose

The standard operating procedure (SOP) describes the workflow and the required test procedures for the testing of suspect falsified tablets.

2. Scope

The SOP is only valid for the good laboratory practices/good manufacturing practices test facility of _____.

3. Sample receipt, documentation and storage

a. Sample receipt

Upon receipt of a shipment of suspect falsified tablets for analysis, the receiving laboratory should:

- record the
 - name and signature of the person delivering the sample or courier company waybill;
 - date and time of receipt of the sample in the laboratory with signature of the staff member;
 - presence of accompanying documentation in the shipment;
- check integrity (e.g. damage, broken sealing) of shipment packaging;
- check completeness of shipment against shipping documents;
- read out and check data logger (e.g. temperature control) – if applicable;
- check and sign shipment documentation – if applicable;
- archive all documents in the corresponding project files as per the corresponding SOP xxx.xxx.xxx.

b. Sample documentation

After sample receipt and unpacking:

- document packaging that contains the suspect falsified tablets as received as photographic image(s);

- document package insert or patient information leaflet as photographic image(s);
- check contents using shipping documents and previously received information from sending party;
- document each sample: secondary packaging and primary packaging (e.g. blister) including labels as photographic image(s);
- archive all documents and photographic images in the appropriate project files as per the corresponding SOP xxx.xxx.xxx;
- store samples under appropriate storage conditions according to SOP xxx.xxx.xxx until testing, record storage location;
- prior to testing let samples equilibrate to ambient temperature.

c. Checklists and records of observations

- All the above observations should be recorded on a checklist and signed and dated upon completion by the staff member responsible for these duties.
- The time and date of storage should be verified and recorded, with the signature of the person responsible.
- The time and date of sample removal from storage for equilibration to room temperature should be recorded, with the signature of the person responsible

d. Remarks

- When using photographic images for documentation purposes, check image quality (e.g. readability of text elements, colour correctness) before proceeding.
- Ideally, sample documentation should include dimensions (e.g. primary and secondary packaging, thickness and diameter of tablets).
- The sending party should be informed of receipt of the sample – if applicable.

e. Observations

Any observations such as damaged packaging, missing or additional samples should be documented and communicated to the sending party in order to decide how to proceed.

4. Sampling and samples

- Split each sample set into three subsets.
- Subset 1 for packaging inspection and documentation and Subset 2 for analytical testing as described in the following sections.
- Keep Subset 3 as a retained sample for any further investigation.

5. Overall aspect

Inspect known product protection features (i.e. holograms, colour-shift inks, etc.)

a. Packaging

- Use Subset 1 (see section 4).
- Visually inspect the secondary and primary packaging, use authentic comparators whenever possible.
- Report observations of the external appearance of the packaging materials (including labels and printing) such as visible damage, holes, discoloration and stains, spelling mistakes and unusual typography.
- Document observations as photographic images and archive them together with corresponding notes in the project files as per the SOP xxx.xxx.xxx.
- Report results.

A reporting form should be signed and dated on completion by the staff member responsible.

b. Samples

- Use Subset 2 (see section 4).
- Visually inspect the tablets.
- Report observations of the external appearance of the tablets, such as visible fissures, holes, inclusions, discoloration or stains, presence or absence of score lines, and presence or absence of film or sugar coating.
- Document observations as photographic images and archive them together with corresponding notes in the project files as per the SOP xxx.xxx.xxx.
- Report results.

A reporting form should be signed and dated on completion by the staff member responsible.

6. Analytical testing

a. Packaging testing

- Use Subset 1 (see section 4).
- Record Fourier transform infrared spectroscopy (FTIR) or Raman spectra according to the SOP xxx.xxx.xxx in order to confirm or elucidate the identity of the primary packaging.
- Report results.

A reporting form should be signed and dated on completion by the staff member responsible.

b. Solid medicine (tablet) testing

i. Active pharmaceutical ingredient (API)

- Use Subset 2 (see section 4).
- Homogenize at least one of the tablets of Subset 2 by mechanical grinding and use the homogenized material for the next steps.
- Confirm identity and concentration of the expected API in the suspect sample using the reference standard and corresponding compendial method. Alternatively, an in-house method can be used as long as the suspect tablet is tested against a suitable reference sample. The suitability of the in-house method for its intended use should be proven by means of validation reports and should be a stability indicative method.
- Report results.

A reporting form should be signed and dated on completion by the staff member responsible.

ii. Excipients

- Use Subset 2 (see Chapter 4).
- Record FTIR or Raman spectra of a reference sample (i.e. certified medicine reference sample) according to the SOP xxx.xxx.xxx.
- Record FTIR or Raman spectra according to the SOP xxx.xxx.xxx of the tablet, which was homogenized by mechanical grinding and compare against a reference sample in order to confirm presence and relative concentration of expected excipients.
- If differences from the data of the reference sample are observed perform in-depth analysis of experimental data (e.g. presence of unexpected substances or lack of expected substances).

- Report results.

There should be a reporting form to be signed and dated on completion by the staff member responsible.

iii. Additional tests

If tests as described in sections i. and ii. do not deliver unambiguous results additional screening tests can be performed on Subset 2. These screening tests can include:

- elemental analysis screening using inductively coupled plasma with optical emission spectroscopy (ICP-OES) or ICP/mass spectrometry (MS) as per SOP xxx.xxx.xxx;
- screening for volatiles and semi-volatiles using thermodesorption gas chromatography (TDS-GC)/MS as per SOP xxx.xxx.xxx;
- screening for volatiles and semi-volatiles via GC/MS as per SOP xxx.xxx.xxx;
- screening for non-volatile, polar compounds via high pressure liquid chromatography mass spectrometry (HPLC)/MS as per SOP xxx.xxx.xxx.

7. Dissolution and disintegration testing

- Use Subset 2.
- Perform dissolution testing in comparison to suitable reference sample.
- Report results.

There should be a reporting form to be signed and dated on completion by the staff member responsible.

8. Abbreviations

GC/MS	gas chromatography/mass spectrometry
HPLC/MS	high-pressure liquid chromatography/mass spectrometry
ICP/OES	inductively coupled plasma/optical emission spectrometry
ICP/MS	inductively coupled plasma/optical mass spectrometry
SOP	standard operating procedure

Appendix 4

Examples of flowcharts for testing of suspect falsified medicines

Explanatory note to the Appendix

This Appendix includes the examples from an “Aide-Memoire for the Testing of Suspected Illegal and Counterfeit Medicines” prepared by the European Official Medicines Control Laboratory (OMCL) Network (Reference: PA/PH/OMCL (06) 81 R6, Strasbourg, July 2016) which has been reproduced with the kind permission from the Network members. Terminology may therefore differ from WHO style.

“The original version of this document was produced in response to many presentations given at a number of Annual General Meetings of the OMCL Network (GEON).

The paper provides some practical and theoretical advice to OMCLs on the development of protocols for the confirmation or determination of counterfeit medicinal products and was adopted by the Network in 2007.

Subsequently, the testing of potentially illegal and counterfeit medicines throughout the Network has expanded and many laboratories now have established processes and expertise.

At the GEON annual meeting in June 2015, it was agreed that the “aide-memoire” document should be revised and updated to provide an overview of the overall approaches that should be taken for OMCLs analysing suspected illegal/counterfeit medicines.

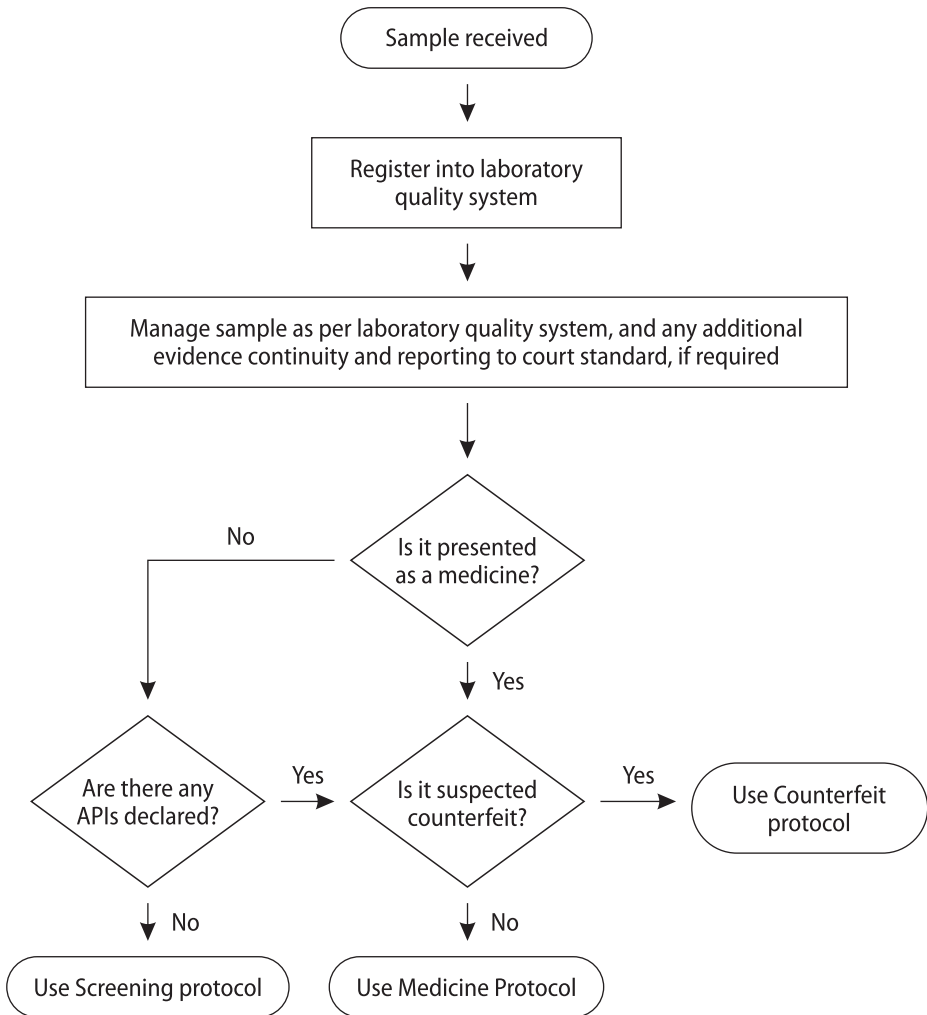
This document has been prepared to include example high-level process flows/ decision trees to assist OMCLs and promote a harmonised approach across the Network. It is recognised that OMCLs will have existing processes in place and this document does not supersede existing systems. This document is intended as an “aide memoire” only and OMCLs are not expected to be audited for compliance with the document.

The techniques listed in this document are examples only and should not be seen as exclusive or even preferred techniques. OMCLs should choose and use appropriate equipment to meet their testing needs.

The individual OMCLs’ choice of specific analytical techniques and detailed testing SOPs are outside the scope of this document and should be decided locally in accordance with local legislation or policies (for example, some OMCLs may routinely quantify APIs found but others may not – either approach is acceptable), equipment availability and staff expertise/preferences.

The final decision on what techniques to use and equipment to purchase and exactly what testing to apply is left to individual OMCLs.”

Example 1. Decision tree to determine testing requirements



Note:

Where no APIs are declared, often the name or marketing of the item can indicate what APIs may be present (for example, products may be marketed as weight loss or sexual potency enhancers, or have suggestive pictures/branding that implies the product's intended effect).

Also Internet searches using the product or producer name of the item can often provide information on APIs, use and/or indication.

Further details of the protocols that may be applied are given in the following sections.

Example 2. Screening protocol (testing for “medicines in disguise”)

Samples may be presented as a food supplement, health tonic, “nutraceutical” or naturally derived or herbal product. Usually there will be either no mention of API(s) in the product or even a more positive statement such as “100% natural extracts” or similar. Alternatively samples may be presented in foreign language variants, or even unlabelled.

In these circumstances the priority of the testing is to establish whether there are any APIs/potential pharmacologically active substances present and, if there is, at what level if required.

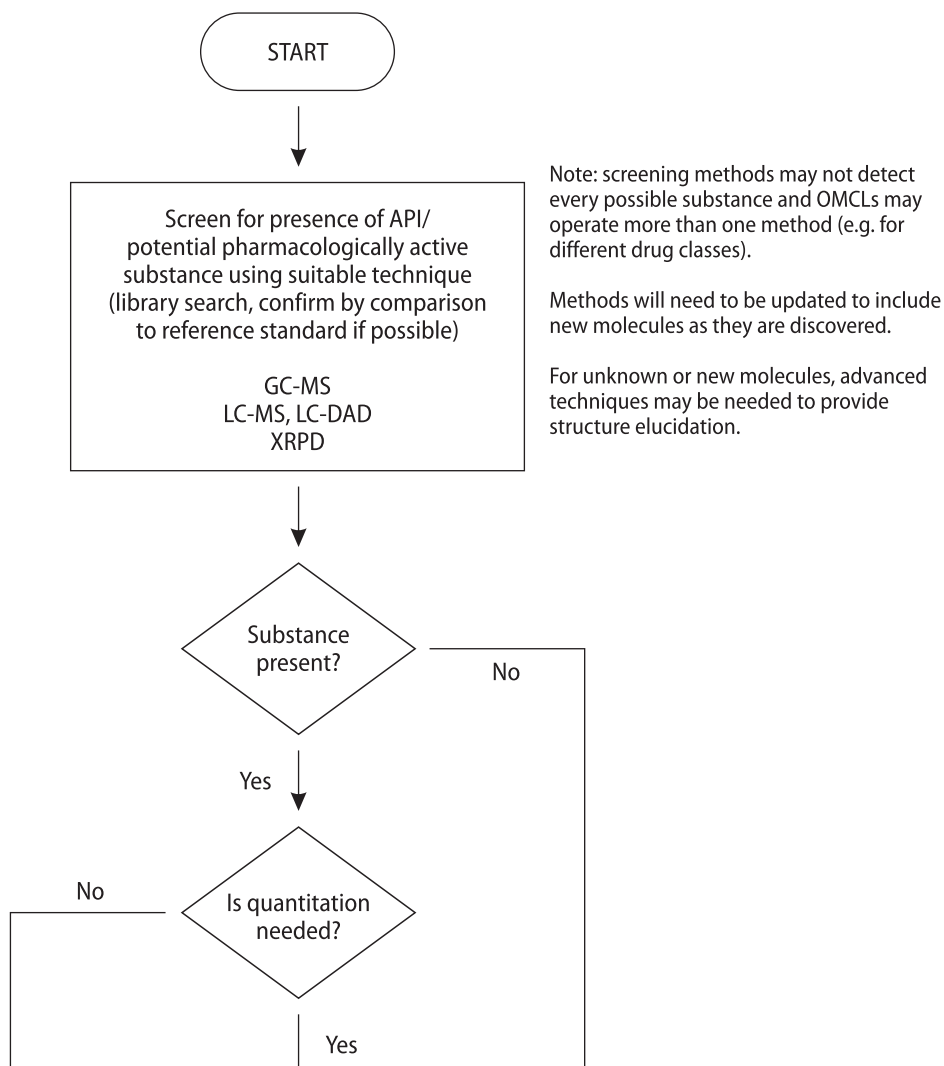
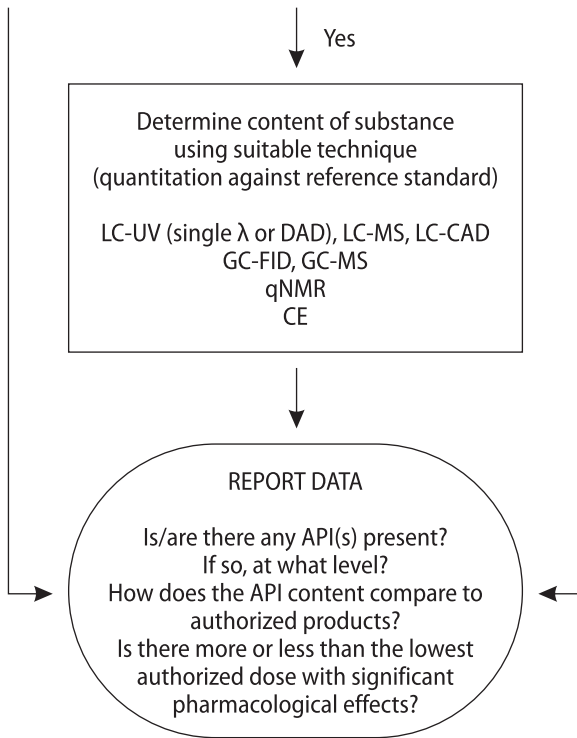


Figure continued



Example 3. Medicine protocol (testing of “unapproved products”)

Samples may be legal, licensed medicines in other countries, but not necessarily in the country where they have been found, or they may be legal medicines sold outside of the correct, legal supply chain. They might also contain drug substances that are not licensed or legally authorized for sale or treatment. Usually the API(s) in the product will be listed on the label and the product will be packaged and presented as a medicine. In some cases, the samples may be presented in foreign language variants, so the API(s) present may be unclear.

The priority of the testing is to establish that the labelled API is present, and (if required) at what level.

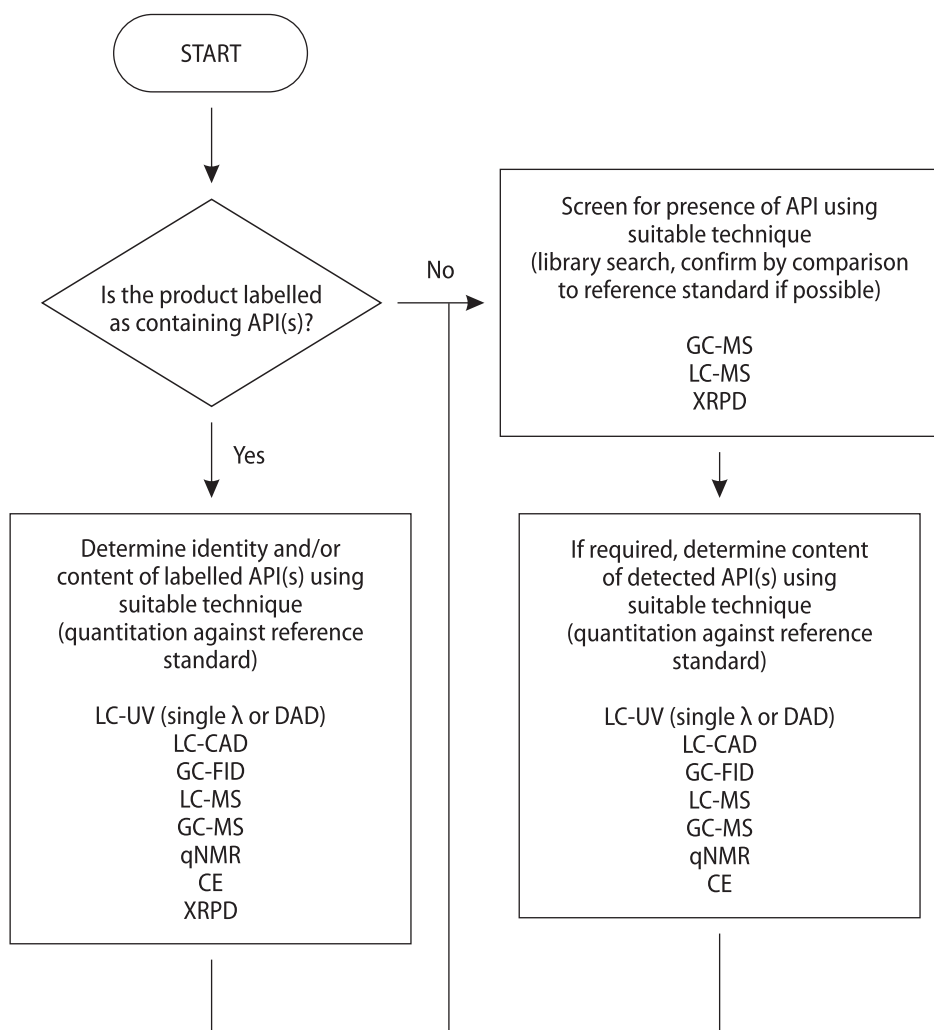
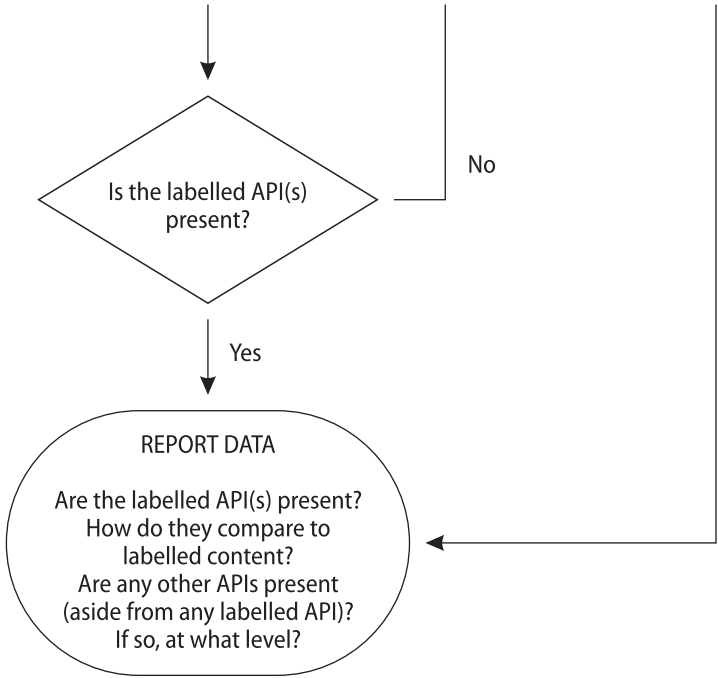
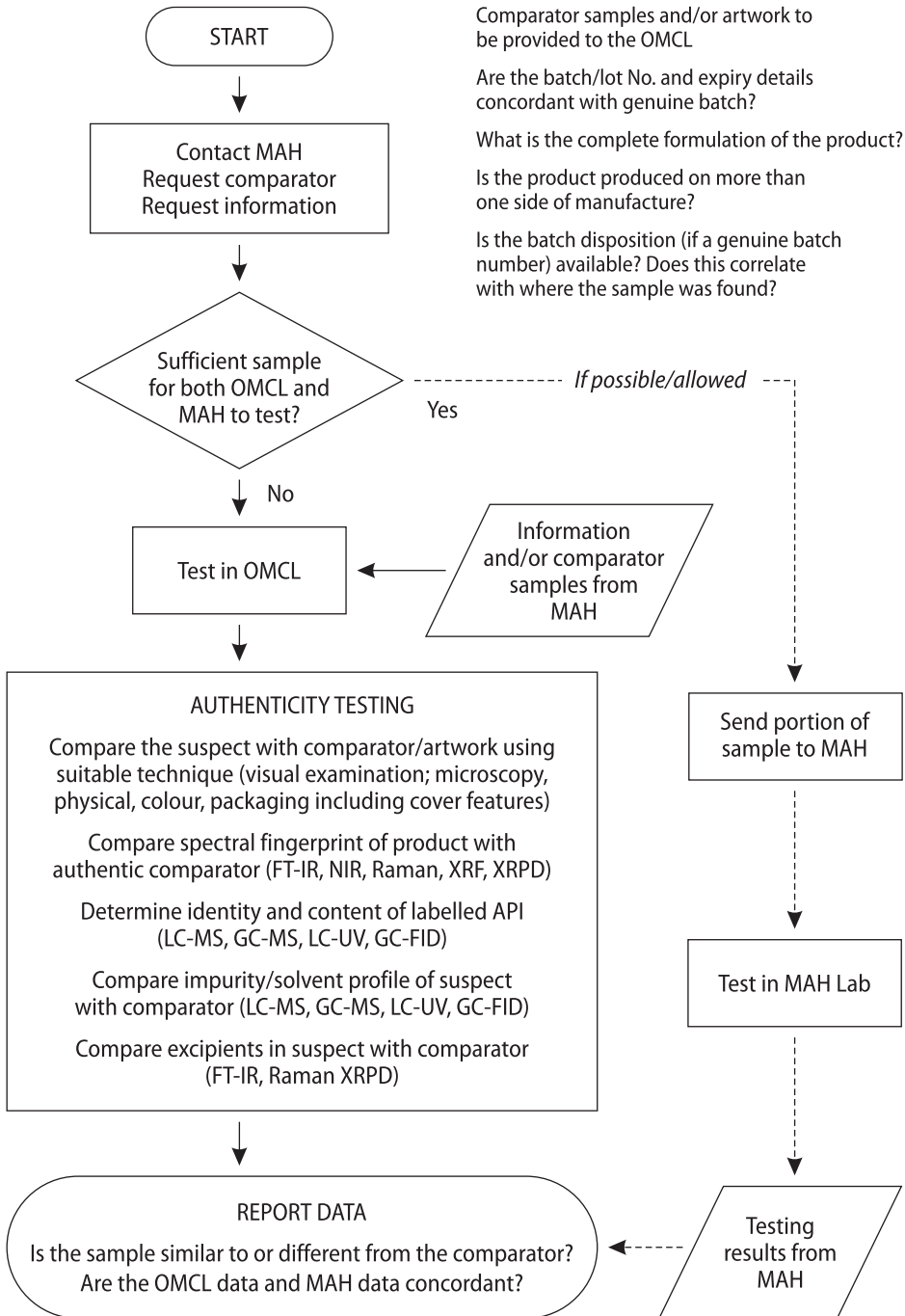


Figure continued



Example 4. Counterfeit protocol

For samples that are presented as licensed medicines but are suspected of being falsified, or counterfeit, it is essential that the OMCL is able to make contact with the market authorization holder of the genuine product. This may either be directly or through the competent authority, inspectorate or enforcement group. Genuine comparator batches (ideally three batches including the suspicious lot) should be obtained. If the product is manufactured at a variety of production sites samples should be obtained from each. It is not usually possible for a laboratory to determine conclusively that a sample of product is counterfeit based on testing alone. The priority of the testing can only be to say whether the suspect sample is consistent with the genuine product or not.



Note: when a suspect sample is found not to contain labelled API, the OMCL may wish to apply the screening protocol to determine what, if anything is present

11. Quality control

11.1 WHO good practices for pharmaceutical quality control laboratories

Annex 4, WHO Technical Report Series, 1052, 2024

Abbreviations	1577
1. General considerations	1577
1.1 Pharmaceutical quality control testing	1579
1.2 National quality control laboratories (NQCLs)	1579
2. Glossary	1580
3. Organization and management system	1587
3.1 Structural and general requirements	1587
3.2 Quality management system	1588
3.3 Control of documentation	1591
3.4 Change control	1592
3.5 Control of records	1592
3.6 Control of data	1593
3.7 Corrective and preventive actions	1595
3.8 Internal audits	1595
3.9 Complaints	1596
3.10 Management review	1596
3.11 Improvement	1597
4. Planning and strategic management	1598
4.1 Externally provided services and supplies	1598
4.2 Review of tenders and contracts	1598
4.3 Performance management	1600
4.4 Quality risk management	1600
4.5 Crisis management	1601
4.6 Communication management	1603
5. Resources	1603
5.1 Personnel	1603
5.2 Premises	1606
5.3 Equipment, instruments and other devices	1608
5.4 Reagents and materials	1612
5.5 Reference substances and reference materials	1615

6. Technical activities	1617
6.1 Sampling	1617
6.2 Incoming samples	1618
6.3 Selection, validation and verification of analytical procedures	1621
6.5 Testing	1625
6.6 Evaluation of test results	1626
6.7 Measurement uncertainty	1627
6.8 Validity of test results	1629
6.9 Out-of-specification results	1629
6.10 Reporting of results	1631
6.11 Nonconforming work	1633
6.12 Retained samples	1634
7. Safety rules	1634
References	1636
Appendix 1 Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory	1638
Appendix 2 Recommendations for the target uncertainty and the maximum permissible uncertainty for normal analytical practice	1645
Appendix 3 Examples of the uncertainty estimation for compliance with normal analytical practice (the “worst case”) for assay of pharmaceutical substances by chromatography	1652

Abbreviations

API	active pharmaceutical ingredient
DQ	design qualification
ECSP	Expert Committee on Specifications for Pharmaceutical Preparations
EQ	equipment qualification
IQ	installation qualification
IT	information technology
LCL	lower content limit
LIMS	laboratory information management system
NAP	normal analytical practice
NMRA	national medicines regulatory authority
NQCL	national quality control laboratory
OQ	operational qualification
PQ	performance qualification
QCL	quality control laboratory
QMS	quality management system
RSD	relative standard deviation
SMART	specific, measurable, achievable, relevant, and time bound
UCL	upper content limit
WHO	World Health Organization

1. General considerations

- 1.1 In 1999, the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Products (ECSP) adopted the WHO *Good practices for national pharmaceutical control laboratories*, which were published as Annex 3 of the WHO Technical Report Series No. 902, 2002. These guidelines were subsequently revised as *WHO good practices for pharmaceutical quality control laboratories*, published as Annex 1 of the WHO Technical Report Series No. 957, 2010.

- 1.2 Since the last revision of the guidelines, the experience from inspections of pharmaceutical quality control laboratories (QCLs) has enabled WHO to identify sections requiring clarification and the need to add new sections. Also, the COVID-19 pandemic made it clear that risk management, crisis management and business continuity are subjects that should be addressed to ensure that laboratories are prepared to face similar situations.
- 1.3 The present document provides advice on the quality management system (QMS) within which the analysis of pharmaceutical products by QCLs should be performed to ensure that accurate and reliable results are obtained. Compliance with the recommendations provided in these guidelines will help promote international harmonization of good practices for pharmaceutical QCLs and facilitate mutual recognition of test results.
- 1.4 This guideline is consistent with the requirements of the *WHO good manufacturing practices for pharmaceutical products* (1) and international standard ISO/IEC 17025:2017 (2), providing detailed guidance for laboratories performing quality control testing of medicines.
- 1.5 The good practice outlined below is to be considered as a general guide, which may be adapted to meet individual needs, provided that an equivalent level of assurance is achieved. For the items in the following subsections (mainly in the new section 4 on “Planning and strategic management”), a period of adaptation will be given to allow laboratories to implement these new requirements properly:
 - 4.3: Performance management
 - 4.4: Quality risk management
 - 4.5: Crisis management
 - 4.6: Communication management
 - 6.7: Measurement uncertainty.
- 1.6 This guideline is applicable to any pharmaceutical QCL, be it a national QCL (NQCL), a commercial QCL, a third-party contract QCL or a QCL of a pharmaceutical manufacturer. However, it does not include guidance for those laboratories involved in the testing of biological products (for example, vaccines and blood products), or for microbiology laboratories. Separate guidance for such laboratories is available, for example, *WHO good practices for pharmaceutical microbiology laboratories* (3), which is based on and supplements the requirements described in this document.
- 1.7 It should be noted that specifications and quality assurance objectives may be different for NQCLs and the QCL of a pharmaceutical manufacturer.

1.1 Pharmaceutical quality control testing

- 1.8 In a QCL of a pharmaceutical manufacturer, testing usually comprises repetitive testing and analysis of pharmaceutical products. However, an NQCL has to be able to test and evaluate a much wider range of products, requiring the application of a wider range of analytical test procedures and techniques. The same is applicable to commercial and third-party contracted laboratories.
- 1.9 For the quality of a pharmaceutical product to be correctly assessed, the following should be considered:
- the submission of a sample to the laboratory should be accompanied by a statement indicating the reason why the analysis has been requested;
 - the analysis should be correctly planned and executed.
- 1.10 The test results should be evaluated to determine whether the sample complies with the specifications or other relevant requirements.

1.2 National quality control laboratories (NQCLs)

- 1.11 A government, normally through the national medicines regulatory authority (NMRA), may establish and maintain an NQCL. Large countries may require several NQCLs to conform with national legislation. The role of NQCLs should be defined in the pharmaceutical legislation of Member States. Appropriate arrangements should, therefore, be in place to monitor compliance with a QMS. Throughout the process of marketing authorization and post-marketing surveillance, the laboratory or laboratories may work closely with the NMRA.
- 1.12 An NQCL should provide effective support to and collaborate with the NMRA. The analytical results obtained should accurately describe the properties of the samples assessed, permitting correct conclusions as to their quality. Where results from testing of samples show non-compliance with specifications, further investigations should be carried out by the NMRA and, where necessary, the appropriate legal action should be instituted.
- 1.13 NQCLs usually encompass two types of activity:
- compliance testing of pharmaceutical products employing official methods, which include pharmacopoeial methods, validated analytical procedures provided by the manufacturer and approved by the relevant national or regional authority for marketing authorization and, whenever necessary, analytical procedures developed and validated by the NQCL;

- investigative testing of suspicious, illegal, or falsified substances or products submitted for analysis, for example by the respective health authorities, customs authorities or police.

1.14 Compliance testing is expected to be performed by NQCLs in accordance with a post-market surveillance testing plan, prepared with the inputs of inspection, assessment and pharmacovigilance and taking into account the criticality of the products, supported by a risk analysis.

1.15 The implementation of these guidelines in NQCLs allows harmonization of laboratory procedures, methodologies and technical competence, enabling mutual trust and recognition among peers.

2. Glossary

2.1 The definitions given below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

acceptance criteria for an analytical result. Predefined and documented criteria by which a result is considered to be within the limits (conforms) or to exceed the limits (does not conform) indicated in the specification.

accuracy. The closeness of agreement between the value that is accepted either as a conventional true value or as an accepted reference value and the value found.

active pharmaceutical ingredient. Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

analytical acceptance criteria. Performance criteria applied to results obtained from the analysis performed. These criteria are predefined and are dependent on the nature of the product, the analytical procedure, and its original validation, as well as the specification limits given in the compendial monograph or in the marketing authorization, such as precision and accuracy.

analytical test report. An analytical test report usually includes a brief description of the test procedures employed, results of the analysis, discussion (if applicable) and conclusions or recommendations for one or more samples submitted for testing.

analytical worksheet. A printed form, an analytical workbook, or electronic means (e records) for recording information about the sample, as well as reagents and solvents used, instruments and equipment used, test procedure applied, calculations made, results and any other relevant information or comments.

batch (or lot). A defined quantity of starting material, packaging material or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches that are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch should correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

batch number (or lot number). A distinctive combination of numbers or letters that uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis.

calibration. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

certificate of analysis. The list of test procedures applied to a particular sample with the results obtained and the acceptance criteria applied. It indicates whether or not the sample complies with the specification.

certified reference material. Reference material, characterized by a metrologically valid procedure for one or more specified properties, accompanied by documentation (a certificate) that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability.

collaborative study. A study performed with a set of laboratories with different purposes, for example to establish a new batch of a reference standard or to validate a new test method to be published with regard to its robustness, which can be used to compare the results between different laboratories.

compliance testing. Active pharmaceutical ingredients, pharmaceutical excipients, packaging material or pharmaceutical products according to the requirements of a pharmacopoeial monograph or a specification in an approved marketing authorization.

confirmed out-of-specification result. A result that has been subjected to a thorough investigation and has been confirmed to be out of specification.

control sample. A sample used for testing the continued accuracy and precision of the procedure. It should have a matrix similar to that of the samples to be analysed. It has an assigned value with its associated uncertainty.

conventional true value. Value attributed to a particular quantity and accepted value.

crisis management. A set of planned strategies defined in advance to assist an organization in managing an unexpected event with a relevant negative impact. These strategies should ensure that business processes, assets and personnel are protected and are able to adapt to function in the event of such a disruption, such as a natural disaster (fire, flood, weather-related events), a cyberattack or a pandemic.

data integrity. The degree to which data are complete, consistent, accurate, trustworthy and reliable, and to which these characteristics of the data are maintained throughout the data life cycle. The data should be collected and maintained in a secure manner, such that they are attributable, legible, contemporaneously recorded, original or a true copy, accurate, complete, consistent, enduring and available (commonly referred to as “ALCOA+”). Assuring data integrity requires appropriate quality and risk management systems, including adherence to sound scientific principles and good documentation practices.

design qualification. A documented collection of activities that define the functional and operational specifications of the instrument and criteria for selection of the vendor, based on the intended purpose of the instrument.

equipment qualification. Action of proving and documenting that any analytical equipment complies with the required specifications and performs suitably for its intended purpose.

expanded uncertainty (U). Quantity defining an interval about the result of a measurement that may be expected to encompass a large fraction of the distribution of values that could reasonably be attributed to the measurand. Typically, it is calculated from a combined standard uncertainty and a coverage factor k . Estimation of uncertainty from a certain source of variation can already be indicated as an expanded uncertainty (for example, the maximum permissible deviation from the nominal volume of a volumetric apparatus).

good manufacturing practices. That part of quality assurance that ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

installation qualification. The performance of tests to ensure that the analytical equipment or system used in a laboratory is correctly installed in accordance with established specifications, enabling it to operate in the expected range.

interlaboratory comparison or testing. The organization, performance and evaluation of measurements or tests on the same or similar items by two or more laboratories in accordance with predetermined conditions.

level of confidence. A number expressing the degree of confidence in a quoted result, for example, 95%. It represents the probability that the conventional true value of the measurand lies within the quoted range of uncertainty.

management review. A formal, documented review of the key performance indicators of a quality management system performed by senior management on a regular basis.

manufacturer. A company that carries out operations such as the production, packaging, testing, repackaging, and labelling or relabelling of pharmaceuticals.

marketing authorization (product licence, registration certificate). A legal document issued by the competent medicines regulatory authority that authorizes the marketing or free distribution of a pharmaceutical product in the respective country after an evaluation for safety, efficacy and quality. In terms of quality, it establishes inter alia the detailed composition and formulation of the pharmaceutical product and the quality requirements for the product and its ingredients. It also includes details of packaging, labelling, storage conditions, shelf-life and approved conditions of use.

measurement uncertainty. A parameter associated with the result of a measurement that characterizes the dispersion of the values that could be reasonably attributed to the measurand.

metrological traceability. The property of a measurement result whereby the result can be related to a reference through a documented, unbroken chain of calibrations, each contributing to the measurement uncertainty.

operational qualification. Documented verification that the analytical equipment performs as intended over all anticipated operating ranges.

out-of-specification result. A test result that has been investigated and confirmed to fall outside the specifications or acceptance criteria established in product dossiers, drug master files, or pharmacopoeias, or by the manufacturer.

out-of-trend result. A result, from a series of analytical results obtained during a certain period of time, that complies with the acceptance criteria (be it specification, internal limits or analytical acceptance criteria) but falls outside the expected and predicted interval or the statistical process control criteria. It requires performance of trend analysis for test results during stability testing, environmental controls and yields, where applicable.

performance qualification. Documented verification that the analytical equipment operates consistently and gives reproducibility within the defined specifications and parameters for prolonged periods.

pharmaceutical excipient. A substance, other than the active pharmaceutical ingredient, that has been appropriately evaluated for safety and is included in a medicines delivery system to:

- aid in the processing of the medicines delivery system during its manufacture;
- protect, support, or enhance stability, bioavailability, or patient acceptability;
- assist in pharmaceutical product identification; or
- enhance any other attribute of the overall safety and effectiveness of the medicine during its storage or use.

pharmaceutical product. Any material or product intended for human or veterinary use, presented in its finished dosage form or as a starting material for use in such a dosage form, which is subject to control by pharmaceutical legislation in the exporting State or the importing State.

precision. The closeness of agreement among individual results when the procedure is applied repeatedly to multiple samplings of a homogeneous sample. Precision, usually expressed as relative standard deviation, may be considered at three levels: repeatability (precision under the same operating conditions over a short period of time), intermediate precision (within laboratory variations) and reproducibility (precision between laboratories).

primary reference substance (or standard). A substance that is widely acknowledged to possess the appropriate qualities within a specified context, and whose assigned content is accepted without requiring comparison with another chemical substance.

proficiency testing. The evaluation of participant performance against pre-established criteria by means of interlaboratory comparisons. It is common that laboratories are provided with aliquots or portions of a large homogeneous bulk material to make the necessary tests and measurements within a defined time period, and are provided with a report describing the global performance of the proficiency testing and the individual performance of the laboratory, supported by statistical calculation leading to a Z-score or an equivalent measure, converted into satisfactory, questionable or unsatisfactory results.

quality control. All measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics.

quality management system. An appropriate system, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

quality manager. A member of staff who has a defined responsibility and authority for ensuring that the management system related to quality is implemented and followed at all times.

quality manual. A handbook that describes the various elements of the quality management system for assuring the quality of the test results generated by a laboratory.

quality risk management. A systematic process for the assessment, control, communication and review of risks to the quality of the product during its life cycle.

quality unit. An organizational unit, independent of production, that fulfils both quality assurance and quality control responsibilities. This can be in the form of separate quality assurance and quality control or a single individual or group, depending on the size and structure of the organization.

reference material. Material sufficiently homogeneous and stable with respect to one or more specified properties that it has been established to be fit for its intended use in a measurement process.

reference substance (or standard). An authenticated, uniform material that is intended for use in specified chemical and physical tests, in which its properties are compared with those of the product under examination, and which possesses a degree of purity adequate for its intended use.

risk. Combination of the probability of occurrence of harm and severity of the harm.

secondary reference substance (or standard). A substance whose characteristics are assigned or calibrated by comparison with a primary reference substance. The extent of characterization and testing of a secondary reference substance may be less than for a primary reference substance.

signed (signature). Record of the individual who performed a particular action or review. The record can be initials, a full handwritten signature, a personal seal or an authenticated and secure electronic signature.

specification. A list of detailed requirements (acceptance criteria for the prescribed test procedures) with which the substance or pharmaceutical product has to conform to ensure suitable quality. “Conformance to specification” means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria (numerical limits, ranges, or other) and is considered acceptable for its intended use. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

standard operating procedure. An authorized written procedure giving instructions for performing operations, both general and specific.

standard uncertainty (U). Uncertainty of the result of a measurement expressed as a standard deviation.

starting material. Any substance of a defined quality used in the production of a pharmaceutical product, including packaging material.

suspected out-of-specification result. The first out-of-specification result obtained for a testing parameter, which has not been investigated and confirmed as out of specification.

system suitability test. A test that is performed to ensure that the analytical procedure fulfils the acceptance criteria that had been established during the validation of the procedure. This test is performed before starting the analytical procedure and is to be repeated regularly, as appropriate, throughout the analytical run to ensure that the system's performance is acceptable at the time of the test.

target uncertainty (U^g). Measurement uncertainty is specified as an upper limit and decided on the basis of the intended use of measurement results. Unless otherwise indicated, U^g is expressed as an expanded uncertainty.

trend analysis. An analysis of sets of data intended to detect patterns or trends, with the purpose of understanding the current behaviour and predicting future behaviours of that same type of data. This analysis enables the implementation of actions to control the trends that are observed.

uncertainty evaluation procedure. The procedure used for estimating the overall uncertainty.

validation of an analytical procedure. The documented process by which an analytical procedure (or method) is demonstrated to be consistently suitable for its intended use.

verification of an analytical procedure. The process whereby a pharmacopoeial method or official method approved by regulatory authorities is demonstrated to be suitable for the samples intended to be tested, and the process whereby a laboratory demonstrates it can adequately operate the pharmacopoeial method or official method approved by regulatory authorities.

verification of performance. A test procedure that is regularly applied to a system (for example, liquid chromatographic system) to demonstrate consistency of response.

3. Organization and management system

3.1 Structural and general requirements

- 3.1 The laboratory, or the organization of which it is part, should be legally authorized to function and be held responsible for the test results, certificates of analysis and other types of work that it performs.
- 3.2 Senior management is responsible for the establishment, implementation and control of an effective quality system and data governance system by ensuring that policies, training and technical systems are in place.
- 3.3 The laboratory should:
- have managerial and technical personnel with the authority and resources (financial, human and infrastructure) needed to carry out their duties;
 - have arrangements to ensure that its management and personnel are not subject to commercial, political, financial and other pressures or conflicts of interest that may adversely affect their work or compromise impartiality;
 - have procedures in place to declare conflicts of interest, as well as possible measures that should be taken to mitigate risks arising from declared interests, and to evaluate, review and document continuously the declarations of interest with respect to the ongoing work;
 - have a policy and procedures to ensure confidentiality of all information (oral, paper and electronic) shared with or generated by the laboratory during the performance of laboratory activities, including information contained in marketing authorizations, analytical methods, and the transfer of results or reports;
 - be responsible, through legally enforceable commitments, for the management of all information obtained or created during the performance of laboratory activities;
 - ensure that all personnel, including contractors, personnel of external bodies or individuals acting on the laboratory's behalf, keep confidential all the information obtained or created during the activities (except as required by law), act impartially and competently, and work in accordance with the laboratory's QMS;
 - define, with the aid of organizational charts, the organization and management structure of the laboratory, its place in any parent organization (such as the ministry of health or the NMRA in the case of an NQCL), and the relationships between management, technical operations, support services and the QMS;

- specify the responsibility, authority and interrelationships of all personnel who manage, perform, verify, review or approve work that affects the results of laboratory activities, for instance, in the job description;
- ensure the precise allocation of responsibilities, particularly in the designation of specific units for particular types of medicines, if deemed necessary;
- nominate trained substitutes or deputies for key management and specialized scientific personnel;
- ensure adequate supervision of staff, including trainees, by senior staff familiar with the testing or calibration, validation and verification of methods and procedures, as well as their purpose and the assessment of the results;
- have management that has the overall responsibility for the technical operations and the provision of resources needed in order to ensure the required quality of laboratory operations;
- designate a member of staff as quality manager, who, irrespective of other duties the staff member may have, will ensure compliance with the QMS. The nominated quality manager should have direct access to the highest level of management;
- ensure adequate information flow and communication between staff at all levels; staff are to be made aware of the relevance and importance of their activities, as well as having a good understanding of the mission, the strategic direction and operational priorities;
- ensure the traceability of the sample from receipt, throughout the stages of testing, to the completion of the analytical test report; a registry should be in place for receiving, distributing and supervising the consignment of the samples to the specific units. The records on all incoming samples and all accompanying documents should be maintained;
- maintain an up-to-date collection of all specifications and related documents (paper or electronic) used in the laboratory;
- have appropriate safety procedures (section 7).

3.2 Quality management system

- 3.4 The quality manager should ensure the establishment, implementation and maintenance of a QMS appropriate to the scope of activities in the laboratory.
- 3.5 The QMS should be communicated and understood by the appropriate personnel prior to its implementation. The elements of this system should be documented (for example, electronically or on paper).

3.6 The quality manual, or equivalent document, should contain, as a minimum:

- a quality policy statement, including at least the following:
 - a statement of the laboratory management's intentions with respect to the standard of service it will provide, including policies and objectives that address the competence, impartiality and consistent operation of the laboratory;
 - a commitment to developing, implementing, and maintaining an effective QMS and continuously improving its effectiveness;
 - the laboratory management's commitment to compliance with the content of these guidelines;
 - a requirement that all personnel concerned have access to the management system documentation and related information applicable to their responsibilities and are aware of the requirements for implementation of the policies and procedures in their work;
- the structure of the laboratory (organizational chart or equivalent document);
- the operational and functional activities pertaining to quality so that the extent and the limits of the responsibilities are clearly defined;
- an outline of the structure of documentation used in the laboratory QMS;
- the general internal quality management procedures and standard operating procedures;
- the requirements of qualification, experience and competencies of personnel and the policy for initial and in-service training of staff;
- policies for:
 - internal and external audits;
 - implementing and verifying corrective and preventive actions;
 - dealing with complaints;
 - performing management reviews of the QMS;
 - selecting, establishing and approving analytical procedures;
 - handling atypical and out-of-specification results;
 - data governance;
 - the employment, handling and storage conditions of appropriate reference substances and reference materials;
 - participation in proficiency testing schemes and collaborative studies, as appropriate, for the assessment of performance (this requirement is optional for the QCL of a pharmaceutical manufacturer);

- addressing risks and opportunities;
- evaluation, selection, monitoring of performance and re-evaluation of select service providers and suppliers.

3.7 The quality manager should ensure the establishment, implementation and maintenance of standard operating procedures for all administrative and technical operations, including the following (numbers in parentheses refer to relevant subsections):

- personnel matters, including qualifications and training (5.1);
- control of documents, records and data integrity (3.3, 3.5 and 3.6);
- change control (3.4);
- corrective and preventive actions (3.7);
- internal audits (3.8);
- complaints (3.9);
- purchase and receipt of consignments of supplies (for example, reagents and materials) (4.1 and 5.4);
- procurement, preparation and control of reference substances and reference materials (5.5);
- qualification of equipment, including calibration (5.3);
- preventive maintenance and verification of instruments and equipment (5.3);
- internal labelling and storage of materials and solutions (5.4);
- sampling, if performed by the laboratory (6.1);
- testing of samples with descriptions of the methods and equipment used (6.5);
- validation and verification of analytical procedures (6.3);
- validity of test results (6.8);
- atypical and out-of-specification results (6.9);
- nonconforming work (6.11);
- risks and opportunities (4.4);
- cleaning of laboratory facilities, including bench tops, equipment, workstations, clean rooms (aseptic suites) and glassware (5.2);
- monitoring of environmental conditions (for example, temperature and humidity) (5.2);
- monitoring of storage conditions (5.2);
- disposal of reagents, standards and samples (5.2, 5.4, 6.2, 6.12 and 7).

- 3.8 The key elements of a qualification and validation programme of the laboratory should be clearly defined and documented in a validation master plan.
- 3.9 The activities of the laboratory should be systematically and periodically audited to verify compliance with the requirements of the QMS through internal (see subsection 3.8) and external audits.

3.3 Control of documentation

- 3.10 A master list identifying the current version and the distribution of documents should be established and be readily available, either electronically or on paper.
- 3.11 The procedures to control and review all documents (both internally generated and from external sources) should ensure that:
- each document, whether a technical or a quality document, has a unique identifier, version number and date of implementation;
 - authorized standard operating procedures are readily accessible at the relevant locations, either electronically or physically;
 - the documents are reviewed regularly and updated if required;
 - any invalid document is removed and replaced with the authorized, revised document with immediate effect (either electronic or paper-based);
 - a revised document includes references to the previous document;
 - previous versions and invalid documents are retained in the archives (either electronic or paper-based) to ensure traceability of the content and the evolution of the procedures; any other existing copies are destroyed;
 - all involved staff are trained on the new and revised standard operating procedures;
 - all documentation, including records (either electronic or paper-based), is retained according to national legislation but for not less than five years.
- 3.12 Staff should be informed when new and revised procedures enter into force. The quality management system in place (see subsection 3.2) should ensure that:
- revised documents are prepared by the initiator (or a person who performs the same function), reviewed, and approved at the same level as the original document and subsequently released by the quality manager (or their team);
 - staff acknowledge that they are aware of applicable changes and their implementation date by a signature (electronic or manual) or by an alternative mechanism.

- 3.13 Detailed recommendations are provided in the WHO guideline on data integrity (4) and should be implemented.

3.4 Change control

- 3.14 The laboratory should have a standard operating procedure to manage changes. Steps in the procedure should include the assessment of impact, gaps, risks and opportunities. Requests for changes should be reviewed and implemented only after approval by management. Records should be kept.
- 3.15 When changes are required, necessitated by, for example, improvement to current procedures or introduction of a new method or relevant procedure, or increase or decrease in workload, range of laboratory activities, or staffing levels, these should be approved and monitored by senior management.
- 3.16 If relevant, change processes should also be addressed as part of management review (see subsection 3.10), enabling monitoring by senior management.
- 3.17 The quality manager should ensure that changes are documented, assessed for impact, approved, planned, implemented and reviewed.
- 3.18 Staff should acknowledge by signature that they are aware of applicable changes and their date of implementation.

3.5 Control of records

- 3.19 Identification, collection, indexing, retrieval, storage, backup, access, maintenance and disposal of all quality and technical or scientific records (paper, electronic or hybrid) should be described in the applicable standard operating procedure.
- 3.20 All original observations, including calculations and derived data, calibration, validation, verification records and final results, should be retained according to national legislation or contractual agreements, but for not less than five years.
- 3.21 The records should include the data recorded in the analytical worksheet by the technician or analyst on consecutively numbered pages with references to the appendices containing the relevant recordings either on paper (for example, balance weighing records) or electronically (for example, chromatograms and spectra).
- 3.22 For the data recorded in forms or templates, a procedure should be in place to control the issuance of blank paper templates (or forms) for data recording with reconciliation and authenticity controls where required (4).
- 3.23 The records for each test should contain sufficient information to permit the tests to be repeated or the results to be recalculated, if necessary. The records should

include the identity of the personnel involved in the sampling, preparation and testing of the samples.

- 3.24 The records of samples to be used in legal proceedings should be kept according to the applicable legal requirements.
- 3.25 A data and information management system ensuring traceability of operations, which is either paper based or software based – for example, a laboratory information management system (LIMS) – should be applied. Access to stored electronic data should be restricted to authorized personnel.
- 3.26 Samples tested in the laboratory should be retained for a shelf-life plus one year for a pharmaceutical product on the market and 15 years for an investigational product, unless national regulations are more stringent or contractual arrangements require otherwise.
- 3.27 All quality and technical or scientific records (including analytical test reports, certificates of analysis and analytical worksheets) should be legible, readily retrievable, stored and retained within a secure and suitable environment preventing damage, deterioration or loss.
- 3.28 The conditions under which all original records are stored should be such so as to ensure their security and confidentiality, and access to them should be restricted to authorized personnel. Electronic storage and signatures are employed but with restricted access and in conformance with requirements for electronic records (4–12).
- 3.29 Quality management records should include reports from internal and external audits, inspections and management reviews, risk assessment, and records of all complaints and their investigations and corrective and preventive actions.

3.6 Control of data

- 3.30 A master plan should be prepared for the validation of any information system used for the collection, processing, recording, reporting, storage or retrieval of data. Any validation report to demonstrate suitability for use should be prepared and verified by the quality manager or designated person for the task and available to the staff concerned after approval of the laboratory director or designated person. A standard operating procedure should be available that describes the use of a LIMS or a paper or electronic recording system, access rules, and the periodicity and type of backup, either cloud-based or on another server, including the restoration of data.
- 3.31 Commercial off-the-shelf software in general use within its designed application range can be considered to be sufficiently validated. When applicable, validation

documentation should be available and readily retrievable, as for any analytical system.

- 3.32 The laboratory should authorize, document and validate any changes before implementation, which includes laboratory software configuration or modifications to commercial off-the-shelf software. Where applicable, a validation report should be available.
- 3.33 The information systems should be:
 - protected from unauthorized access to ensure data integrity (that is, using individual access login and password);
 - safeguarded against tampering and loss;
 - operated in an environment that complies with provider or laboratory specifications;
 - capable of recording system failures and the appropriate immediate and corrective actions.
- 3.34 The quality manager should ensure that for test data in computerized systems:
 - electronic data are protected from unauthorized access, and an audit trail is enabled, maintained and periodically checked;
 - computer software developed by the user is documented in sufficient detail and appropriately validated or verified as being suitable for use;
 - computers and automated equipment are maintained so as to function properly and are provided with the environmental and operating conditions necessary to ensure the integrity of test data;
 - electronic data are backed up at appropriate regular intervals, are retrievable and are stored suitably to prevent data loss.
- 3.35 Electronic forms, prepared from modifications to commercial off-the-shelf software (such as Microsoft Excel), should be duly validated and their validation should be described in a validation report (12).
- 3.36 When a LIMS is managed and maintained off site or through an external host, it should be ascertained that the host of the system complies with all applicable requirements of this document.
- 3.37 Further information (4) can be consulted. Further guidance on the validation of data-processing equipment can be found in other sources (7, 9–12).

3.7 Corrective and preventive actions

- 3.38 Any deviation or nonconformity reported by any member of the staff or otherwise found should be investigated by conducting a root cause analysis with the analyst to identify the problem found and take appropriate action to rectify the nonconformity.
- 3.39 The laboratory should:
- identify the responsible persons for any action deemed necessary and establish timelines for implementation;
 - review the effectiveness of any corrective action taken to eliminate the problem;
 - evaluate any risks and opportunities that were identified;
 - prepare a report to include evidence of the nature of the deviations, determined causes, any subsequent actions taken, and the results of any corrective action implemented, which should be recorded and retained.
- 3.40 A critical analysis of the deviations and nonconformities detected by the laboratory and their impact on the management system and the risks and opportunities identified by the laboratory should be performed on a regular basis (see subsection 3.10).
- 3.41 Any situation that may lead to a potential deviation or nonconformity should be adequately addressed, leading to preventive action. Preventive actions can be treated as a risk or as an opportunity, depending on the type of potential impact of the action (see subsection 4.4).

3.8 Internal audits

- 3.42 The quality manager is responsible for organizing internal audits addressing all relevant elements of the QMS, comprising the following actions: plan, establish, implement and maintain an audit programme including the frequency, methods and responsibilities, which also takes into consideration the importance of the laboratory activities concerned, changes affecting the laboratory and the results of previous audits.
- 3.43 A standard operating procedure should be established, incorporating a detailed procedure for the planning and performance of the audits, which will:
- ensure that internal audits are planned and scheduled periodically by the quality manager (at least once a year) to enable systematic assessments;
 - define the scope of each audit and use risk-based criteria to determine the most critical activities to be audited, including the implementation of corrective and preventive actions after the last audit, if relevant;

- ensure that audits are carried out by trained personnel who are independent of the activity to be audited;
- ensure that the results of the audits (audit conclusion) are reported to relevant management, discussed during management review (see subsection 3.10), and communicated to staff;
- implement appropriate corrections and corrective actions without delay should any nonconformity be identified;
- monitor the effectiveness of the implemented corrective actions;
- retain records as evidence of the implementation of the audit programme and the audit results.

3.44 Laboratories may also be subject to audits by external auditors to assess their procedures and systems (for example, medicine inspectorate for manufacturers, peer review or ISO accreditation for NQCLs and other types of QCLs).

3.9 Complaints

3.45 The laboratory director should be aware of complaints received and ensure that the process for handling complaints is coordinated and comprises, as a minimum, the following:

- a description of the process for receiving, verifying, investigating and tracking a submitted complaint, and deciding what actions are to be taken in response;
- assurance that the appropriate action is taken within previously defined timelines to resolve the complaint, if needed;
- verification that the whole process is documented and fully traceable;
- informing the complainant of the outcome of the investigation performed, where possible and if requested.

3.46 Where possible, the process should include a member of the staff not directly related to the matter of the complaint. The quality manager should ensure that all the necessary information is collected, verified and recorded and inform the complainant of the outcome of the process, if the complainant's identity is available.

3.10 Management review

3.47 Laboratory management reviews should be convened at planned intervals (at least annually) to monitor the effectiveness of the management system.

3.48 Senior management consisting of, as a minimum, the responsible management board director, the laboratory director (or equivalent job title) and the quality manager should ensure that the decisions taken previously have had the expected

impact on the laboratory's activities and resources. Additionally, planning for the following period should be undertaken to enable the continued suitability, adequacy and effectiveness of the laboratory QMS.

- 3.49 The outcomes of management reviews should be recorded, documenting all decisions and actions related to the effectiveness of the QMS, improvement of the laboratory activities, required resources and necessary improvements.
- 3.50 The records of the management review should also include information related to the following specific activities or items:
- suitability of policies and procedures;
 - performance management (see subsection 4.3);
 - status of actions from previous management reviews;
 - changes in internal and external factors that have an impact on the laboratory;
 - outcome of internal and external audits or inspections and any follow-up required to correct any deficiencies;
 - changes in the laboratory activities (type, volume, range);
 - adequacy of resources (human, financial, material);
 - training programme;
 - feedback from customers and staff;
 - the outcome of complaints received;
 - corrective and preventive actions;
 - effectiveness of any implemented improvements;
 - follow-up and monitoring of identified risks and opportunities;
 - the results of external quality control (collaborative studies or proficiency tests) and any investigations carried out when doubtful or unsatisfactory results are obtained;
 - results of trend analysis;
 - atypical and out-of-specification results.

3.11 Improvement

- 3.51 The laboratory should identify and select opportunities for improvement and implement any necessary actions. These opportunities can be identified through a review of policies, procedures and objectives, audit and inspection results, corrective and preventive actions, risk assessment, management review, staff suggestions, and analysis of data, trends, and proficiency testing results.

- 3.52 The laboratory should request feedback from its customers, for instance, using customer satisfaction surveys, communication records and review of reports. This information should be used as an improvement tool.

4. Planning and strategic management

4.1 Externally provided services and supplies

- 4.1 The process for the selection and purchase of products (supplies) and services that the laboratory requires should be described, for example, measurement materials (including reference materials and certified reference materials), chemical and biological reference substances, equipment, reagents and services (for example, calibration, qualification, sampling, testing, maintenance, proficiency testing schemes, and assessment and auditing).
- 4.2 The laboratory should record:
- the review and approval of the laboratory's requirements for externally provided products and services;
 - the definition of the criteria for evaluation, selection, and monitoring of performance and re-evaluation of the external providers;
 - the evaluation of suppliers of critical products and services that affect the quality of testing, and listing of approved suppliers that have been demonstrated to be of suitable quality with respect to the requirements of the laboratory;
 - any actions taken arising from evaluation, monitoring of performance and re evaluation of the external providers.
- 4.3 The laboratory should communicate its requirements to external providers for:
- the products and services to be provided and their acceptance criteria;
 - competence (if applicable), including any required qualification of personnel;
 - activities that the laboratory or its customer intends to perform at the external provider's premises.
- 4.4 The laboratory should prepare a master list of suitable external suppliers for the products and services considered to be essential.

4.2 Review of tenders and contracts

- 4.5 The procedure established by the laboratory (customer) for the review of requests, tenders and contracts should ensure that:

- the requirements are adequately defined and documented;
 - the contract laboratory or a contracted organization has the capability and resources to meet the requirements;
 - appropriate methods or procedures are selected, which are capable of meeting the requirements of the laboratory and suitable for the samples to be tested;
 - the contracted laboratory informs the laboratory when the method requested is considered to be inappropriate or out of date and provides any clarification to the customer's request.
- 4.6 There should be a written contract that clearly establishes the duties and responsibilities of each party and defines the contracted work and any technical arrangements made in connection with it, which may include monitoring the contract laboratory's performance in relation to the work performed.
- 4.7 Any differences between the request or tender and the contract should be resolved before laboratory activities commence, and each contract should be acceptable to both the contracted laboratory and the customer. Deviations requested by the customer should not compromise the integrity of the contract laboratory or the validity of the results.
- 4.8 The customer should be informed of and agree to any deviation from the contract.
- 4.9 If there is a need for an amendment to the contract after the commencement of the work, the contract should be reviewed, and the affected personnel of the contract laboratory should be informed. Records of reviews should be retained.
- 4.10 Records of relevant discussions with a customer relating to the customer's requirements or the results of the contract laboratory activities should be retained.
- 4.11 When subcontracting is required:
- only organizations approved for the type of activity required should be addressed;
 - the contract should allow the laboratory to audit the facilities and competencies of the contracted organization and ensure access by the laboratory to records and retained samples;
 - the contracted laboratory should inform and gain approval from the customer about the specific activities to be performed;
 - the contracted organization should not pass any work entrusted to it under contract to a third party without the laboratory's prior evaluation and approval of the arrangements.

- 4.12 The laboratory is responsible for periodically assessing the competence of any contracted organization.
- 4.13 The laboratory should maintain a register of all subcontractors used, with records of the assessment of their competences.
- 4.14 The laboratory takes responsibility for all results reported, including those supplied by the subcontracting organization.

4.3 Performance management

- 4.15 The laboratory management review should set objectives, performance indicators and measurable targets for its activities for a specific time frame, which should be monitored regularly and, if necessary, appropriate actions taken. The objectives should be SMART: specific, measurable, achievable, relevant, and time bound. Some examples of performance indicators are the number of products tested versus the number of products planned to be tested, the percentage of complaints resolved within the given time frame, or the percentage of analytical test reports issued within a specific time frame.
- 4.16 If the laboratory is part of an organization, such as an NMRA, the objectives and targets should be fully aligned with the mission, vision and strategic goals of the organization and should be translated into operational plans and individual staff objectives, which should be monitored.
- 4.17 The laboratory should monitor the technical performance regularly with regard to the following:
 - the competence of personnel (see subsection 5.1);
 - the validity of test results (see subsection 6.8), in particular, the regular assessment of performance related to participation in a proficiency test scheme;
 - nonconforming work (see subsection 6.11) and its impact in terms of risk management.

4.4 Quality risk management

- 4.18 The laboratory should have a formal, well established approach to risk management involving the identification, assessment, treatment, prioritization, continuous monitoring and review of risks. It should consider the potential impact of all types of risks associated with processes, activities, stakeholders, products and services, and should define procedures and methodologies to minimize, monitor and control the probability or impact of unfortunate and undesired events and potential failures (13).

4.19 Two primary principles of quality risk management are:

- the evaluation of the risk to quality should be based on scientific knowledge and, ultimately, link to the protection of the patient;
- the level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

4.20 The laboratory should establish, whenever possible and if applicable, an interdisciplinary team led by the quality manager, including experts from different areas, to coordinate, facilitate and improve science-based decision-making with respect to risks – whether they be general risks for the laboratory or risks related to analytical testing. Possible steps to initiate and plan a quality risk management process may include:

- defining the risk (or opportunity), including the potential cause of the event identified;
- assembling background information on the potential impact (positive or negative, or opportunity);
- specifying a timeline, deliverables and an appropriate level of decision-making for the risk management process.

4.21 The laboratory should plan:

- actions to address the risks and opportunities identified, which should be appropriate to the potential impact on the validity of laboratory results or any laboratory activities (this can include identifying and avoiding threats, eliminating the risk source, changing the likelihood of losses or consequences, adopting new practices, or using new technologies);
- how to integrate and implement these actions into its management system;
- how to evaluate the effectiveness of these actions.

4.22 The process of identification and treatment of risks and opportunities should be recorded, monitored and duly reviewed on a regular basis by senior management during management review (see subsection 3.10).

4.23 The risks and opportunities identified and monitored should be sufficiently communicated to staff.

4.5 Crisis management

4.24 Specific concerns relate to ensuring the correct and efficient functioning of the laboratory at all times, which depends on suitable planning and budgeting to

obtain the necessary resources (maintenance of infrastructure and energy supply, as well as securing the continuity of laboratory activities). Business continuity planning allows the laboratory to take effective measures when issues or incidents arise, enabling management of those issues and providing continuity of business. Thus, key functions of the business, in particular key public health functions, can be fully recovered in the shortest possible time at acceptable costs.

- 4.25 The laboratory should establish and document a system of prevention and recovery in the event of an unplanned disruption to service, which guarantees employees' security and allows the continuation of work.
- 4.26 The established system or plan should be preventive and defined in advance, so that business processes, assets, and personnel are protected and able to regain functional competency quickly in the event of a significant disruption, such as a natural disaster (fire, flood or weather-related events), a cyberattack or a pandemic. The documented recovery plan should include the following:
- inputs from key stakeholders and personnel;
 - the definition of critical activities, which will determine key resources, such as information technology (IT), infrastructure and key personnel;
 - the performance of a risk analysis to establish any risk that can affect the laboratory's activities and the impact of those risks;
 - implementation of measures to mitigate risks and recover activities that are identified as critical to the organization, which should be tested for efficacy and reviewed periodically to ensure that the risk analysis is up to date;
 - where possible, the definition of a continuity team of adequately trained members, responsible for establishing and implementing appropriate planning and recovery strategies, and, when necessary, adapting these strategies to changing circumstances.
- 4.27 Recovery strategies for IT should be developed, such as implementing manual workflows so that the activities will continue while computer systems are being restored. An IT disaster recovery plan should be defined.
- 4.28 The laboratory should test the business continuity plan established, for example by simulation, to confirm its suitability for the intended purpose. Evidence of the testing of the business continuity plan should be maintained.
- 4.29 Other departments within the organization (if applicable) and stakeholders should be informed whenever a situation capable of presenting a risk to public health occurs, and should be apprised of the remedial actions taken.

4.6 Communication management

- 4.30 The laboratory should ensure that staff and stakeholders are informed and aware of the results of performance monitoring, either from management review (see subsection 3.10) or from other monitoring tools (see subsection 4.3).
- 4.31 A laboratory that is part of an organization, such as an NMRA or manufacturing company, should have communication channels with other parts of the organization that are defined and established to facilitate decision-making processes and other relevant processes.

5. Resources

5.1 Personnel

- 5.1 Personnel with the necessary education, training, technical knowledge and experience for their assigned functions should be employed either permanently or under contract. The competence requirements for personnel for each function should be documented. The laboratory should have procedures and criteria for selecting and assessing the competence of the personnel in accordance with the QMS.
- 5.2 Job descriptions should be in place for all personnel involved in tests and other laboratory activities, for example, calibration, validation, verification, qualification and maintenance. The laboratory should maintain records of the competencies of the personnel, including their education, qualification, training and experience.
- 5.3 The laboratory should have the following managerial and technical personnel:
- A laboratory director (or manager or head of the laboratory, or an appropriate job title) with appropriate qualifications (university degree in an appropriate discipline) for the position, with experience in a supervisory role in pharmaceutical analysis in a quality control laboratory, in the regulatory sector or in industry, who assumes full responsibility for all operations, including analytical, organizational, administrative and educational. This person is also responsible for ensuring that:
 - members of the laboratory staff have the competencies and qualifications appropriate to their required functions and their grades reflect their responsibilities;
 - the adequacy of existing training procedures for staff is reviewed periodically;
 - the technical management is adequately supervised;

- the certificates of analysis, analytical test reports and other important reports and protocols are approved.
- The laboratory director should preferably be supported and complemented by one or more technical managers (or senior analysts) with extensive experience in pharmaceutical analysis in a quality control laboratory, who have been designated responsibility for the analytical operations and for direct management and supervision of the team of analysts and technicians.
- A quality manager who shall have the responsibility and authority to implement and ensure compliance with the QMS and quality control activities. The quality manager should remain independent of routine laboratory analytical activities, depending on the size of the laboratory. The quality manager organizes internal audits of various laboratory activities, with the participation, preferably, of another member of staff from another section, according to a schedule approved during the management review. The quality manager, with the support of technical managers whenever necessary, ensures that:
 - personnel operating specific equipment, instruments or other devices are competent for the tasks they are performing;
 - personnel involved in tests or calibrations, validations or verifications are competent for the tasks they are performing;
 - regular in-service training programmes are arranged to update and extend the skills of both analysts and technicians;
 - the laboratory participates regularly in suitable proficiency testing schemes and, whenever possible, collaborative studies (as applicable);
 - due arrangements are made for the safekeeping and control of substances that are subject to poison regulation or to the controls applied to narcotic, psychotropic and radioactive substances, and which should be stored under lock and key, and handled and used in designated places under the supervision of an authorized person.
- Qualified analysts, who normally should be graduates in pharmacy, analytical chemistry or other relevant subject, with the requisite knowledge, skills and ability to adequately perform the tasks assigned to them by managers or supervisors. Appropriately qualified and experienced analysts with a thorough understanding of the management system, including the review, interpretation and reporting of test results, the maintenance of an internal chain of custody, and proper implementation of corrective and preventive actions in response to analytical problems, should also be available to serve as laboratory supervisors.

- Technicians should hold diplomas in their subjects awarded by technical or vocational schools or have the requisite hands-on experience to perform the assigned activities.
- 5.4 Staff undergoing training should be appropriately supervised and assessed upon completion of the training. This assessment should be fully documented.
- 5.5 The laboratory director or designated person should authorize personnel to perform specific laboratory activities. Only sufficiently qualified and trained personnel should be allowed to perform specific laboratory activities.
- 5.6 The laboratory should have procedures and criteria for the continuous assessment of personnel competence, which should be documented.
- 5.7 The laboratory should provide training or requalification of personnel, as appropriate.
- 5.8 The laboratory should maintain a list or matrix of the competencies of each staff member, documented procedures, and criteria for the continuous assessment of personnel competencies, which may include:
- performance of specific tests (such as pH, density and dissolution);
 - verification and review of results;
 - performance of analytical equipment qualification;
 - preparation and management of laboratory solutions;
 - preparation of standard operating procedures (at the request of the quality manager).
- 5.9 The laboratory director, or designated person, is responsible for:
- the consignment of samples to specific units;
 - approval of analytical test reports and certificates of analysis.
- 5.10 Any designated qualified personnel are responsible for:
- review of all analytical data to ensure the validity of the test results by checking the work performed and results obtained by the technician or analyst;
 - general technical activities that, by definition, are performed by the technical management, such as the review of technical documents (for example, analytical test reports and certificates of analysis), as long as this activity is delegated;
 - the implementation and execution of specific tests or analytical techniques requiring advanced technical training and knowledge, including verifying and reviewing raw data and analytical worksheets.

- 5.11 The laboratory should have an appropriate training schedule for staff, particularly for those staff who respond to the technical and managerial needs of the laboratory. Inputs to the training plan can be gathered from internal audits, management reviews, risk and opportunity assessments, or other available options. On successful completion of training, the results of evaluation should be recorded and made available, and the information should be added to the competency matrix or master list.

5.2 Premises

- 5.12 The requirements for facilities intended for laboratory activities should be documented and should be of a suitable size, construction and location.
- 5.13 Premises should adequately accommodate the features required of a pharmaceutical testing laboratory and should minimize the risk to the health of staff and the quality of the analytical results. Emergency exits should be available.
- 5.14 Appropriate entrance and sample reception areas must be provided for staff, visitors and samples.
- 5.15 Rest and refreshment rooms and toilets should be separate from laboratory areas.
- 5.16 Changing areas should be easily accessible and appropriate for the number of users.
- 5.17 The laboratory storage facilities should be organized for the correct storage of samples, reagents and equipment. Separate storage facilities should be maintained for the secure storage of samples, retained samples, reagents, laboratory accessories, and reference substances or materials. In general, storage facilities should ensure the following criteria are met.
- Storage facilities should be appropriate to store samples and reagents at the appropriate temperature and humidity conditions to maintain stability, if necessary, under refrigeration (2–8 °C) and frozen (–20 °C) conditions, or other necessary storage conditions, and be securely locked.
 - Reagents, reference substances and samples subject to poison regulations or to the controls applied to narcotic and psychotropic substances should be clearly marked and be kept separately in locked cabinets in accordance with national legislation. A designated responsible member of staff should have responsibility for their safekeeping, maintaining a register of these substances, and controlling their use.
 - The head of each unit should accept personal responsibility for the safekeeping of any of these controlled reagents or other controlled substances kept in the workplace. All specified storage conditions should

be controlled and monitored, and records maintained. Access should be restricted to designated personnel.

- The appropriate safety procedures should be rigorously implemented wherever toxic or flammable reagents are stored or used.
- The laboratory should provide appropriate separate storage rooms for storing flammable substances, fuming and concentrated acids and bases, volatile amines, peroxide-forming reagents, and self-igniting materials, such as metallic sodium and potassium.
- Small stocks of acids, bases and solvents may be kept in the laboratory.
- Gases can come from installed generators or external gas tanks stored outdoors in a well ventilated area, preferably isolated from the main building. Wherever possible, gas bottles are to be avoided in the laboratory. If gas bottles are present in the laboratory, they should be firmly and safely secured. However, it is recommended that gas generators be installed.

5.18 The laboratory should be equipped with adequate instruments and equipment, including workbenches, workstations and fume hoods. Separate instrument rooms for different measurement techniques should be available as required for method performance or to avoid contamination. There should be adequate safety equipment appropriately located, and measures should be in place to ensure good housekeeping and cleaning routines.

5.19 Weighing areas should be located where adequate environmental conditions of temperature and humidity are controlled.

5.20 Where necessary, the preparation and analysis of cytotoxic and genotoxic substances should be performed in a room equipped with, for example, an isolator and laminar flow workbench to handle, weigh, and manipulate cytotoxic and genotoxic (and highly toxic) substances. Appropriate procedures should be in place to avoid exposure and contamination of the staff, such as the use of gowns, suitable particle masks, goggles and protective gloves.

5.21 Archive facilities should be provided to ensure the secure storage and retrieval of all documents. The design and condition of the archives should be such as to protect the contents from deterioration.

- Records should be kept in a secure room with access restricted to authorized personnel.
- Electronic records should be retained, and duplicate copies should be retained in an external facility, for example, saved to an external server or cloud.

- 5.22 The environmental conditions, including lighting, energy sources, temperature, humidity and air pressure, should be appropriate to the functions and operations to be performed in the various locations. The specific conditions requiring control and monitoring should be based on the needs of the activity. The laboratory should ensure that the relevant environmental conditions are monitored, controlled and documented.
- 5.23 Procedures should be in place for the safe removal of types of waste, conforming to the local environmental standards, including toxic waste (chemical and biological), reagents, samples, solvents and air filters.

5.3 Equipment, instruments and other devices

- 5.24 The laboratory should have the required apparatus, equipment, instruments or instrument system used in pharmacopoeial analyses (analytical equipment) for the correct performance of the tests and related activities.
- 5.25 A list of equipment considered by the Expert Committee to be adequate, for either a first-stage or medium-sized pharmaceutical quality control laboratory, is provided in Appendix 1.
- 5.26 All equipment and their modules and accessories must be uniquely identified, including:
 - the manufacturer's name, instrument name, model and serial number;
 - any identifying number allocated by the laboratory;
 - the location, where appropriate;
 - the equipment manufacturer's instructions, if available, or an indication of their location;
 - the version and due date for requalification of any computer hardware, firmware and software.
- 5.27 All analytical equipment should be fit for its intended purpose, which is demonstrated by equipment qualification (EQ), which encompasses design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ).
- 5.28 All four stages will apply to the purchase of new equipment. Aspects of DQ and IQ may need to be repeated following major changes (see subsection 3.4). PQ aspects of OQ should be carried out throughout the entire life cycle of the equipment.
- 5.29 EQ must comply primarily with pharmacopoeial requirements and should address the intended purpose, and should follow the manufacturer's recommendations.

- 5.30 The laboratory is ultimately responsible for EQ. For complex equipment, the laboratory may use a specialized service.
- 5.31 The laboratory should ensure that the EQ process meets compliance requirements and that qualification processes are being followed and supported by complete, valid and documented data.
- 5.32 In the equipment purchasing phase, the laboratory should compile a user requirement specification document for each piece of equipment and specify in it that the supplier of the equipment provides documents, tools and services to support EQ – in particular, to provide clear instructions and details of tests required to demonstrate satisfactory performance, either performed by the laboratory or by the supplier or other external service provider. The laboratory should maintain oversight of such testing, ensuring that the qualification protocols are followed and supported by data, fully complete and documented. The laboratory should also ensure that the supplier or an external service provider delivers the necessary training, maintenance, repair and installation support.
- 5.33 The laboratory should establish a policy for when equipment should be serviced (that is, subject to maintenance, calibration and qualification). The following must be clearly described for each type of analytical equipment in use:
- the regularity of any service
 - the events after which service is necessary.
- 5.34 An EQ plan or matrix should be available to allow a clear overview of which equipment undergoes any intervention, when the intervention will take place, and whether or not it is performed by staff or by an external service provider. The laboratory should keep track of the interventions that were performed and when they were performed in case there is a significant deviation from the established schedule (see subsection 3.7).
- 5.35 A preventive maintenance schedule should be established in an equipment qualification and maintenance plan. Activities under the plan can be performed by the laboratory or entrusted to a competent organization and should be followed by appropriate EQ tests.
- 5.36 All analytical equipment requiring qualification, calibration or maintenance should be labelled, coded or otherwise identified to indicate the status and the date when the applicable action is scheduled.
- 5.37 All calibrations or equipment qualifications should be (where relevant and possible) traceable to an appropriate reference, for example, certified reference materials,

or to the relevant national or international standards, such as the International System of Units (SI).

- 5.38 The laboratory should ensure a change control process to guide the assessment, execution, documentation and approval of any changes to the analytical equipment. Designated qualified personnel should assess the effects of any changes to determine if any requalification activities are required.
- 5.39 Typical changes, after which analytical equipment should undergo the appropriate requalification, are:
 - movement or relocation of the equipment;
 - interruption to services or utilities;
 - repair or maintenance (including preventive);
 - modifications;
 - change of purpose or use;
 - suspect analytical results that, after a suitable investigation, indicate that an analytical instrument employed does not meet EQ requirements.
- 5.40 Analytical equipment shown to be defective or out of the specified limits should be taken out of service and clearly labelled or marked. It should not be used until it has been repaired and requalified.
- 5.41 Each stage of the qualification process involves:
 - the preparation of a qualification plan defining the scope of qualification (for example, the tests to be performed with their acceptance criteria, which can be combined with the qualification protocol);
 - the implementation of the plan to ensure that the results of the tests are recorded as the tests are performed;
 - the issuance of a report (and, if required, a certificate) in which the results of EQ are documented.
- 5.42 Specific standard operating procedures for the maintenance and qualification of analytical equipment performed regularly should be established. The personnel responsible for each operation with analytical equipment (authorized) must be clearly defined.
- 5.43 Documentation covering EQ should satisfy at least the following requirements:
 - define clearly the responsible persons to perform the required tests for maintenance, calibration and EQ;

- provide details of each check and test to be performed, the specification and acceptance criteria;
- provide sufficient information on the procedures and materials required to perform each check and test;
- state the date on which the EQ test was performed and the result of qualification for each check or test;
- state the reason for performing qualification (for example, following the installation of new equipment, following routine service, or following equipment malfunction);
- provide clear information about the action to be taken in the event of test or qualification failure;
- state the circumstances that may or will necessitate requalification of the equipment (for example, following repair, service or recalibration);
- provide the name and signature of the person (or persons) who actually performed the tests, and the name and signature of the quality manager or designated qualified personnel authorizing the completion of a qualification.

5.44 Equipment logbooks should be maintained to:

- identify the individual modules and accessories that constitute the equipment;
- record the overall history of the equipment (including the initial qualification and entry into service);
- include dates of when subsequent maintenance, calibration and qualification have been performed and when these are next scheduled.

5.45 The software used by the laboratory must be appropriately validated, preferably at the time of development; otherwise, if the laboratory is unable to control the development of the software, a software validation certificate from the manufacturer, ensuring compliance with the requirements of the pharmaceutical sector, should be acceptable.

5.46 The level of software validation is determined by its function. It is customary to distinguish between firmware levels (lack of user access) and software used for equipment control, data acquisition and processing.

- Further guidance on qualification of equipment is available in the literature (6, 14–17).

5.4 Reagents and materials

- 5.47 Reagents and chemicals, including solvents and materials used in tests and assays, should be of appropriate quality and suitable for the intended use.
- 5.48 Commercial reagents should be obtained from verified and approved qualified providers.
- 5.49 Reagents from external providers should be accompanied by the certificate of analysis and the safety data sheet, if required.
- 5.50 Management of the reagents must cover the entire life cycle of the reagents from purchasing and preparation (in the case of preparations) to use and disposal, and should be covered by a standard operating procedure.
- 5.51 The following major points should be considered in the life cycle of reagents:
 - type of reagents and the quality, depending on their use;
 - selection of the supplier;
 - verification of reagents upon receipt;
 - labelling of the reagent (avoiding misuse or misidentification);
 - storage conditions;
 - ensuring that the reagent is not compromised in any way before being used;
 - checking the expiry dates of reagents before use (it is not necessary to document this verification);
 - documenting the use of reagents used in analyses, ensuring traceability at least to batch number and expiry date;
 - disposal of the reagent.
- 5.52 The verification should comprise an administrative part (a documented check of the invoice, delivery note, and the integrity of the container, including storage temperature) and a scientific part (a documented check of the actual quality of the reagent given on the label or certificate against the requested quality). Specific in house testing may be required for some reagents.
- 5.53 For reagents purchased in their original container and purchased reagents that have been transferred into another container, the verification on receipt should be made.
- 5.54 The level of detail of the verification should be determined by the laboratory, unless otherwise stated.

5.55 The labelling information for all types of reagents should be stated on the container or in a leaflet, register or LIMS (or equivalent), which should include the following:

- name of the substance or reagent;
- date of receipt and date of opening of the container (or preparation date);
- expiry date (or retest date, as justified);
- storage conditions and, if applicable, any specific protection measures (such as protection from heat, light or atmosphere);
- concentration or purity of the reagent, if applicable;
- hazard and precaution codes.

5.56 For purchased reagents in their original container, the following additional information is expected on the label:

- manufacturer, supplier, brand and reference of the substance;
- batch number;
- identification: where the same batch is supplied in several containers, appropriate identification (for example, vial 1, 2, 3) can be indicated in the labels;
- name or initials of the person who opened it.

5.57 For purchased reagents that have been transferred into another container, the following additional information is expected on the label:

- name or initials of the person who transferred the reagent;
- batch number;
- transfer date;
- identification – in cases of transfer to several vials (aliquoted), appropriate identification (for example, vial 1, 2, 3) should be indicated in the labels.

5.58 In-house reagents (preparation of reagent solutions in the laboratory) should have the following labelling:

- name or initials of the person who prepared the reagent;
- date of preparation and validity period;
- name, reference, batch number and quantity of the reagents in the preparation (can be replaced by a reference, for example a project number);
- titre (or concentration or standardization factor);
- date of the determination of the titre and validity period, based on risk management and sound scientific principles;
- name or initials of the person who determined the titre.

5.59 For water manufactured by the laboratory, the following labelling is expected:

- name or initials of the person who dispensed the water and date of dispensing;
- if more than one production apparatus is available, the identity of the apparatus used must be documented.

5.60 For volumetric solutions, the following labelling is expected:

- name or initials of the person who prepared the reagent;
- date of preparation and validity period;
- name of the reagents in the preparation;
- titre (or concentration or standardization factor);
- date of the determination of the titre and validity period, based on risk management and sound scientific principles;
- name or initials of the person who determined the titre.

5.61 For the preparation of reagent solutions in the laboratory:

- responsibility for this task should be clearly stated in the qualification matrix or in the job description of the assigned staff member;
- standard operating procedures should be used that cover the entire life cycle of the use of reagents in the laboratory and are in accordance with published pharmacopoeial or other appropriate standards (18);
- records should be kept of the preparation of reagent solutions and standardization of volumetric solutions.

5.62 For the transportation and subdivision of reagents:

- whenever possible, they should be transported in the original containers;
- when subdivision is necessary, suitable clean containers should be used and appropriately labelled.

5.63 All reagent containers should be visually inspected to ensure that the seals are intact, both when they are delivered to the store and when they are distributed to the units. Containers that appear to have been tampered with should be rejected.

5.64 The appropriate grade of water for a specific test should be used as described by the pharmacopoeias or in an approved test.

5.65 The quality of the water should be verified regularly to ensure that the required grade of water complies with the appropriate specification.

- 5.66 Reagents should be stored under the appropriate storage conditions (temperature, ventilation, fire hazard) and appropriately maintained (organized, tidy, segregated).
- 5.67 A designated staff member trained in safe handling of chemicals should be responsible for the storage facilities and their inventory, and for noting the expiry date of chemicals and reagents (18).
- 5.68 The expiry period policy must be documented by the laboratory (as part of standard operating procedures).
- 5.69 The expiry date (before opening) given by the manufacturer must be considered valid. In the following cases, the laboratory shall determine a suitable expiry date, and a justification for assigning a new expiry date shall be documented:
- no expiry data is provided by the supplier;
 - when, after opening or transfer, environmental conditions (such as air or humidity) or further operations (such as dissolving a lyophilized material) affect the quality of the reagent.
- 5.70 The expiry date can be prolonged by providing scientifically sound and documented justifications, for example in cases where expired reagents can be used for a special purpose. In this case, the container must be relabelled appropriately.
- 5.71 Reagents should be disposed of appropriately when the expiry date is exceeded or when they are no longer required.
- 5.72 Disposal may be done at defined intervals or when the expiry date is checked prior to potential use, as applicable.
- 5.73 Reagents must be disposed of appropriately, safely and in compliance with legal requirements.

5.5 Reference substances and reference materials

- 5.74 Reference substances are necessary to ensure adequate quality control of pharmaceutical products.
- 5.75 Pharmacopoeial reference substances should be employed when available and appropriate for the analysis. Otherwise:
- An NQCL should use reference substances from a reputable commercial source or supplied by the manufacturer of the pharmaceutical product approved by the national medicines licensing authority (19) and used for the testing of a sample. The use of secondary reference substances by an NQCL is discouraged when primary reference substances are available and suitable for the intended use.

- The manufacturer's laboratory should establish primary reference substances. It can establish secondary (working) reference substances traceable to primary reference substances for use in routine analyses, provided that metrological traceability is ensured for the property value concerned. Pharmacopoeial reference substances are considered primary reference substances against which secondary (working) reference substances can be calibrated.

5.76 A nominated staff member should be responsible for the control of reference substances and reference materials.

5.77 An identification number should be assigned to all reference substances and reference materials. The laboratory may exclude pharmacopoeial reference substances from this identification system, as they are fully traceable by their pharmacopoeial reference number and batch or lot number.

- A new identification number should be assigned to each new batch.
- This number should be marked on each vial of the reference substance.
- The identification number, along with the validity statement, should be quoted in the analytical worksheet each time the reference substance is used.

5.78 A register for all reference substances and reference materials should be maintained and contain the following information:

- the identification number of the substance or material;
- a precise description of the substance or material;
- the source;
- the date of receipt;
- the batch designation or other identification code;
- the intended use of the reference substance or reference material;
- the location of storage in the laboratory and any special storage conditions;
- any further necessary information (such as the results of visual inspections);
- expiry date or retest date (if applicable), and valid use-by date;
- a certificate or leaflet of a pharmacopoeial reference substance and a certified reference material that indicates the use, the assigned content, if applicable, and its status (validity);
- in the case of secondary reference substances or certified reference material, the certificate of calibration or analysis;

- a file (paper-based or electronic) should be kept in which all information on the properties of each reference substance is entered, including the safety data sheets.

- 5.79 The intended use, expiry date or retest date of reference substances and reference materials used in the laboratory should be confirmed before use, and the corresponding information should be included in the test report. The use of the pharmacopoeial reference substance for purposes other than those specified in the pharmacopoeia is discouraged and is at the user's discretion, based on a risk assessment.
- 5.80 Reference substances prepared and stored in the laboratory should be retested at regular intervals to ensure that deterioration has not occurred. The interval for retesting depends on a number of factors, including the stability of the substance, storage conditions, type of container (for single or multiple uses) and the frequency of opening the container. If a non-compliant result is obtained on retesting a reference substance, a retrospective check of the tests performed using that reference substance should be carried out. For the evaluation of outcomes of retrospective checks and consideration of possible corrective actions, a risk analysis should be applied.
- 5.81 More detailed information on the handling, storage and retesting of reference substances established by the laboratory is given in the WHO *General guidelines for the establishment, maintenance and distribution of chemical reference substances* (19).

6. Technical activities

6.1 Sampling

- 6.1 If the laboratory is responsible for the sampling of pharmaceutical products for subsequent testing, a standard operating procedure should be established to include both a recognized sampling plan to ensure that a representative sample is obtained and measures to ensure that the chain of custody is effective.
- 6.2 The laboratory should have a sampling plan when it carries out sampling of substances, materials or products for subsequent testing or calibration. The sampling method should address the factors to be controlled to ensure the validity of subsequent testing or calibration results. The sampling plan and method shall be available at the site where sampling is undertaken. Sampling plans should, whenever reasonable, be based on appropriate statistical methods.
- 6.3 The laboratory shall retain records of sampling data that form part of the testing that is undertaken. These records shall include, where relevant:

- reference to the sampling method used;
- date and time of sampling;
- data to identify and describe the sample (for example, amount, name, number, and correspondence to container from which it was taken, when applicable);
- identification of the personnel performing sampling;
- identification of the tools used for sampling;
- environmental or transport conditions;
- diagrams or other equivalent means to identify the sampling location, when appropriate;
- deviations from, additions to or exclusions from the sampling method and sampling plan.

6.4 Further information is provided in *WHO guidelines for sampling of pharmaceutical products and related materials* (20) and *WHO guidance on testing of “suspect” falsified medicines* (21).

6.2 Incoming samples

6.5 Paragraphs 6.6 and 6.7 are applicable to NQCLs. The principle of the four W’s (who, what, when and where) should be applied. The chain of custody of each sample should be recorded.

6.6 Samples received by a laboratory may be for compliance testing or investigative testing.

- Samples for compliance testing include routine samples for control or samples submitted in connection with a marketing authorization process. Close collaboration with the providers of the samples is important. In particular, the quantity or amount of a sample should be sufficient to enable, if required, a number of replicate tests to be carried out and for part of the sample to be retained.
- Samples for investigative testing comprise suspicious, illegal, falsified or suspected substandard pharmaceutical products (21). Well documented screening procedures should be in place, as well as confirmatory analytical procedures to verify the identity of the substance or the ingredients. If an estimation of the content of an identified ingredient is required, then an appropriate quantitative analytical procedure should be applied. The value obtained may be reported with an indication of the uncertainty of measurement, if required, especially in the case of borderline test results.

- 6.7 It is common for a sample to be divided into three approximately equal portions for submission to the laboratory: one for immediate testing, the second for confirmation of testing, and the third for retention in case of dispute. It is important to ensure that the sample is large enough to enable, if required, a number of replicate tests to be carried out, and to ensure that, if there is a need for microbiological testing, a separate container for testing is provided.
- 6.8 A standard test request form should be completed for each sample submitted to the laboratory. In the case of a pharmaceutical manufacturer's laboratory, the requirements may be given in the master production instructions.
- 6.9 The test request form should contain the following information:
- the name of the person or institution that provided the sample and the date of receipt;
 - the source of the material;
 - a full description of the sample, including stated composition, international nonproprietary name and brand names (if available and whenever relevant);
 - the package and container;
 - dosage form and concentration or strength, the manufacturer's name, and the batch or lot number (if available);
 - the size of the sample;
 - the reason for requesting the analysis;
 - the date of sampling;
 - the size of the consignment from which it was taken (if appropriate);
 - the expiry date or retest date, if known;
 - reference documents and the specifications to be used for testing;
 - a record of any further comments (for example, discrepancies found or associated hazard);
 - the required storage conditions.
- 6.10 The laboratory should review the test request to ensure that:
- the sample amount is sufficient for the tests requested;
 - the laboratory has the required capability and resources to perform the appropriate analytical tests, as previously defined;
 - the appropriate tests or methods available are capable of meeting customers' requirements.

- 6.11 Any issue should be resolved with the originator of the request for analysis before testing starts, and a record of the review should be retained. If the laboratory is responsible for deciding which samples are to be tested, the test request form should be adapted accordingly.
- 6.12 Each sample and accompanying documentation (for example, the test request) should be assigned a unique registration number. Separate numbers should be assigned to requests referring to two or more medicines, different dosage forms, different batches of the same medicine, or different sources of the same batch.
- 6.13 A label bearing the unique registration number should be affixed to each container of the sample. Care should be taken to avoid masking any other markings or inscriptions.
- 6.14 A register should be kept in which the following information is recorded:
 - the registration number of the sample;
 - the date of receipt;
 - the specific unit or units to which the sample is to be forwarded for analysis.
- 6.15 The sample received should be visually inspected by laboratory staff to ensure that the labelling conforms with the information contained in the test request. The findings should be recorded, dated and signed. If discrepancies are found, or if the sample is obviously damaged, this should be recorded without delay on the test request form. Any queries should be immediately referred back to the provider of the sample.
- 6.16 The sample prior to testing, the retained sample and any portions of the sample remaining after the performance of all the required tests should be retained and stored appropriately.
- 6.17 The specific unit to which the sample is sent for testing is determined by the laboratory director (or designated person).
- 6.18 A request for analysis may be accepted verbally only in emergencies. All details should immediately be placed on record pending the receipt of written confirmation.
- 6.19 Unless a computerized system is used, copies or duplicates of all documentation should accompany each numbered sample when sent to the specific unit in order to verify the identification, origin and purpose of the sample for receipt and testing activities, as well as any relevant additional information.

6.20 Testing should be performed as described in subsection 6.5.

6.3 Selection, validation and verification of analytical procedures

- 6.21 The analytical procedures to be used for testing – either compliance testing or investigative testing – should be selected by the laboratory prior to the start of the analysis.
- 6.22 All analytical procedures employed for testing should be suitable for the intended use. When a non-pharmacopeial substance or product is to be analysed, it is preferable to apply the approved methods of the manufacturer; otherwise, validation of the method to be employed should be undertaken (6), which also serves to establish acceptance criteria for the system suitability tests that are subsequently employed for the verification of the analytical procedure before analysis.
- 6.23 For investigative testing, well documented screening procedures should be in place, as well as confirmatory analytical procedures to verify the identity of the substance or the ingredients. If an estimation of the content of an identified ingredient is required, then an appropriate quantitative analytical procedure should be applied. The value obtained should be reported with an indication of the uncertainty of measurement, if required, especially in the case of borderline test results.
- 6.24 Validation should be performed according to an approved validation protocol, which includes analytical performance characteristics to be verified for various types of analytical procedures. Typical characteristics that should be considered are listed in Table A4.1 (in the development phase of an analytical procedure, robustness, such as the ability of the procedure to provide results of acceptable accuracy and precision under a variety of conditions, should also be considered). The results are to be documented in the validation report. Some large-scale pharmaceutical manufacturers control the production of products by applying real-time release testing on the production site, using process analytical technology. Such technology must be validated to ensure that the product meets the specification throughout the production cycle and has been approved by the relevant licensing authority.

Table A4.1

Characteristics to be considered during validation of analytical procedures

Type of analytical procedure	Identification	Testing for impurities		Assay
Characteristics		Quantitative tests	Limit tests	dissolution (measurement only) content/potency
Accuracy	–	+	–	+
Precision				+
Repeatability	–	+	–	+
Intermediate	–	+ ^a	–	+
Precision				+
Specificity	+	+	+	+
Detection limit	–	– ^b	+	–
Quantitation limit	–	+	–	–
Linearity	–	+	–	+
Range	–	+	–	+

– Characteristic is normally not evaluated; + characteristic should normally be evaluated.

^a In cases where a reproducibility study has been performed, intermediate precision is not needed.

^b May be needed in some cases.

6.25 Pharmacopoeial procedures and those approved by the licensing authority can be considered as validated for the use described in the monograph. If validation is not required, method verification should be performed according to an approved protocol or procedure to demonstrate that the laboratory can successfully execute the method and that the pharmacopoeial procedure used is suitable for the sample being tested. The laboratory should, in particular, confirm that:

- for a finished pharmaceutical product, no interferences arise from the excipients present;
- for an active pharmaceutical ingredient (API), impurities coming from the route of synthesis are adequately differentiated;
- the system suitability requirements are fulfilled;
- the reporting threshold for related substances is met;
- the accuracy and the precision of the procedure are within predefined limits.

- 6.26 If the pharmacopoeial method is adapted for a new purpose other than the purpose described in the pharmacopoeia, it should be validated for such a use. Similarly, the sample preparation process must be critically assessed for the need for validation.
- 6.27 System suitability tests should be performed prior to and throughout the analysis of samples to ensure that the complete analytical system (including instrument, reagents, columns and analysts) is continuously suitable for the intended application.
- 6.28 Verification is not required for basic pharmacopoeial methods, such as colour of solution, pH determination and wet chemical methods. However, requirements given in the respective general chapters must be fulfilled at all times to ensure suitability for the intended use.
- 6.29 If method verification is required, but the results obtained do not comply with the analytical acceptance criteria, then they should be considered as nonconforming work (see subsection 6.11).
- 6.30 A major change to the analytical procedure, or in the composition of the product tested or in the synthesis of the API, should require revalidation (or reverification) of the compendial procedure or the analytical procedure approved by the licensing authority.
- 6.31 The performance of analytical procedures should be monitored throughout their life cycle.
- 6.32 Further guidance on the validation of analytical procedures is available in *WHO good manufacturing practices: guidelines on validation* (6).
- 6.4 Technical records
- 6.33 The analytical worksheet, or any suitable alternative document, is an internal document to be used by the analyst for recording information about the sample, the test procedure, reagents, standards, materials, calculations and the results of testing. It includes all raw data obtained in the analysis. An electronic system, such as LIMS, can also be used.
- 6.34 The analytical worksheet contains documentary evidence either to confirm that the sample being examined is in accordance with the requirements or to support an out-of-specification result.
- 6.35 A unique analytical worksheet should be used for each numbered sample or group of samples.

6.36 Completed analytical worksheets from different units relating to the same sample should be combined.

6.37 The analytical worksheet should provide the following information:

- registration number of the sample;
- page numbering, including the total number of pages (including annexes);
- date of the test request;
- dates on which the analysis was started and completed;
- name and signature of the analyst;
- a description of the sample received;
- references to the specifications and a full description of test methods by which the sample was tested, including the limits, if applicable; as an alternative, a traceable reference to the test method is acceptable;
- identification of the test equipment used;
- reference substances used (including the provider, lot number, potency or content);
- results of the system suitability test, if applicable, as well as any analytical acceptance criteria;
- identification of reagents, solvents and columns (if applicable) employed;
- results obtained, including those obtained from another internal analytical section or external laboratory, if applicable;
- interpretation of the results and the final conclusions (whether or not the sample was found to comply with the specifications), approved and signed by designated qualified personnel;
- further comments, for example, any deviation from a prescribed procedure, which should be approved and reported or treated as nonconforming work (see subsection 6.11), or whether the sample had been forwarded to another unit or contract laboratory for a specific analysis, and the dates on which it was transferred and the result was received.

6.38 All values obtained from each test, including blank results, should immediately be entered on the analytical worksheet, and all graphical data, whether obtained from recording instruments or plotted by hand, should be attached or be traceable to an electronic record file or document.

6.39 The completed analytical worksheet should be signed by the responsible analyst and reviewed and approved by designated qualified personnel (either in paper

format or electronically). Calculations and data transfers should be checked in an appropriate and systematic manner or controlled by a validated electronic system.

- 6.40 Any changes made to original records, either in paper or electronic format, should be traceable to what was changed, who was responsible, when it was performed, and why. The deletion of data is not acceptable.
- 6.41 When a mistake is made in an analytical worksheet or when data or text need to be amended, the correction must be traceable.
- 6.42 The analytical worksheet and any attachments, including calculations and recordings of instrumental analyses, should be archived together with the specification (4).
- 6.43 Detailed recommendations are provided in the WHO *Guideline on data integrity* (4) and should be implemented.

6.5 Testing

- 6.44 Testing of production samples from pharmaceutical manufacturers may be conducted entirely in the laboratory or, for some with high output, as a combination of in-process controls (as for real-time release testing), using process analytical technology, and laboratory testing. Samples for laboratory testing are taken and analysed throughout the production process and tested as soon as possible. Samples received by an NQCL are stored appropriately before being included in the laboratory workplan.
- 6.45 Pharmaceutical manufacturers apply testing methods that have been approved by the medicine licensing authority, whereas NQCLs apply, whenever available, the monograph of the appropriate pharmacopoeia when testing for compliance with the specification. Otherwise, the approved testing methods of the manufacturer are applied.
- 6.46 The sample should be stored appropriately in a dedicated sample storage facility within a controlled environment until testing can be performed according to the workplan of the laboratory.
- 6.47 When a test method included in the specification is not within the scope of the laboratory, the sample may be outsourced to a contract laboratory having the test method within its scope (see subsection 4.2). The responsible analyst prepares the request and arranges to transfer the required number of units (bottles, vials or tablets). Each of these units should bear the correct registration number. When the analytical test report contains the results of the tests performed by the contract laboratory, these results should be identified as such in the final report.

- 6.48 Detailed guidance on pharmacopoeial requirements is usually given in the general notices and specific monographs of the pharmacopoeia. Test procedures should be described in detail and should provide sufficient information to allow trained analysts to perform the analysis in a reliable and reproducible manner. System suitability criteria defined in the method should be fulfilled. The implementation of any deviation from the test procedure should be approved and documented and, where applicable, addressed as nonconforming work (see subsection 6.11).
- 6.49 Compliance with internal quality control criteria should be ensured (see subsection 6.11).
- 6.50 Detailed recommendations on chromatographic testing and processing are provided in the WHO guidance on *Good chromatography practices* (22) and should be followed.

6.6 Evaluation of test results

- 6.51 Quantitative test results, particularly those obtained in the manufacture of a finished dosage form of a pharmaceutical product, should be recorded in such a way that trends are detectable and, where practical, should be reviewed and evaluated statistically after completion of the tests. The evaluation should take into consideration established action and rejection limits to decide if the product meets the acceptance requirement.
- 6.52 For compliance testing, the product should meet all the acceptance requirements of the analytical tests included in the approved specification. Test results are compared with the specification limits to ascertain if the sample meets the requirements, and a conclusion is prepared as to the conformance of the test result with the specification.
- 6.53 Any test result should be traceable to a suitable primary reference substance, either of a pharmacopoeia or of a manufacturer or, if appropriate, to a certified reference material.
- 6.54 Atypical results should be investigated.
- 6.55 Neither pharmacopoeias nor NMRAs require the assay value found to be expressed with its associated uncertainty, as the upper and lower limits set already take into account the uncertainty of the measurement and, hence, no further tolerances are to be applied to the limits specified. However, for investigative testing in an unknown sample, it may also be necessary to report the content with its associated uncertainty.
- 6.56 Test results should be reviewed and approved or rejected by designated qualified personnel according to the competency master list or matrix (see subsection 5.1).

6.7 Measurement uncertainty

- 6.57 The uncertainty of measurement results is an essential component of the overall assessment and interpretation of analytical data. Understanding and appropriately addressing the measurement uncertainty is fundamental to ensuring the accuracy, reliability and reproducibility of the analytical results.
- 6.58 The requirements for measurement uncertainty apply to all quantitative tests performed by NQCLs.
- 6.59 When compliance testing is conducted using pharmacopoeial analytical procedures and analytical procedures described in the marketing authorization documentation, the requirements for evaluation of measurement uncertainty are considered to be met if all critical sources of uncertainty are controlled. In such cases, there is no obligation to report the measurement uncertainty. The decision on whether to estimate and take account of the measurement uncertainty in the statement of conformity with a specification limit rests with the laboratory. The decision is made on a case-by-case basis, and should be documented in advance.
- 6.60 When compliance testing is performed by internally developed analytical procedures that have undergone appropriate validation for their intended use, the specification limits, which must account for estimated measurement uncertainty, must be such that an unquestionable decision on compliance can be reached.
- 6.61 A thorough assessment of the measurement uncertainty may be required, for instance, when:
- employing ad hoc methods such as screening, analysis of unknown products or trace analysis;
 - using methods with limited uncertainty information;
 - confirming out-of-specification results, particularly if the test cannot be repeated;
 - establishing limits for performance tests of measurement apparatus and critical parameters of methods.
- 6.62 If an analytical procedure is frequently employed in a laboratory and its measurement uncertainty has already been established and verified, there is no requirement to evaluate the measurement uncertainty for each individual result. However, the laboratory must be able to demonstrate that the critical factors that affect the measurement uncertainty have been properly managed and controlled. By ensuring that these influential factors are under control, the laboratory can have confidence in the previously established measurement uncertainty and its applicability to subsequent results obtained using the same analytical procedure.

- 6.63 Applying the concept of measurement uncertainty to compliance testing enables managing the risk of making the wrong acceptance or rejection decisions, provided the following elements of the concept of uncertainty are implemented:
- the decision rule on compliance of pharmaceutical products with specifications is defined;
 - the laboratory evaluates the uncertainty of the analysis results.
- 6.64 The laboratory has the discretion to conduct an assessment of the measurement uncertainty as an internal quality control measure, when deemed appropriate.
- 6.65 The pharmacopoeial decision rule should be applied to all specification limits stated in the pharmacopoeial monographs and marketing authorization documentation.
- 6.66 The pharmacopoeial decision rule is based on the following principles:
- analytical variation typical of normal (routine) analytical practice is taken into account in the specified limits;
 - the decision on compliance is made only on the basis of whether the result of the analysis meets the specified limits. No further tolerances (for example, obtained by evaluation of measurement uncertainty or setting the acceptance and rejection zones) should be applied to the specified limits.
- 6.67 The pharmacopoeial decision rule is simple: accept or reject, with a guard bandwidth equal to the analytical variation typical of normal analytical practice. The analyte concentration must be within a range narrower than the specification width (by analytical variation accounted for in the specification), ensuring a low probability of rejecting a product (low manufacturer risk). The pharmacopoeial decision rule works correctly only if the actual value of the uncertainty (in practice – estimated uncertainty) is fixed – that is, does not exceed the critical value, which is the target uncertainty set for the test. A decision on compliance is considered conclusive if the estimated uncertainty is less than or equal to the target uncertainty of a reportable result (pass). If the estimated uncertainty is greater than the target uncertainty, then a decision is considered inconclusive, and an investigation is required to establish the reasons for the unacceptably high uncertainty. The laboratory should ensure that the estimated uncertainty does not exceed the target uncertainty when performing the analysis.
- 6.68 For an NQCL to correctly reproduce an analytical procedure described in the pharmacopoeial monograph or marketing authorization documentation, the actual analytical variability should not exceed the variability characteristic of normal analytical practice.

- 6.69 Target uncertainty and the maximum permissible uncertainty for standard analytical operations (for normal analytical practice) are provided in Appendix 2.
- 6.70 The application of the concept of standard analytical practice for the evaluation of measurement uncertainty is provided in Appendix 3.

6.8 Validity of test results

- 6.71 The laboratory should have a procedure for ensuring the validity of results by reviewing the following activities, as appropriate:
- reference substances or reference materials;
 - verification of measuring and testing equipment;
 - appropriate quality control checks;
 - data analysis that does not require additional experiments (use of control charts, trend analysis and different kinds of correlation of results of the sample being tested);
 - replicate tests or calibrations using the same or different methods;
 - retesting of retained samples;
 - review of all raw data and reported results;
 - review of measurement uncertainty results, if required.
- 6.72 Apart from the QCL of a pharmaceutical manufacturer, the performance of the laboratory should be assessed regularly by participation in:
- proficiency testing schemes, organized both internally and externally;
 - interlaboratory comparisons, such as collaborative studies.
- 6.73 Data from monitoring activities should be subject to management review, at least annually, to ensure that necessary actions to control and, if applicable, to improve the laboratory's activities are effective.
- 6.74 If the results of the analysis of data from monitoring activities are found to be outside predefined criteria, appropriate action should be taken to prevent the reporting of incorrect results.

6.9 Out-of-specification results

- 6.75 An out-of-specification result is a result that does not comply with the acceptance criteria of any test in the specification, found in drug master files, company documentation, approved marketing submissions, or official compendia (6, 23).
- 6.76 When a suspected out-of-specification result has been identified, a review of the different procedures applied during the testing process should be undertaken by

the supervisor with the analyst or technician by using a checklist and before any retesting is performed. The investigation should ensure that:

- if stable, original sample preparations are not discarded until the investigation is complete;
- the appropriate procedures were applied and followed correctly, including requirements for validation and verification, and internal quality control tools;
- examination of the raw data is undertaken to identify possible discrepancies;
- all calculations are checked;
- the equipment used was qualified and calibrated, and system suitability tests were performed and were acceptable;
- the appropriate reagents, solvents and reference substances were used;
- the correct glassware was used.

- 6.77 The identification of an error that caused an aberrant result invalidates the result, and a retest of the sample will be necessary, which should be conducted by the same technician or analyst.
- 6.78 Suspected out-of-specification results can be rejected only if they are clearly due to an identified error. When an investigation is inconclusive, a confirmatory determination is to be performed by another trained analyst. A similar result would indicate a confirmed out-of-specification result. If comparable results are not obtained by the second analyst, the lack of consistency should be investigated. Further confirmation using another validated method, if available, may be advised and, if performed, should be fully documented.
- 6.79 If available, hypothesis testing should be considered in order to better define the root cause.
- 6.80 A standard operating procedure should be in place for the conduct of an investigation into a suspected out-of-specification test result. All investigations and their conclusions should be recorded. In the event of an error, root cause analysis should be performed, and any corrective actions should be documented, implemented, and recognized as risks and as opportunities for improvement.
- 6.81 All test data should be recorded and retained. If no error was identified, all test results should be reported. The standard operating procedure defined above should also consider the general rules to report this type of result.
- 6.82 All conclusions should be recorded (either on the analytical worksheet or in another support) by the analyst and reviewed and approved by the supervisor.

- 6.83 A critical review of the nature, number and root cause of out-of-specification results obtained within a given period, either confirmed or not confirmed, should be conducted during the management review (see subsection 3.10).

6.10 Reporting of results

- 6.84 The analytical test report (hard copies or by electronic means) is a compilation, by the study supervisor, of the analytical test results obtained for approval by the quality manager, laboratory director or designated person. Subsequently, the dossier containing all the information pertaining to the sample, including the origin, chain of custody and analytical data, is archived.
- 6.85 Any amendments or changes to the original analytical test report will require the issue of a new corrected document, where:
- any change of information should be clearly identified and dated;
 - the reason for the change should be included in the new corrected document;
 - the new report should be uniquely identified and contain a reference to the original document it will replace.
- 6.86 When using pharmacopoeial methods and manufacturer's approved methods for compliance testing, it is not required that the expanded uncertainty be reported.
- 6.87 The laboratory decides when to report the uncertainty of a result and how conformance to specifications was evaluated (see recommendations in subsection 6.7).
- 6.88 The analytical test report should provide the following information:
- a title (for example, "test report", "analytical test report", or another suitable title);
 - the laboratory registration number of the sample;
 - the laboratory test report number;
 - the name and address of the laboratory testing the sample;
 - the name and address of the originator of the request for analysis;
 - the name, description and batch number of the sample, where appropriate;
 - an introduction giving the background to and the purpose of the investigation, if applicable;
 - a reference to the specifications used for testing the sample or a detailed description of the procedures employed (sample for investigative testing), including the limits;

- the results of all the tests performed or the numerical results, with the standard deviation of all the tests performed (if applicable);
- when applicable, the expanded measurement uncertainty of the reportable result with reference to its assessment and an explanation of how it was used in making the compliance decision;
- a discussion of the results obtained, where appropriate;
- a conclusion as to whether or not the samples were found to be within the limits of the specifications used, or, for a sample for investigative testing, the substances or ingredients identified;
- a statement to the effect that the results relate only to the items tested, calibrated or sampled;
- a clear identification when results are from external providers;
- the date on which the tests were completed;
- the signature of the laboratory director or other authorized person reviewing and authorizing the report;
- the name and address of the original manufacturer and, if applicable, those of the repacker or trader;
- whether or not the samples comply with the requirements;
- if applicable, opinions and interpretations, adequately supported by evidence and issued by authorized personnel;
- the date on which the sample was received;
- the expiry date or retest date, if applicable;
- a statement indicating that the analytical test report, or any portion thereof, cannot be reproduced without the authorization of the laboratory.

6.89 A certificate of analysis is prepared for each batch of a substance or product. The certificate of analysis contains the same information as the analytical test report.

6.90 For NQCLs, the issuance of a certificate of analysis is not obligatory as long as the analytical test report is adequately issued and remains at the laboratory as an internal document.

6.91 The laboratory is responsible for all the information provided in the report, except when the customer provides the information.

- Data provided by the customer should be clearly identified.
- In addition, a disclaimer should be included in the report when the information is supplied by the customer, which could compromise the validity of the results.

- Where the laboratory has not been responsible for the sampling stage (for example, the sample has been provided by the customer), the report should state that the results apply to the sample as received.

6.11 Nonconforming work

6.92 The term “nonconforming work” refers to any instance where analytical activities deviate from established procedures, internal requirements, or the analytical specifications that have been agreed upon with the customer. Such deviations encompass a range of issues, including equipment, environment conditions, internal quality control criteria and system suitability criteria. All instances of nonconforming work must be duly recorded, addressed and managed. Essentially, nonconforming work represents a technical or analytical deviation from the specified limits.

6.93 Managing nonconforming work follows the same rationale as described in subsection 3.7 and can be treated under the same system, ensuring that:

- actions (including the halting or repeating of work and withholding of reports, as necessary) are based upon the risk levels established for the affected activity;
- an evaluation is made of the significance of the nonconforming work, including an analysis of the impact on previous results;
- a decision is taken on the acceptability of the nonconforming work;
- where necessary, the customer is notified, and work is recalled;
- the responsibility for authorizing the resumption of work is defined.

6.94 Records of the nonconforming work are retained, as well as all defined actions.

6.95 Corrective actions (see subsection 3.7) should be implemented if the evaluation indicates that there is a possibility that the nonconforming work could recur or there is a doubt about the conformity with the QMS.

6.96 Analysis of the data obtained from nonconforming work should be performed, addressing specifically those issues for which a trend is observed throughout time (for example a systematic nonconforming work obtained for the same testing method, which may indicate a possible cause when trend analysis is performed). The results from this analysis and possible impacts on the identified risks and opportunities should be reviewed periodically (see subsection 3.10), and an assessment should be made of the impact of the nonconforming work on the reported results.

6.12 Retained samples

- 6.97 Samples should be retained (see subsection 6.2) as required by legislation or by the originator of the request for analysis (24).
- 6.98 The minimum amount of sample to be delivered for testing to the laboratory should be communicated to the authority, the manufacturer or the person responsible for sampling. There should be a sufficient amount of retained sample to allow at least two reanalyses.
- 6.99 The retained sample should be contained in its original packaging.
- 6.100 Sample disposal criteria should be established, according to national legislation or applicable international recommendations, or, if required, by the originator of the request for analysis.

7. Safety rules

- 7.1 Environmental health and safety policies should be followed to protect the staff, the public and the environment. A documented laboratory safety policy, which should include general and specific safety instructions reflecting identified risk, should be available to and applied by each member of staff. A staff member should be given the responsibility of overseeing the policy and ensuring compliance by all staff.
- 7.2 A waste management system conforming to local legislation should be in place to ensure the safe disposal of chemicals, solvents and other relevant materials.
- 7.3 General and specific safety procedures reflecting identified risk should be made available to each staff member. Seminars on safety-related issues should be held at predefined intervals, as specified in QMS documentation.
- 7.4 General rules for safe working should be included in standard operating procedures in accordance with national regulations and normally include the following requirements.
- Safety data sheets should be available to staff before testing is carried out.
 - Smoking, eating and drinking in the laboratory should be prohibited.
 - Staff should be familiar with the use of firefighting equipment, including fire extinguishers, fire blankets and gas masks.
 - Staff should wear laboratory coats or other suitable protective clothing, as required, including eye protection.
 - Special care should be taken, as appropriate, in handling highly potent, infectious or volatile substances.

- Highly toxic or genotoxic samples should be handled in a specially designed facility to avoid the risk of contamination.
 - All containers of chemicals should be appropriately labelled and include prominent warnings (for example, “poison”, “flammable”, “radioactive”), whenever appropriate.
 - Adequate insulation and spark-proofing should be provided for electrical wiring and equipment, including refrigerators.
 - Rules on the safe handling of cylinders of compressed gases should be observed and staff should be familiar with the relevant colour identification codes.
 - Staff should not work alone in the laboratory.
 - First-aid materials should be provided, and staff instructed in first-aid techniques, emergency care and the use of antidotes.
- 7.5 Protective clothing should be available, including eye protection, masks and gloves, and should be fit for purpose. Safety showers (eyes and full body) should be installed at a suitable location and should be fit for purpose. Rubber suction bulbs should be used on manual pipettes and siphons. Staff should be instructed in the safe handling of glassware, corrosive reagents and solvents, including the use of safety containers or baskets to avoid spillage from containers. Warnings, precautions and instructions should be incorporated, when appropriate, in standard operating procedures for work with violent, uncontrollable or dangerous reactions when handling specific reagents (for example, mixing water and acids or acetone–chloroform and ammonia), flammable products, and oxidizing or radioactive agents. Peroxide-free solvents should be used. Staff should be aware of methods for the safe disposal of unwanted corrosive or dangerous products by neutralization or deactivation and of the need for safe and complete disposal of mercury and its salts.
- 7.6 A standard operating procedure for the storage and handling of controlled substances complying with applicable national legislation should be available and enforced.
- 7.7 Poisonous or hazardous products should be identified, labelled appropriately and kept separately from other products.
- 7.8 Unnecessary contact with reagents, especially solvents and their vapours, should be avoided. The use of known carcinogens and mutagens as reagents should be limited or totally excluded.
- 7.9 Replacement of toxic solvents and reagents with less toxic materials or reduction of their use should always be the aim, particularly when new techniques are developed and validated.

References

1. WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. WHO Technical Report Series No. 986, Annex 2. Geneva: World Health Organization; 2014 (<https://apps.who.int/iris/rest/bitstreams/516100/retrieve>, accessed 15 January 2024).
2. ISO/IEC 17025. General requirements for the competence of testing and calibration laboratories. Geneva: International Organization for Standardization; 2017.
3. WHO good practices for pharmaceutical microbiology laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. WHO Technical Report Series No. 961, Annex 2. Geneva: World Health Organization; 2011 (<https://apps.who.int/iris/rest/bitstreams/52428/retrieve>, accessed 15 January 2024).
4. Guideline on data integrity. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fifth report. WHO Technical Report Series No. 1033, Annex 4. Geneva: World Health Organization; 2021 (<https://apps.who.int/iris/rest/bitstreams/1337931/retrieve>, accessed 16 January 2024).
5. Management of documents and records: guideline for OMCLs. General European Official Medicines Control Laboratories (OMCL) Network (GEON): Quality Management Document PA/PH/OMCL (14) 19 R9. European Directorate for the Quality of Medicines & HealthCare; 2016 (<https://www.edqm.eu/documents/52006/287801/Guideline+on+Management+of+Documents+and+Records.pdf/f14de606-8228-57cc-56a4-0f18e8e53511?t=1648127848657>, accessed 16 January 2024).
6. WHO good manufacturing practices: guidelines on validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. WHO Technical Report Series No. 1019, Annex 3. Geneva: World Health Organization; 2019 (<https://apps.who.int/iris/rest/bitstreams/1217390/retrieve>, accessed 16 January 2024).
7. Good automated manufacturing practice (GAMP) good practice guides: validation of laboratory computerized systems. International Society for Pharmaceutical Engineering (ISPE); 2005.
8. Application of good laboratory practice principles to computerised systems. Paris: Organisation for Economic Co-operation and Development; 2016.
9. Good automated manufacturing practice (GAMP) good practice guides: electronic data archiving. International Society for Pharmaceutical Engineering (ISPE); 2007.
10. Guidance for industry. Part 11: Electronic records: electronic signatures – scope and application. Rockville, MD: United States Food and Drugs Administration; 2003 (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/part-11-electronic-records-electronic-signatures-scope-and-application>, accessed 16 January 2024).
11. Volume 4: Good manufacturing practice: medicinal products for human and veterinary use. Annex 11: Computerised systems. In: EudraLex: The Rules Governing Medicinal Products in the European Union. European Commission; 2011 (https://health.ec.europa.eu/document/download/8d305550-dd22-4dad-8463-2ddb4a1345f1_en?filename=annex11_01-2011_en.pdf, accessed 16 January 2024).
12. Validation of computerized systems. General European Official Medicines Control Laboratories (OMCL) Network (GEON): Quality Management Document PA/PH/OMCL (08) 69 R7. European Directorate for the Quality of Medicines & HealthCare; 2016 (<https://www.edqm.eu/documents/52006/128968/guidelines-omcl-computerised-systems-core-document-march2018.pdf/d219100d-db90-2907-4a7a-3966a93e32b4?t=1628491794338>, accessed 16 January 2024).

13. WHO guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. WHO Technical Report Series No. 981, Annex 2. Geneva: World Health Organization; 2013 (<https://apps.who.int/iris/rest/bitstreams/285925/retrieve>, accessed 16 January 2024).
14. Qualification of equipment: core document. General European Official Medicines Control Laboratories (OMCL) Network (GEON): Quality Management Document PA/PH/OMCL (08) 73 R5. European Directorate for the Quality of Medicines & HealthCare; 1999 (<https://www.edqm.eu/documents/52006/128968/omcl-qualification-of-equipment-core-document-paphomcl-08-73-r5.pdf/6c9934e0-035a-8b28-5d26-a5c525371044?t=1628491788296>, accessed 17 January 2024).
15. General chapter on analytical instrument qualification. Rockville, MD: United States Pharmacopeia; 2020.
16. Bedson P, Sargent M. The development and application of guidance on equipment qualification of analytical instruments. Accreditation Qual Assur. 1996;1:265–74. doi:10.1007/s007690050083.
17. The International Pharmacopoeia, 11th edition. Geneva: World Health Organization; 2023 (<https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/international-pharmacopoeia>, accessed 13 January 2024).
18. Management of reagents. General European Official Medicines Control Laboratories (OMCL) Network (GEON): Quality Management Document PA/PH/OMCL (11) 157 R8. European Directorate for the Quality of Medicines & HealthCare; 2012 (<https://www.edqm.eu/documents/52006/287801/Management+of+Reagents.pdf/1fe2e770-5d93-21f7-942a-410e24a77a65?t=1638795768493>, accessed 17 January 2024).
19. General guidelines for the establishment, maintenance and distribution of chemical reference substances. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-first report. WHO Technical Report Series No. 943, Annex 3. Geneva: World Health Organization; 2007 (<https://apps.who.int/iris/rest/bitstreams/51819/retrieve>, accessed 17 January 2024).
20. WHO guidelines for sampling of pharmaceutical products and related materials. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-ninth report. WHO Technical Report Series No. 929, Annex 4. Geneva: World Health Organization; 2005 (<https://apps.who.int/iris/rest/bitstreams/51204/retrieve>, accessed 17 January 2024).
21. WHO guidance on testing of “suspect” falsified medicines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. WHO Technical Report Series No. 1010, Annex 5. Geneva: World Health Organization; 2018 (<https://apps.who.int/iris/rest/bitstreams/1136504/retrieve>, accessed 17 January 2024).
22. Good chromatography practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. WHO Technical Report Series No. 1025, Annex 4. Geneva: World Health Organization; 2020 (<https://www.who.int/publications/m/item/trs1025-annex4>, accessed 11 January 2024).
23. Center for Drug Evaluation and Research. Guidance for industry: investigating out-of-specification test results for pharmaceutical production. Rockville, MD: United States Food and Drug Administration; 2006 (<https://www.fda.gov/media/71001/download>, accessed 18 January 2024).
24. Management of samples. General European Official Medicines Control Laboratories (OMCL) Network (GEON): Quality Management Document PA/PH/OMCL(16) 89 R2. European Directorate for the Quality of Medicines & HealthCare; 2012 (<https://www.edqm.eu/documents/52006/128968/omcl-quality-management-document-management-of-samples.pdf/2aaac092-9831-0e01-3972-5634b307c325?t=1628491789121>, accessed 18 January 2024).

Appendix 1

Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory

A list of equipment considered by the Expert Committee to be adequate, either for a first-stage or medium-sized pharmaceutical quality control laboratory, is given in Table 1.

This list does not represent any requirements that should be fulfilled to comply with these guidelines. National medicines regulatory authorities (NMRAs) or laboratories wishing to perform pharmaceutical analyses may consider the following list in the establishment or upgrading of their testing facilities. For budgetary reasons it is necessary, besides the cost of equipment, to take into consideration the cost of reference materials, reagents, solvents, glassware, other laboratory commodities and personnel. Experience has shown that, for sustainability, a laboratory should allow a margin of 10–15% per year of the purchasing expenditure on equipment to cover the cost of maintenance.

Table 1
Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory

First-stage laboratory	
Equipment and major instruments	Quantity
Top-loading balance	1
Analytical balance (5 digits)	1 or 2
Melting-point apparatus	1
pH meter (with assorted electrodes)	1
Microscope	1
Polarimeter	1
High-performance liquid chromatograph with ultraviolet detector	2
Ultraviolet/visible spectrophotometer	1
Infrared spectrophotometer with pellet press	1
Karl Fischer titrator (semi-micro determination of water)	1
Agate mortar with pestle	1

First-stage laboratory <i>(continued)</i>	
Equipment and major instruments	Quantity
Equipment for thin-layer chromatography	1
Temperature and humidity probe	1
Thin-layer chromatography spotter	1
Developing chambers	6 + 1 ^a
Atomizers	6
Ultraviolet viewing lamp	1
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution apparatus	1
Soxhlet extraction apparatus (60 mL)	3 + 1 ^a
Micrometer calipers	1
Pycnometers	2
Burettes/pipettes (10 mL and 25 mL/1, 2, 5, 10, 20, 25, 50 mL)	3 of each
Desiccator	1 + 1 ^a
Centrifuge (table-top model, 4-place swing rotor)	1
Water bath (20 litres)	1
Hot plates with magnetic stirrers	3
Vacuum pump (rotary, oil)	1
Drying oven (60 litres)	1
Vacuum oven (17 litres)	1
Muffle furnace	1
Refrigerator (explosion-proof)	1
Water distilling apparatus (8 litres/hour)	1
Water deionizer (10 litres/hour)	1
Dehumidifier (where needed)	1
Fume hood	1

First-stage laboratory <i>(continued)</i>	
Optional items	Quantity
Analytical microbalance	1
Flame photometer (including air compressor)	1
Refractometer	1
Viscometer	1
Vortex mixer	1
Shaker (wrist-action)	1
Pipette rinser	1
Constant temperature water bath	1
Ultrasonic cleaner (5 litres)	1
Medium-sized laboratory	
Equipment and major instruments	
Top-loading balance	1 or 2
Analytical balance (5 digits)	2
Analytical microbalance	1
Microscope	1 or 2
Equipment for thin-layer chromatography	1
Thin-layer chromatography multispotter	1
Developing chambers	6
Atomizers	6
Ultraviolet viewing lamp	1
Temperature and humidity probe	2
Potentiometric titrimer	1
Micro Kjeldahl equipment (including fume flasks)	1
Soxhlet extraction apparatus (60 mL)	3
Densimeter, combined with viscometer	1
Burettes/pipettes (10 mL and 25 mL/1, 2, 5, 10, 20, 25, 50 mL)	6 of each
Micrometer calipers	1

Medium-sized laboratory (continued)	
Equipment and major instruments	Quantity
Heating mantles for flasks (assorted sizes: 50, 200 and 2000 mL)	6
Sieves (assorted sizes)	1 set
Centrifuge (floor model)	1
Shaker (wrist-action)	1
Vortex mixers	2
Water bath (electrical, 20 litres)	2 or 3
Hot plates with magnetic stirrers	3 or 4
Vacuum pump (rotary, oil)	2
Vacuum rotary evaporator	1
Drying oven (60 litres)	2 or 3
Muffle furnace (23 litres)	1
Vacuum oven (17 litres)	1
Desiccators	2
Refrigerator (explosion-proof)	2
Freezer	1
Ultrasonic cleaners (5 litres)	2
Laboratory glassware washing machine	1
Water distilling apparatus (8 litres/hour)	1
Water deionizing equipment (10 litres/hour)	1
Fume hoods	2
Melting-point apparatus	1
Polarimeter	1
pH meters (with assorted electrodes)	2
High-performance liquid chromatograph with variable wavelength:	
Ultraviolet/visible detector	2 or 3
Ultraviolet/visible spectrophotometer, double-beam	1
Diode array	1 or 2

Medium-sized laboratory (<i>continued</i>)	
Equipment and major instruments	Quantity
Infrared spectrophotometer (MIR, NIR) with pellet press	1
Agate mortar with pestle	1
Gas chromatograph (flame ionization, direct and static head space injection)	1
Karl Fischer titrators (1 semi-micro and 1 coulometric for microdetermination of water)	2
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution test equipment (for 6 tablets/capsules)	1
Oxygen flask combustion apparatus	1
Optional items	
Refractometer	1
Atomic absorption spectrophotometer (flame, furnace)	1
Spectrofluorometer	1
High-performance liquid chromatograph detectors:	1
Fluorescence	1
Mass spectrometric (MS)	1
Evaporative light scattering (ELSD)	1
Charged aerosol (CAD)	1
Refractive index	1
Gas chromatograph detectors:	1
Electron capture detector (ECD)	1
Nitrogen/phosphorous (NPD)	1
Mass spectrometric (MS)	1
Capillary electrophoresis equipment	1
Thin-layer chromatography scanner	1
Hardness tester	1
Friability tester	1

Medium-sized laboratory (continued)	
Optional items	Quantity
Ice machine	1
Solvent recovery apparatus	1
Equipment for microbiology unit	
pH meter	1
Ultraviolet/visible spectrophotometer, single-beam	1
Microscopes (for bacteriology)	1
Membrane filter assembly for sterility tests	2
Colony counter with magnifier	1
Laminar air flow unit	1
Hot-air sterilizer	1
Incubators, 60 litres	1
Anaerobic jar	2 or 3
Zone reader	1
Centrifuge	1
Water bath (thermostatically controlled)	1
Autoclaves (100 litres, top-loading)	2
Refrigerators (340 litres)	2
Deep freeze	2
Laboratory glassware washing machine	1
Equipment for pharmacognosy/phytochemistry unit	
Grinder/mill (for preparation of sample of herbal materials)	1
Top-loading balance	1
Sieves	1
Microscope ^b	1 set
Soxhlet extraction apparatus	1
Water bath	2 or 3
Heating mantles for flasks	1

Equipment for pharmacognosy/phytochemistry unit (<i>continued</i>)	
	Quantity
Hot plates with magnetic stirrers	1 or 2
Equipment for thin-layer chromatography	2
Developing chambers	1 or 2
Desiccators	3 or 4
Rotary vacuum apparatus	2
Distillation equipment	1
Conical percolators	1
Apparatus for determination of water content by azeotropic method ^b	2 or 3
Apparatus for determination of volatile oils ^b	1
Apparatus for determination of arsenic limit test ^c	1

^a Needed in the case that herbal medicines are also tested.

^b Quality control methods for herbal materials. Geneva: World Health Organization; 2011 (https://apps.who.int/iris/bitstream/handle/10665/44479/9789241500739_eng.pdf?sequence=1, accessed 19 January 2024).

^c WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues. Geneva: World Health Organization; 2006 (https://apps.who.int/iris/bitstream/handle/10665/43510/9789241594448_eng.pdf?sequence=1&isAllowed=y, accessed 19 January 2024).

Appendix 2

Recommendations for the target uncertainty and the maximum permissible uncertainty for normal analytical practice

To effectively apply the concept of uncertainty to compliance testing in the pharmaceutical sector, the following key recommendations should be formulated (see subsection 6.7):

- recommendations for the target uncertainty for pharmacopoeial tests;
- recommendations for the maximum permissible uncertainty for standard analytical operations (recommendations for normal analytical practice).

Recommendations for the target uncertainty for pharmacopoeial tests

To assess the risk of making an incorrect decision on compliance, the estimated uncertainty (U^{est}) should be compared with the target uncertainty (U^g).

For the assay of an API or excipient, the minimum value of measurement uncertainty usually comprises (1–3):

- 1.0% for volumetric titration of the conjugate acids, non-aqueous and acid–base titrations;
- 1.5% for redox and argentometric titrations;
- 2.0% for complexometric titrations;
- 2.0% and 3.0% for ultraviolet spectrophotometry assays, using the reference substance and specific absorbance, respectively;
- 2.0% for liquid chromatographic assays.

U^g is an expanded uncertainty, expressed as a 90% two-sided confidence interval, which is equivalent to a 95% one-sided confidence interval.

The minimum value of U^g corresponds to the minimum width of content limits for assay. Therefore, the minimum value of $U^g = 2.0\%$ means that the metrologically correct content limits should not be narrower than 98–102%.

For finished pharmaceutical products, the following requirements for U^g can usually be applied (4).

- For assay, the target uncertainty should be insignificant compared to the half-width of the symmetrical two-sided content limits, $U^g = (UCL - LCL)/2 \times 0.32$, where UCL and LCL are upper and lower content limits, respectively.

- For assay with a one-sided content limit (known as “not less than ...”), $U^{lg} = 6.4\%$. This requirement can also be applied to APIs and excipients with a one-sided content limit.
- For tests for dissolution and uniformity of dosage units, $U^{lg} = 3.0\%$.
- For related impurities and residual solvents, $U^{lg} = 16.0\%$ (the found quantity of impurity is used only for comparison with the specification limit). This requirement can also be applied to APIs or excipients.

Recommendations for the maximum permissible uncertainty for normal analytical practice

The approach of normal (routine) analytical practice (NAP) establishes the maximum permissible level of uncertainty from standard analytical operations (U_i^{lg}) U^{lg} and reflects the minimum pharmacopoeial requirements that should be met by all laboratories performing compliance testing (see subsection 6.7). Adherence to NAP is assumed when performing analytical procedures outlined in monographs (5–7) and marketing authorization documentation (8).

Currently, most of the analytical procedures described in pharmacopoeias and marketing authorization documentation have been validated without the use of the concept of uncertainty; hence, without considering that when the procedures are reproduced in another laboratory, the actual uncertainty of the analytical result (in practice, the estimated uncertainty, or U^{est}) can be as large as the maximum permissible value (NAP recommendations), which can be greater than that achieved during the analytical procedure development or validation. Therefore, some sources of variation, which may become significant when reproducing the analytical procedure in another laboratory, may not be accounted for, since they were insignificant in the developer's laboratory (and in the interlaboratory trials for pharmacopoeial analytical procedures).

Thus, the classic approach to quality assurance does not consider the “worst case”, that is, when the laboratory meets the NAP recommendations minimally, which may result in approving metrologically incorrect analytical procedures for which reproducibility problems may occur with an unacceptably high risk.

To control the risk of obtaining an unacceptably large value of U^{est} , it is reasonable to carry out the bottom-up evaluation of measurement uncertainty during the development of a procedure based on the NAP recommendations (that is, perform an uncertainty estimation for the “worst case”). If the uncertainty estimated for the worst case (U^{NAP}) exceeds U^{lg} , then there is a high risk that U^{est} will also exceed U^{lg} when reproducing the procedure, and the laboratory will not be able to make a conclusive decision on compliance. In such a case the analytical procedure needs optimization of measurements and sample preparation steps.

Here and below, measurement uncertainty is an expanded uncertainty, expressed as a 90% two-sided confidence interval, which is equivalent to a 95% one-sided confidence interval.

Typically, variability sources can be divided into measurement related (for example, random variability of an analytical signal) and associated with sample preparation operations (weighing, dilution).

The requirements for the maximum permissible uncertainty (target uncertainty) for standardized analytical operations (NAP recommendations – U_i^{tg}) may be specified directly in the analytical procedure (as a requirement for the suitability of the analytical system) or other regulations (for example, as a requirement for the qualification of analytical equipment in the pharmacopoeias).

The example of a variability source for which U_i^{tg} is harmonized between pharmacopoeias is the random variability of the analytical signal for assay by separation technique of an API (or excipient) where the value is 100% for a pure substance (2, 9, 10). This approach assumes that random variability from the analytical signal is the main component of uncertainty associated with measurements. Requirements for the maximum permitted relative standard deviation ($\%RSD_{max}$) for the given assay upper content limits are set so that a 90% two-sided confidence interval (equal to a 95% one-sided interval), calculated for the uncertainty component of the analysis result related to the precision of measurements, does not exceed 0.5 of U_i^{tg} .

The recommendations for $\%RSD_{max}$ for assay by separation technique for finished pharmaceutical products with symmetrical assay content limits are shown in Table 1 (11). These requirements are set so that a 95% one-sided confidence interval calculated for the uncertainty component of the analysis result related to the precision of measurements does not exceed U_i^{tg} . It is recommended that U_i^{tg} for finished pharmaceutical preparations should comprise not more than 0.32 of the half-width of symmetrical content limits.

Table 1

Requirements for maximum permitted relative standard deviation ($\%RSD_{max}$) of the analytical signal for assay by separation technique for finished pharmaceutical products with symmetrical assay content limits

	Number of individual injections n^a						
	2	3	4	5	6	7	8
(UCL – LCL)/2 ^b	$\%RSD_{max}$						
5	0.25	0.67	0.96	1.19	1.38	1.54	1.69
7.5	0.38	1.01	1.44	1.78	2.06	2.31	2.53
10	0.51	1.34	1.92	2.37	2.75	3.08	3.38
15	0.76	2.01	2.88	3.56	4.13	4.62	5.07
20	1.01	2.68	3.85	4.75	5.50	6.16	6.76

^a Assuming that the same number of repetitive injections is made for the test and reference solutions.

^b UCL and LCL are upper and lower content limits, respectively, expressed in per cent in relation to the nominal content value.

For spectrophotometric assays the next recommendations can be used as NAP recommendations (12):

- for a series of measurements of the absorbance with cuvette withdrawal
RSD $\leq 0.52\%$;
- not less than three measurements for the test and reference solutions.

NAP recommendations for individual operations with volumetric glassware ISO class A are shown in Tables 2–4 (1, 4). It should be noted that these estimates of uncertainty exceed the maximum permissible deviation from the nominal volume under the requirements for ISO class A volumetric glassware, as the NAP recommendations additionally account for the random variability introduced by the analyst in routine analysis.

Table 2

Target uncertainties typical of NAP due to the use of volumetric flasks ISO class A of different volumes

Volumetric flask volume, mL	Target uncertainty, mL	Target uncertainty, %
10	0.05	0.50
20	0.057	0.28
25	0.0575	0.23
50	0.085	0.17
100	0.12	0.12
200	0.20	0.10
250	0.20	0.08
500	0.35	0.07
1000	0.50	0.05

Table 3

Target uncertainties typical of NAP due to the use of transfer pipettes ISO class A of various volumes

Transfer pipette volume, mL	Target uncertainty, mL	Target uncertainty, %
1.0	0.010	0.98
2.0	0.012	0.61

Table 3 *continued*

Transfer pipette volume, mL	Target uncertainty, mL	Target uncertainty, %
5.0	0.018	0.37
10.0	0.025	0.25
20.0	0.037	0.18
25.0	0.037	0.15
50.0	0.061	0.12

Table 4

Target uncertainties typical of NAP due to the use of graduated pipettes ISO class A of different volumes

Graduated pipette volume, mL	Target uncertainty, mL	Target uncertainty, % ^a
0.5	0.0061	1.23
1.0	0.0074	0.74
2.0	0.012	0.62
5.0	0.037	0.74
10.0	0.062	0.62
25.0	0.123	0.49

^a Indicated in relation to the total volume of the pipette.

For weighing operations, it is recommended to use $U^g = 0.2$ mg as the NAP recommendation (1, 4). This recommendation reflects typical minimum requirements for balances in NQCLs.

If the NQCL has a balance of a higher class, then to estimate uncertainty in line with NAP recommendations when reproducing the analytical procedure, it becomes essential to employ a criterion for the balance qualification (maximum permissible uncertainty).

For the initial reproduction of the analytical procedure in an NQCL, it is advisable to use the bottom-up approach for the uncertainty estimation as per the NAP recommendations. The text of the procedure and a priori knowledge of the analytical technique indicate the significant sources of variability.

Often the risk of obtaining an unacceptably large U^{est} can be mitigated by increasing the accuracy of the concentration of the test and reference solutions. This

can be achieved by increasing the test portions or volumes of the volumetric glassware used, without changing the final concentration of the test and reference solutions. Such an adjustment of the approved analytical procedure is allowed by pharmacopoeial practice (13).

However, the actual uncertainty in a particular NQCL may be greater than the NAP recommendations. Therefore, it is necessary to confirm experimentally that actual uncertainties from variability sources regulated by NAP do not exceed the recommended value of U_i^{95} during the real analysis. That is, the uncertainty estimation for the “worst case” (NAP recommendation) does not override the estimation of uncertainty in the laboratory, as described, for example, in (8).

An example of the uncertainty estimation based on NAP recommendations for chromatographic assays of an API is provided in Appendix 3.

References

1. Technical guide for the elaboration of monographs. Strasbourg: European Directorate for the Quality of Medicines & HealthCare, Council of Europe; 2022.
2. 2.2.46. Chromatographic separation techniques. In: The European Pharmacopoeia, 11th edition. Strasbourg: European Directorate for the Quality of Medicines & HealthCare, Council of Europe; 2022.
3. Daas AG, Miller JHM. Content limits in the European Pharmacopoeia (Part 2). *Pharmeuropa*. 1998;10(1):137–46.
4. 5.3.N.2. Validation of analytical procedures and tests. In: The State Pharmacopoeia of Ukraine, second edition, Supplement 4. Kharkiv: Ukrainian Scientific Pharmacopoeial Centre for Quality of Medicines; 2020.
5. 5. General requirements. In: The International Pharmacopoeia, 11th edition. Geneva: World Health Organization; 2023 (<https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/international-pharmacopoeia>, accessed 13 January 2024).
6. 1.5.1.9. Tests and assays. In: The European Pharmacopoeia, 11th edition. Strasbourg: European Directorate for the Quality of Medicines & HealthCare, Council of Europe; 2022.
7. General notices and requirements. In: The United States Pharmacopeia, 43rd edition. Rockville, MD: United States Pharmacopeia Convention; 2023.
8. Evaluation of measurement uncertainty: core document. General European Official Medicines Control Laboratories (OMCL) Network (GEON): Quality Management Document PA/PH/OMCL (18) 145 R1 CORR. European Directorate for the Quality of Medicines & HealthCare; 2019 (<https://www.edqm.eu/documents/52006/128968/omcl-evaluation-of-measurement-uncertainty-core-document.pdf/b9b88e44-e831-4221-9926-d8c6e8afe796?t=1628491784923>, accessed 13 January 2024).
9. 1.14.1. Chromatography. In: The International Pharmacopoeia, 11th edition. Geneva: World Health Organization; 2023 (<https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/international-pharmacopoeia>, accessed 13 January 2024).

10. General chapter: 621. Chromatography. In: The United States Pharmacopeia, 43rd edition. Rockville, MD: United States Pharmacopeia Convention; 2022.
11. 2.2.46. Chromatographic separation techniques. In: The State Pharmacopoeia of Ukraine, second edition, Supplement 2. Kharkiv: Ukrainian Scientific Pharmacopoeial Centre for Quality of Medicines; 2018.
12. 2.2.25N. Absorption spectrophotometry, ultraviolet and visible. In: The State Pharmacopoeia of Ukraine, second edition, Supplement 5. Kharkiv: Ukrainian Scientific Pharmacopoeial Centre for Quality of Medicines; 2021.
13. 6.50.20.1. Adjustments to solutions. In: The United States Pharmacopeia, 43rd edition. Rockville, MD: The United States Pharmacopeia Convention; 2022.

Appendix 3

Examples of the uncertainty estimation for compliance with normal analytical practice (the “worst case”) for assay of pharmaceutical substances by chromatography

The pharmacopoeias state that the normal (routine) analytical practice (NAP) or (routine) analytical errors are considered in pharmacopoeial acceptance criteria (1–3). This means that the laboratory can reproduce a pharmacopoeial analytical procedure only if the actual uncertainty for the standard analytical operations (NAP operations) does not exceed that accounted for in the specifications. The same statement is correct regarding analytical procedures from marketing authorization because, here, the same decision rule is used (hence, the same approach to the construction of criteria) (4).

The recommendations for the permissible uncertainty associated with standard analytical operations can be found in the *European Pharmacopoeia* (5), Table 1, and the *State Pharmacopoeia of Ukraine* (6). The recommendations for maximum permissible uncertainty for standard analytical operations in a routine analysis (sample preparation – weighing and dilution using volumetric glassware ISO class A, and measurements) are given in Appendix 2.

The uncertainty estimation for the case of minimum compliance with NAP (the “worst case”) is based on the text of the analytical procedure without the use of any experimental data. This allows the developer to optimize the text of the analytical procedure before its approval or the reproduction of an already approved procedure in the laboratory (to reduce the uncertainty of the preparation of solutions or measurements). This enables mitigation of the risk of obtaining an unacceptably large actual value of uncertainty, which could lead to inconclusive decisions on compliance during the reproduction of an analytical procedure.

It is important to highlight that when estimating uncertainty for NAP compliance (for the “worst case” scenario), the resulting uncertainty estimation applies universally to any laboratory required to meet pharmacopoeial requirements. Conversely, the general procedure for estimating uncertainty aims to provide a real estimation of uncertainty within a specific laboratory environment, which may vary for different laboratories performing the same analytical procedure. The uncertainty estimation for NAP compliance should not be considered a substitute for the generally accepted practice of individual uncertainty estimation in each laboratory to determine the actual uncertainty.

The uncertainty estimation for NAP compliance is based on the premise that:

- the significant sources of variation are usually identified in the text of the analytical procedure (primarily, they follow from the calculation formula).

Such sources of variation are present in any laboratory and, therefore, need to be standardized and controlled;

- “unexpected” and non-standardized sources of variation (such as incomplete analyte extraction during sample preparation, or interference of excipients with measurements) are absent or insignificant. This should be ensured at the development and validation stages of the analytical procedure.

The purpose of uncertainty estimation for the case of NAP compliance is to calculate the expanded uncertainty for a reportable result (combined uncertainty) based on the maximum permissible uncertainties (according to the NAP) for standard analytical operations (given in Appendix 2). The rules for combined uncertainty estimation are determined by how the parameters that are sources of variation are included in the calculation formula for the reportable result (X). It is supposed that all sources of variability are independent, and there is no correlation between them.

Here and below, measurement uncertainty is an expanded uncertainty expressed as a 90% two-sided confidence interval, which is equivalent to a 95% one-sided confidence interval.

Sources of uncertainty for the assay can be grouped as follows: (group 1) measurement uncertainty (U_{Meas}); (group 2) sample preparation uncertainty (U_{SP}), which is subdivided into (group 2.1) weighing uncertainty ($U_{m,i}$) and (group 2.2) dilutions uncertainty ($U_{V,i}$); and (group 3) uncertainty of the value assigned to a reference substance (U_{RS}).

The typical formula for the assay is:

$$X = \frac{r}{r_0} \times \frac{m}{m_0} \times \frac{V_{01} \times V_{02} \times V_{03} \dots V_{0n}}{V_1 \times V_2 \times V_3 \dots V_n} \times \frac{P_{RS} \%}{100\%} \times K$$

1	2		3	4
	2.1	2.2		

Where:

r and r_0 are analytical signals (peak area, peak height, or their ratio) for the test solution and the reference solution;

m and m_0 are the test portions of the test sample and reference substance;

V is the nominal volume for volumetric flasks and pipettes used for making dilutions;

P_{RS} is the analyte content in the reference substance, expressed as a percentage;

K is the coefficient for converting the concentration into a reportable result (in most cases for assay of API, $K = 1$).

All sources of variation from the calculation formula, except for U_{Meas} , are expressed as intervals (not as standard deviations). Therefore, for uncertainty estimation, it is reasonable to directly combine uncertainties from individual sources of variability as intervals without converting them to standard deviations and then back to intervals (6). This approach leads to the same uncertainty estimates as the classical approach (4).

For the assay by chromatographic methods, for a typical case, all sources of variability are reflected in the calculation formula as a product or quotient. Therefore, the combined uncertainty for X can be estimated as the square root of the sum of the squares of the partial components of the uncertainty (in this case, expressed as a percentage).

The typical sources of variability arising from measurements (group 1) and sample preparation (group 2) are standardized (Appendix 2); they are the primary focus for the uncertainty estimation for NAP compliance.

For the uncertainty estimation, it is acceptable to assume that for pharmacopoeial reference substances, U_{RS} is insignificant compared to the U^ig and may not be considered in the uncertainty estimation. The U_{RS} is insignificant for any pharmacopoeial applications if it does not exceed 0.5% (7).

1. An example of uncertainty estimation for NAP compliance for a chromatographic assay of API

For metrologically correct analytical procedures for a chromatographic assay of API, the upper content limit is not less than 102.0%; therefore, $U^ig = 2.0\%$ (Appendix 2).

Uncertainty for the analytical signal. Following the harmonized approach (8), the uncertainty for the analytical signal (U_{Meas}^ig) is (Appendix 2):

$$U_{Meas}^ig = 0.5 \times U^ig = 0.5 \times 2.0\% = 1.0\%.$$

Sample preparation uncertainty. It is rational to make requirements that the combined uncertainty of sample preparation (U_{SP}^ig) also be not more than 0.5 of U^ig :

$$U_{SP}^ig = 0.5 \times U^ig = 0.5 \times 2.0\% = 1.0\%.$$

2. An example of the analytical procedure for which an uncertainty estimation for NAP compliance is made

An amount of 50.0 mg of the substance being tested (m) or reference substance (m_0) is dissolved in the diluent and diluted to 50.0 mL (V_1 and V_{01}). Then, 1.0 mL of this solution (V_2 and V_{02}) is diluted to 10.0 mL (V_3 and V_{03}).

The calculation formula for the substance content in % w/w (without calculation to dry/volatile solvent-free substance) is as follows:

$$X = \frac{r}{r_0} \times \frac{m}{m_0} \times \frac{V_{01} \times V_{02}}{V_1 \times V_2} \times \frac{P_{RS} \%}{100\%}.$$

Uncertainty related to the sources of variation during sample preparation (group 2) is estimated as in Table 1.

Table 1
Uncertainty related to the sources of variation during sample preparation

Variability sources	Associated expanded uncertainty (%)
Test solution	
1. Taking a test portion of 50.0 mg of the substance being tested	$= 0.2 \text{ mg}^a/50\text{mg} \times 100\% = 0.4\%$
2. Dilution to 50.0 mL (V_1)	0.17% ^b
3. Taking an aliquot of 1.0 mL (V_2)	0.74% ^c
4. Dilution to 10.0 mL (V_3)	0.50% ^b
Reference solution	
5. Taking a test portion of 50.0 mg of reference substance	$= 0.2 \text{ mg}^a/50 \text{ mg} \times 100\% = 0.4\%$
6. Dilution to 50.0 mL (V_{01})	0.17% ^b
7. Taking an aliquot of 1.0 mL (V_{02})	0.74% ^c
8. Dilution to 10.0 mL (V_{03})	0.50% ^b

^a 0.2 mg is the recommended target uncertainty for the weighing operation (normal analytical practice recommendation, Appendix 2).

^b Appendix 2, Table 2.

^c Appendix 2, Table 4.

In this case, it is better to use a graduated pipette of 1.0 mL because formally it assures lower uncertainty than a transfer pipette of 1.0 mL.

The uncertainty for sample preparation according to NAP recommendations (U_{SP}^{ig}) can be estimated as follows:

$$U_{SP}^{ig} = \sqrt{(0.4^2 + 0.17^2 + 0.74^2 + 0.5^2) \times 2} = 1.40\%.$$

U_{SP}^{ig} exceeds critical value $U_{SP}^{ig} = 1.0\%$; therefore, this analytical procedure creates an unacceptably high risk of obtaining too high uncertainty of X at reproduction of this

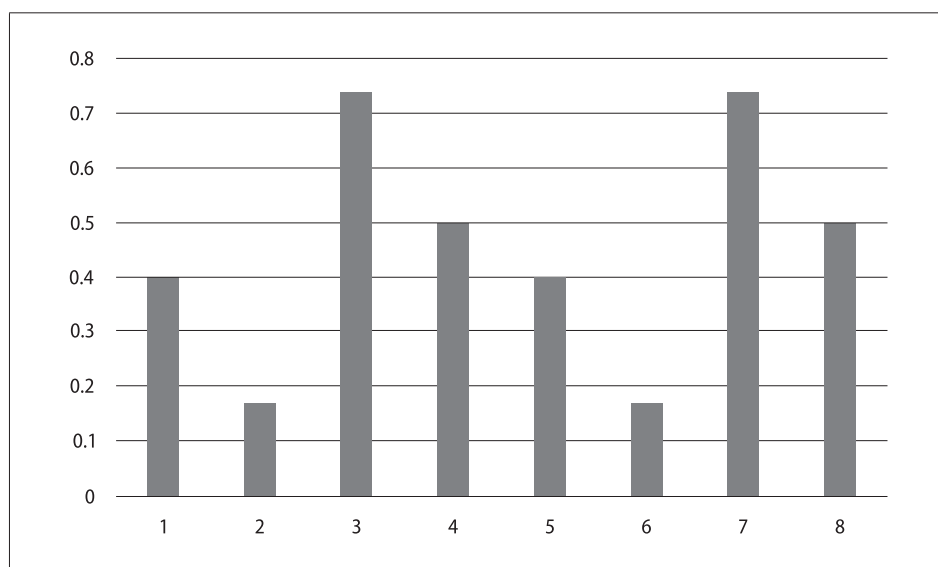
analytical procedure in a laboratory, which complies with pharmacopoeial requirements at the minimum level (NAP recommendations).

It is recommended to optimize the accuracy of the test and reference solutions preparation.

The efficacy of sample preparation can be visualized as in Fig. 1: the x-axis shows the number of the sample preparation operation (numbers 1–8); the y-axis shows associated uncertainty (%).

Fig. 1

Relative contribution of the uncertainty of sample preparation operations (1)



The uncertainty estimates tend to decrease and converge with the optimization of the sources of variation.

Operations of the second dilution, numbers 3 and 7 (taking an aliquot of 1.0 mL) need optimization first, and then operations numbers 4 and 8 (dilution to 10.0 mL).

Using glassware of standard volumes, the modification of the second dilution without changing the final concentration can be proposed as follows: 5.0 mL of solution (V_2 and V_{02}) is diluted to 50.0 mL (V_3 and V_{03}).

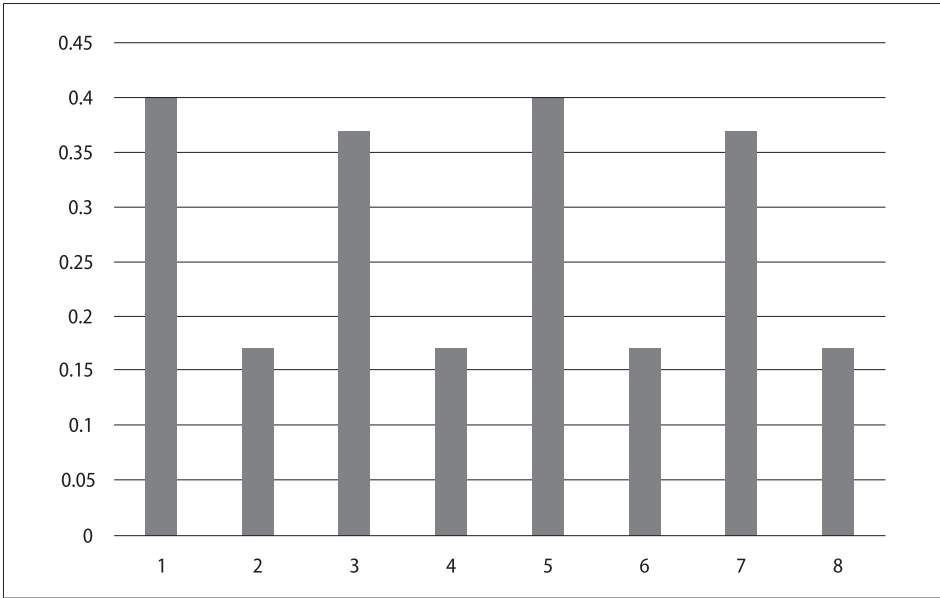
Then, the uncertainty of sample preparation operations is estimated as in Table 2.

Table 2
Uncertainty related to the sources of variation during sample preparation: second dilution

Variability sources	Associated expanded uncertainty (%)
Test solution	
3. Taking an aliquot of 5.0 mL (V_2)	0.37%
4. Dilution to 50.0 mL (V_3)	0.17%
Reference solution	
7. Taking an aliquot of 5.0 mL (V_{02})	0.37%
8. Dilution to 50.0 mL (V_{03})	0.17%

The ratio for estimated uncertainties is shown in Fig. 2.

Fig. 2
Relative contribution of the uncertainty of sample preparation operations (2)



The estimated uncertainty for sample preparation (U_{SP}^{tg}) can be calculated as follows:

$$U_{SP}^{tg} = \sqrt{(0.4^2 + 0.17^2 + 0.37^2 + 0.17^2) \times 2} = 0.84\%.$$

As can be seen, after optimizing the accuracy of the preparation of solutions, U_{SP}^g does not exceed the critical value $U_{SP}^g = 1.0\%$. Therefore, this analytical procedure does not lead to an unacceptably high risk of obtaining too high uncertainty of X and can be approved by the developer or used by NQCLs.

References

5. General requirements. In: The International Pharmacopoeia, 11th edition. Geneva: World Health Organization; 2023 (<https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/international-pharmacopoeia>, accessed 13 January 2024).
- 1.5.1.9. Tests and assays. In: The European Pharmacopoeia, 11th edition. Strasbourg: European Directorate for the Quality of Medicines & HealthCare, Council of Europe; 2022.
- General notices and requirements. In: The United States Pharmacopoeia, 43rd edition. Rockville, MD: United States Pharmacopoeia Convention; 2023.
- Evaluation of measurement uncertainty: core document. General European Official Medicines Control Laboratories (OMCL) Network (GEON): Quality Management Document PA/PH/OMCL (18) 145 R1 CORR. European Directorate for the Quality of Medicines & HealthCare; 2019 (<https://www.edqm.eu/documents/52006/128968/omcl-evaluation-of-measurement-uncertainty-core-document.pdf/b9b88e44-e831-4221-9926-d8c6e8afe796?t=1628491784923>, accessed 13 January 2024).
- Technical guide for the elaboration of monographs. Strasbourg: European Directorate for the Quality of Medicines & HealthCare, Council of Europe; 2022.
- General text 2.2.N.2. Validation of analytical procedures. In: The State Pharmacopoeia of Ukraine, second edition, Addendum 4. Kharkiv: Ukrainian Scientific Pharmacopoeial Centre for Quality of Medicines; 2020.
- 5.12.N. Reference standards. In: The State Pharmacopoeia of Ukraine, second edition. Kharkiv: Ukrainian Scientific Pharmacopoeial Centre for Quality of Medicines; 2023.
- 1.14.1. Chromatography. In: The International Pharmacopoeia, 11th edition. Geneva: World Health Organization; 2023 (<https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/international-pharmacopoeia>, accessed 13 January 2024).

11.2 WHO good practices for pharmaceutical microbiology laboratories

Annex 2, WHO Technical Report Series, 961, 2011

Background

The WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted in 2009 a revised version of the *Good practices for pharmaceutical quality control laboratories* (1).

During the inspections carried out when prequalifying laboratories, the inspectors had noticed that some of the texts of these guidelines might benefit from additional guidance, with a special focus on microbiology.

In light of the above, the Expert Committee recommended that the WHO Secretariat initiate the process of developing a new text on good practices for pharmaceutical microbiology laboratories.

The following text is proposed to cover this specific type of laboratory.

Introduction and scope of document	1661
Glossary	1661
1. Personnel	1663
2. Environment	1664
2.1 Premises	1664
2.2 Environmental monitoring in the laboratory	1665
2.3 Cleaning, disinfection and hygiene	1665
2.4 Sterility test facilities	1665
3. Validation of test methods	1667
4. Equipment	1667
4.1 Maintenance of equipment	1668
4.2 Qualification	1668
4.3 Calibration, performance verification and monitoring of use	1668
5. Reagents and culture media	1671
5.1 Reagents	1671
5.2 Media	1671
5.3 Labelling	1672
5.4 Organism resuscitation	1672

6. Reference materials and reference cultures	1673
6.1 International standards and pharmacopoeial reference substances	1673
6.2 Reference cultures	1673
7. Sampling	1674
8. Sample handling and identification	1675
9. Disposal of contaminated waste	1675
10. Quality assurance of results and quality control of performance	1676
10.1 Internal quality control	1676
11. Testing procedures	1676
12. Test reports	1676
References	1676
Further reading	1677
Appendix 1 Examples of zones in which operations could be carried out	1678
Appendix 2 Examples of maintenance of equipment	1679
Appendix 3 Examples of calibration checks and intervals for different laboratory equipment	1681
Appendix 4 Examples of equipment qualification and monitoring	1682
Appendix 5 General use of reference cultures	1684

Introduction and scope of document

Pharmaceutical microbiology laboratories may be involved in:

- sterility testing;
- detection, isolation, enumeration and identification of microorganisms (bacteria, yeast and moulds) and testing for bacterial endotoxins in different materials (e.g. starting materials, water), products, surfaces, garments and the environment; and
- assay using microorganisms as part of the test system.

These guidelines relate to all microbiology laboratories involved in the above-mentioned testing activities, whether they are independent or a department or unit of a pharmaceutical manufacturing facility.

These guidelines are based on and supplement the requirements described in *Good practices for pharmaceutical quality control laboratories* (1); *General guidelines for the establishment, maintenance and distribution of chemical reference substances. Revision* (2); *The International Pharmacopoeia*, Fourth Edition (3); First Supplement to *The International Pharmacopoeia*, Fourth Edition (4); and ISO/IEC 17025 (5).

Glossary

calibration

The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

certified reference material

Reference material, characterized by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that provides the value of the specified property, its associated uncertainty and a statement of metrological traceability.

limit of detection

The lowest number of microorganisms that can be detected, but in numbers that cannot be estimated accurately.

precision

The degree of agreement among individual results.

quantitation limit (limit of quantitation)

Applied to quantitative microbiological tests. The lowest number of microorganisms within a defined variability that may be counted under the experimental conditions of the method under evaluation.

reference cultures

Collective term for reference strain and reference stocks.

reference material

Material sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process.

reference method

A method which has been validated as being fit for purpose, with which an alternative method may be compared.

reference stocks

A set of separate identical cultures obtained by a single subculture from the reference strain (6).

reference strains

Microorganisms defined at least to the genus and species level, catalogued and described according to its characteristics and preferably stating its origin (6). Normally obtained from a recognized national or international collection.

repeatability

Closeness of the agreement between the results of successive measurements of the same measure and under the same conditions of measurement (adapted from ISO).

reproducibility

Reproducibility expresses precision between laboratories.

robustness (or ruggedness)

The ability of the procedure to provide analytical results of acceptable accuracy and precision under a variety of conditions.

sensitivity

The fraction of the total number of positive cultures or colonies correctly assigned in the presumptive inspection (7).

specificity (selectivity)

The ability of the method to detect the required range of microorganisms that might be present in the test sample.

validation

Action of proving, in accordance with the principles of good practice quality guidelines and regulations (GxP), that any procedure, process, equipment (including the software or hardware used), material, activity or system actually and consistently leads to the expected results.

verification

The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with GxP principles.

working culture

A primary subculture from a reference stock (6).

1. Personnel

- 1.1 Microbiological testing should be performed and supervised by an experienced person, qualified in microbiology or equivalent. Staff should have basic training in microbiology and relevant practical experience before being allowed to perform work covered by the scope of testing.
- 1.2 Current job descriptions for all personnel involved in tests and/or calibrations, validations and verifications should be maintained. The laboratory should also maintain records of all technical personnel, describing their qualifications, training and experience.
- 1.3 If the laboratory includes opinions and interpretations of test results in reports, this should be done by authorized personnel with suitable experience and relevant knowledge of the specific application including, for example, regulatory and technological requirements and acceptability criteria.
- 1.4 The laboratory management should ensure that all personnel have received adequate training for the competent performance of tests and operation of equipment. This should include training in basic techniques, e.g. plate pouring, counting of colonies, aseptic technique, media preparation, serial dilutions, and basic techniques in identification, with acceptability determined using objective criteria where relevant. Personnel may only perform tests on samples if they are either recognized as competent to do so, or if they do so under adequate supervision. Competence should be monitored continuously with provision for retraining where necessary. Where a method or technique is not in regular use, the competency of the personnel to perform the test should be verified before testing is undertaken. In some cases it is acceptable to relate competence to a general technique or instrument being used rather than to particular methods.

- 1.5 Personnel should be trained in necessary procedures for containment of microorganisms within the laboratory facility.
- 1.6 Personnel should be trained in safe handling of microorganisms.

2. Environment

2.1 Premises

- 2.1.1 Microbiology laboratories and certain support equipment (e.g. autoclaves and glassware) should be dedicated and separated from other areas, especially from production areas.
- 2.1.2 Microbiology laboratories should be designed to suit the operations to be carried out in them. There should be sufficient space for all activities to avoid mix ups, contamination and cross-contamination. There should be adequate suitable space for samples, reference organisms, media (if necessary, with cooling), testing and records. Due to the nature of some materials (e.g. sterile media versus reference organisms or incubated cultures), separate storage locations may be necessary.
- 2.1.3 Laboratories should be appropriately designed and should take into account the suitability of construction materials to enable appropriate cleaning, disinfection and minimize the risks of contamination.
- 2.1.4 There should be separate air supply to laboratories and production areas. Separate air-handling units and other provisions, including temperature and humidity controls where required, should be in place for microbiological laboratories. The air supplied to the laboratory should be of appropriate quality and should not be a source of contamination.
- 2.1.5 Access to the microbiological laboratory should be restricted to authorized personnel. Personnel should be made aware of:
 - the appropriate entry and exit procedures including gowning;
 - the intended use of a particular area;
 - the restrictions imposed on working within such areas;
 - the reasons for imposing such restrictions; and
 - the appropriate containment levels.
- 2.1.6 Laboratory activities, such as sample preparation, media and equipment preparation and enumeration of microorganisms, should be segregated by space or at least in time, so as to minimize risks of cross-contamination, false-positive results and false-negative results. Where non-dedicated areas are used,

risk management principles should be applied. Sterility testing should always be performed in a dedicated area.

- 2.1.7 Consideration should be given to designing appropriate classified areas for the operations to be performed within the microbiology laboratory. The classification should be based on the criticality of the product and the operation being carried out in the area. Sterility testing should be performed under the same class as used for sterile/aseptic manufacturing operations. Appendix 1 shows recommendations for zone classifications.
- 2.1.8 In general, laboratory equipment should not routinely be moved between areas of different cleanliness class, to avoid accidental cross-contamination. Laboratory equipment used in the microbiology laboratory should not be used outside the microbiology area, unless there are specific precautions in place to prevent cross-contamination.

2.2 Environmental monitoring in the laboratory

- 2.2.1 Where necessary and appropriate (e.g. in areas for sterility testing) an environmental monitoring programme should be in place which covers, for example, use of active air monitoring, air settling or contact plates, temperature and pressure differentials. Alert and action limits should be defined. Trending of environmental monitoring results should be carried out.

2.3 Cleaning, disinfection and hygiene

- 2.3.1 There should be a documented cleaning and disinfection programme. Results of environmental monitoring should be considered where relevant.
- 2.3.2 There should be a procedure for dealing with spillages.
- 2.3.3 Adequate hand-washing and hand-disinfection facilities should be available.

2.4 Sterility test facilities

- 2.4.1 Sterility test facilities have specific environmental requirements to ensure the integrity of tests carried out. *WHO good manufacturing practices (GMP) for sterile pharmaceutical products* (8) requires that sterility testing should be carried out and specifies requirements for sterility testing. This section details the clean-room requirements for a sterility test facility.
- 2.4.2 Sterility testing should be performed under aseptic conditions, which should be equivalent to air quality standards required for the aseptic manufacture of pharmaceutical products. The premises, services and equipment should be subject to the appropriate qualification process.

- 2.4.3 The sterility testing should be carried out within a Grade A unidirectional airflow protected zone or a biosafety cabinet (if warranted), which should be located within a clean room with a Grade B background. Alternatively, the testing can be carried out within a barrier isolator. Care should be taken with the design of the facility layout and room airflow patterns, to ensure that the unidirectional airflow patterns are not disrupted.
- 2.4.4 The clean-room classification and air-handling equipment of the sterility test facilities should be requalified at least annually by a competent person or contractor. The environment should comply with the non-viable and viable limits, and verification of high efficiency particulate air (HEPA) filter integrity and room airflows should be performed. However, an alternative frequency of the monitoring may be justified based on quality risk management (QRM). Mapping locations for sample points for routine monitoring should be documented, as well as exposure duration, and frequency of all types of microbiological environmental monitoring should be specified in written procedures.
- 2.4.5 Air supplied to Grade A and B zones should be via terminal HEPA filters.
- 2.4.6 Appropriate airflow alarms and pressure differentials and indication instruments should be provided (*GMP: Heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms* (8); and *GMP for sterile pharmaceutical products* (8).
- 2.4.7 Room pressure readings should be taken and recorded from externally mounted gauges unless a validated continuous monitoring system is installed. As a minimum, readings should be taken prior to entry of the operator to the test suite. Pressure gauges should be labelled to indicate the area served and the acceptable specification.
- 2.4.8 Entry to the clean room should be via a system of airlocks and a change room where operators are required to don suitable clean-room garments. The final change room should be under “at rest” conditions of the same grade as the room it serves. Change rooms should be of adequate size for ease of changing. There should be clear demarcation of the different zones.
- 2.4.9 Garments for the sterility test operator should comply with the principles of section 10 of *WHO GMP for sterile pharmaceutical products* (8). Operators should be trained and certified in gowning procedures with training records maintained.
- 2.4.10 The fittings and finishes of the premises should comply with section 11 of *WHO GMP for sterile pharmaceutical products* (8).

2.4.11 Environmental microbiological monitoring should reflect the facility used (room or isolator) and include a combination of air and surface sampling methods appropriate to the facility, such as:

- active air sampling;
- settle (exposure) plates;
- surface contact — replicate organism detection and counting (RODAC) plates, swabs or flexible films;
- operators' glove prints.

Microbial environmental monitoring of the sterility test zone should be performed during every work session under operational (dynamic) conditions.

There should be written specifications, including appropriate alert and action limits for microbial contamination. Limits for microbiological environmental monitoring are given in the *WHO GMP for sterile pharmaceutical products* (8).

3. Validation of test methods

- 3.1 Standard (pharmacopoeial) test methods are considered to be validated. However, the specific test method to be used by a specific laboratory for testing of a specific product needs to be shown to be suitable for use in recovering bacteria, yeast and mould in the presence of the specific product. The laboratory should demonstrate that the performance criteria of the standard test method can be met by the laboratory before introducing the test for routine purposes (method verification) and that the specific test method for the specific product is suitable (test method suitability including positive and negative controls).
- 3.2 Test methods not based on compendial or other recognized references should be validated before use. The validation should comprise, where appropriate, determining accuracy, precision, specificity, limit of detection, limit of quantitation, linearity and robustness. Potentially inhibitory effects from the sample should be taken into account when testing different types of sample. The results should be evaluated with appropriate statistical methods, e.g. as described in the national, regional or international pharmacopoeias.

4. Equipment

Each item of equipment, instrument or other device used for testing, verification and calibration should be uniquely identified.

As part of its quality system, a laboratory should have a documented programme for the qualification, calibration, performance verification, maintenance and a system for monitoring the use of its equipment.

4.1 Maintenance of equipment

- 4.1.1 Maintenance of essential equipment should be carried out at predetermined intervals in accordance with a documented procedure. Detailed records should be kept. (For examples of maintenance of equipment and intervals see Appendix 2.)

4.2 Qualification

- 4.2.1 For qualification of equipment see sections 8 and 12 in *Good practices for pharmaceutical quality control laboratories (1)*.

4.3 Calibration, performance verification and monitoring of use

- 4.3.1 The date of calibration and servicing and the date when recalibration is due should be clearly indicated on a label attached to the instrument.
- 4.3.2 The frequency of calibration and performance verification will be determined by documented experience and will be based on need, type and previous performance of the equipment. Intervals between calibration and verification should be shorter than the time the equipment has been found to take to drift outside acceptable limits. (For examples of calibration checks and intervals for different laboratory equipment, see Appendix 3; and for equipment qualification and monitoring, see Appendix 4.) The performance of the equipment should conform to predefined acceptance criteria.

4.3.3 Temperature measurement devices

- 4.3.3.1 Where temperature has a direct effect on the result of an analysis or is critical for the correct performance of equipment, temperature measuring devices should be of appropriate quality to achieve the accuracy required (e.g. liquid-in-glass thermometers, thermocouples and platinum resistance thermometers (PRTs) used in incubators and autoclaves).
- 4.3.3.2 Calibration of devices should be traceable to national or international standards for temperature.

4.3.4 Incubators, water-baths and ovens

The stability of temperature, uniformity of temperature distribution and time required to achieve equilibrium conditions in incubators, water-baths, ovens and temperature-controlled rooms should be established initially and documented, in particular with respect to typical uses (for example, position, space between, and height of, stacks of Petri dishes). The constancy of the characteristics recorded during initial validation

of the equipment should be checked and recorded after each significant repair or modification. The operating temperature of this type of equipment should be monitored and records retained. The use of the equipment should be considered when determining what temperature controls are required.

4.3.5 Autoclaves, including media preparators

4.3.5.1 Autoclaves should be capable of meeting specified time and temperature tolerances; monitoring pressure alone is not acceptable. Sensors used for controlling or monitoring operating cycles require calibration and the performance of timers should be verified.

4.3.5.2 Initial validation should include performance studies (spatial temperature distribution surveys) for each operating cycle and each load configuration used in practice. This process must be repeated after any significant repair or modification (e.g. replacement of thermoregulator probe or programmer, change to loading arrangements or operating cycle) or where indicated by the results of quality control checks on media or risk assessment. Sufficient temperature sensors should be positioned within the load (e.g. in containers filled with liquid/medium) to enable location differences to be demonstrated. In the case of media preparators, where uniform heating cannot be demonstrated by other means, the use of two sensors, one adjacent to the control probe and one remote from it, would generally be considered appropriate. Validation and revalidation should consider the suitability of come-up and come-down times as well as time at sterilization temperature.

4.3.5.3 Clear operating instructions should be provided based on the heating profiles determined for typical uses during validation/revalidation. Acceptance/rejection criteria should be established and records of autoclave operations, including temperature and time, maintained for every cycle.

4.3.5.4 Monitoring may be achieved by one of the following:

- using a thermocouple and recorder to produce a chart or printout;
- direct observation and recording of maximum temperature achieved and time at that temperature.

In addition to directly monitoring the temperature of an autoclave, the effectiveness of its operation during each cycle may be checked by the use of chemical or biological indicators for sterilization or decontamination purposes. Autoclave tape or indicator strips should be used only to show that a load has been processed, not to demonstrate completion of an acceptable cycle.

Laboratories should have a separate autoclave for decontamination. However, in exceptional cases one autoclave may be acceptable provided that extensive precautions are taken to separate decontamination and sterilization loads, and a documented cleaning programme is in place to address both the internal and external environment of the autoclave.

4.3.6 Weights and balances

Weights and balances shall be calibrated traceably at regular intervals (according to their intended use) using appropriate standard weights traceable to certified standard weights.

4.3.7 Volumetric equipment

4.3.7.1 Microbiology laboratories should carry out initial verification of volumetric equipment (automatic dispensers, dispenser/diluters, mechanical hand pipettes and disposable pipettes) and then make regular checks, as appropriate, to ensure that the equipment is performing within the required specification. Initial verification should not be necessary for glassware which has been certified to a specific tolerance. Equipment should be checked for the accuracy of the delivered volume against the set volume (for several different settings in the case of variable volume instruments) and the precision of the repeat deliveries should be measured.

4.3.7.2 For “single-use” disposable volumetric equipment, laboratories should obtain supplies from companies with a recognized and relevant quality system. After initial validation of the suitability of the equipment, it is recommended that random checks on accuracy are carried out. If the supplier does not have a recognized quality system, laboratories should check each batch of equipment for suitability.

4.3.8 Other equipment

Conductivity meters, oxygen meters, pH meters and other similar instruments should be verified regularly or before each use. The buffers used for verification purposes should be stored in appropriate conditions and should be marked with an expiry date.

Where humidity is important to the outcome of the test, hygrometers should be calibrated, the calibration being traceable to national or international standards.

Timers, including the autoclave timer, should be verified using a calibrated timer or national time signal.

When centrifuges are used in test procedures, an assessment of the rotations per minute (RPM) should be made. Where it is critical, the centrifuge should be calibrated.

5. Reagents and culture media

Laboratories should ensure that the quality of reagents and media used is appropriate for the test concerned.

5.1 Reagents

- 5.1.1 Laboratories should verify the suitability of each batch of reagents critical for the test, initially and during its shelf-life.

5.2 Media

- 5.2.1 Media may be prepared in-house or purchased either partially or fully prepared. Vendors of purchased media should be approved and qualified. The qualified vendor may certify some of the quality parameters listed subsequently. Growth promotion and, if appropriate, other suitable performance tests (see section 5.2.2) should be done on all media on every batch and on every shipment. Where the supplier of fully prepared media is qualified and provides growth promotion certification per batch of media and transportation conditions have been qualified, the user may rely on the manufacturer's certificate with periodic verification of his or her results.
- 5.2.2 The suitable performance of culture media, diluents and other suspension fluids should be checked, where relevant, with regard to:
- recovery or survival maintenance of target organisms. Recovery of 50–200% (after inoculation of not more than 100 colony-forming units (CFU or cfu) should be demonstrated;
 - inhibition or suppression of non-target organisms;
 - biochemical (differential and diagnostic) properties; and
 - other appropriate properties (e.g. pH, volume and sterility).

Quantitative procedures for evaluation of recovery or survival are preferred.

- 5.2.3 Raw materials (both commercial dehydrated formulations and individual constituents) and media should be stored under appropriate conditions recommended by the manufacturer, e.g. cool, dry and dark. All containers, especially those for dehydrated media, should be sealed tightly. Dehydrated media that are caked or cracked or show a colour change should not be used.
- 5.2.4 Water of a suitable microbiological quality and which is free from bactericidal, inhibitory or interfering substances, should be used for preparation unless the test method specifies otherwise.

- 5.2.5 Media containing antimetabolites or inhibitors should be prepared using dedicated glassware, as carry-over of these agents into other media could inhibit the growth and detection of microorganisms present in the sample under test. If dedicated glassware is not used, washing procedures for glassware should be validated.
- 5.2.6 Repartition of media after sterilization should be performed under unidirectional airflow (UDAF) to minimize potential for environmental contamination. This should be considered a minimum requirement for media to be used in relation to sterile product testing. This includes the cooling of media, as container lids will need to be removed during cooling to prevent build-up of condensation.
- 5.2.7 Plated media which is to be irradiated may require the addition of an antioxidant and free radical scavenger to provide protection from the effects of the irradiation process. The irradiated media should be validated by performing quantitative growth promotion testing on both irradiated and non-irradiated media.
- 5.2.8 Shelf-life of prepared media under defined storage conditions shall be determined and verified.
- 5.2.9 Batches of media should be identifiable and their conformance with quality specifications documented. For purchased media the user laboratory should ensure that it will be notified by the manufacturer of any changes to the quality specification.
- 5.2.10 Media should be prepared in accordance with any manufacturer's instructions, taking into careful account specifications such as time and temperature for sterilization.
- 5.2.11 Microwave devices should not be used for the melting of media due to the inconsistent distribution of the heating process.

5.3 Labelling

- 5.3.1 Laboratories should ensure that all reagents (including stock solutions), media, diluents and other suspending fluids are adequately labelled to indicate, as appropriate, identity, concentration, storage conditions, preparation date, validated expiry date and/or recommended storage periods. The person responsible for preparation should be identifiable from records.

5.4 Organism resuscitation

- 5.4.1 Organism resuscitation is required where test methodologies may produce sublethally injured cells. For example, exposure to:

- injurious effects of processing, e.g. heat;
- antimicrobial agents;
- preservatives;
- extremes of osmotic pressure; and
- extremes of pH.

5.4.2 Organism resuscitation may be achieved by:

- exposure to a liquid media like a simple salt solution at room temperature for 2 hours;
- exposure to a solid repair medium for 4–6 hours.

6. Reference materials and reference cultures

6.1 International standards and pharmacopoeial reference substances

6.1.1 Reference materials and certified reference materials are generally used in a microbiological laboratory to qualify, verify and calibrate equipment.

Whenever possible these reference materials should be used in appropriate matrices.

International standards and pharmacopoeial reference substances are employed, for example, to:

- determine potency or content;
- validate methods;
- enable comparison of methods;
- perform positive controls; and
- perform growth promotion tests.

If possible reference materials should be used in appropriate matrices.

6.2 Reference cultures

6.2.1 Reference cultures are required for establishing acceptable performance of media (including test kits), for validating methods, for verifying the suitability of test methods and for assessing or evaluating ongoing performance. Traceability is necessary, for example, when establishing media performance for test kit and method validations. To demonstrate traceability, laboratories must use reference strains of microorganisms obtained directly from a recognized national or

international collection, where these exist. Alternatively, commercial derivatives for which all relevant properties have been shown by the laboratory to be equivalent at the point of use may be used.

- 6.2.2 Reference strains may be subcultured once to provide reference stocks. Purity and biochemical checks should be made in parallel as appropriate. It is recommended to store reference stocks in aliquots either deep-frozen or lyophilized. Working cultures for routine use should be primary subcultures from the reference stock (see Appendix 5 on general use of reference cultures). If reference stocks have been thawed, they must not be refrozen and reused.
- 6.2.3 Working stocks should not normally be subcultured. Usually not more than five generations (or passages) from the original reference strain can be subcultured if defined by a standard method or laboratories can provide documentary evidence that there has been no change in any relevant property. Commercial derivatives of reference strains may only be used as working cultures.

7. Sampling

For general principles reference is made to *Good practices for pharmaceutical quality control laboratories (1)*.

- 7.1 Where testing laboratories are responsible for primary sampling to obtain test items, it is strongly recommended that this sampling be covered by a quality assurance system and it should be subject to regular audits.
- 7.2 Any disinfection processes used in obtaining the sample (e.g. disinfection of sample points) should not compromise the microbial level within the sample.
- 7.3 Transport and storage of samples should be under conditions that maintain the integrity of the sample (e.g. chilled or frozen where appropriate). Testing of the samples should be performed as soon as possible after sampling. For samples where a growth in the microbial population during transport and storage is possible it should be demonstrated that the storage conditions, time and temperature, will not affect the accuracy of the testing result. The storage conditions should be monitored and records kept. The responsibility for transport, storage between sampling and arrival at the testing laboratory should be clearly documented.
- 7.4 Sampling should only be performed by trained personnel. It should be carried out aseptically using sterile equipment. Appropriate precautions should be taken to ensure that sample integrity is maintained through the use of sterile sealed containers for the collection of samples where appropriate. It may be necessary to monitor environmental conditions, for example, air contamination and temperature, at the sampling site. Time of sampling should be recorded, if appropriate.

8. Sample handling and identification

- 8.1 The laboratory should have procedures that cover the delivery and receipt of samples and sample identification. If there is insufficient sample or the sample is in poor condition due to physical deterioration, incorrect temperature, torn packaging or deficient labelling, the laboratory should consult with the client before deciding whether to test or refuse the sample.
- 8.2 The laboratory should record all relevant information, e.g.
- date and, where relevant, the time of receipt;
 - condition of the sample on receipt and, when necessary, temperature; and
 - characteristics of the sampling operation (including sampling date and sampling conditions).
- 8.3 Samples awaiting testing should be stored under suitable conditions to minimize changes to any microbial population present. Storage conditions should be validated, defined and recorded.
- 8.4 The packaging and labels of samples may be highly contaminated and should be handled and stored with care so as to avoid any spread of contamination. Disinfection processes applied to the outer container should not affect the integrity of the sample. It should be noted that alcohol is not sporicidal.
- 8.5 Subsampling by the laboratory immediately prior to testing may be required as part of the test method. It may be appropriate that it is performed according to national or international standards, where they exist, or by validated in-house methods. Subsampling procedures should be designed to collect a representative sample.
- 8.6 There should be a written procedure for the retention and disposal of samples. If sample integrity can be maintained it may be appropriate that samples are stored until the test results are obtained, or longer if required. Laboratory sample portions that are known to be contaminated should be decontaminated prior to being discarded (see section 11.1).

9. Disposal of contaminated waste

- 9.1 The procedures for the disposal of contaminated materials should be designed to minimize the possibility of contaminating the test environment or materials. It is a matter of good laboratory management and should conform to national/international environmental or health and safety regulations.

10. Quality assurance of results and quality control of performance

10.1 Internal quality control

- 10.1.1 The laboratory should have a system of internal quality assurance or quality control (e.g. handling deviations, use of spiked samples, replicate testing and participation in proficiency testing, where appropriate) to ensure the consistency of results from day to day and their conformity with defined criteria.

11. Testing procedures

- 11.1 Testing should normally be performed according to procedures described in the national, regional and international pharmacopoeias.
- 11.2 Alternative testing procedures may be used if they are appropriately validated and equivalence to official methods has been demonstrated.

12. Test reports

- 12.1 If the result of the enumeration is negative, it should be reported as “not detected for a defined unit” or “less than the detection limit for a defined unit”. The result should not be given as “zero for a defined unit” unless it is a regulatory requirement. Qualitative test results should be reported as “detected/not detected in a defined quantity or volume”. They may also be expressed as “less than a specified number of organisms for a defined unit” where the specified number of organisms exceeds the detection limit of the method and this has been agreed with the client. In the raw data the result should not be given as zero for a defined unit unless it is a regulatory requirement. A reported value of “0” may be used for data entry and calculations or trend analysis in electronic databases
- 12.2 Where an estimate of the uncertainty of the test result is expressed on the test report, any limitations (particularly if the estimate does not include the component contributed by the distribution of microorganisms within the sample) have to be made clear to the client.

References

1. Good Practices for pharmaceutical quality control laboratories. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report*. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y), Annex 1.

2. General guidelines for the establishment, maintenance and distribution of chemical reference substances. Revision. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report*. Geneva, World Health Organization, 2007 (WHO Technical Report Series, No. 943; https://iris.who.int/bitstream/handle/10665/43632/WHO_TRS_943_eng.pdf?sequence=1&isAllowed=y), Annex 3.
3. *The International Pharmacopoeia*, Fourth Edition. Geneva, World Health Organization, 2006. Also available on CD-ROM.
4. *The International Pharmacopoeia*, Fourth Edition, First Supplement. Geneva, World Health Organization, 2008. Also available on CD-ROM.
5. ISO/IEC 17025 (2005) *General requirements for the competence of testing and calibration laboratories*.
6. ISO 11133-1 (2000) *Microbiology of food and animal feeding stuffs — Guidelines on preparation and production of culture media — Part 1: General guidelines on quality assurance for the preparation of culture media in the laboratory*.
7. ISO 13843 (2000) *Water quality — Guidance on validation of microbiological methods*.
8. WHO good manufacturing practices: main principles for pharmaceutical products. In: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, 2nd updated edition. Good manufacturing practices (GMP) and inspection*. Geneva, World Health Organization, 2007, and subsequent updates, including WHO GMP for sterile pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth report*. Geneva, World Health Organization. WHO Technical Report Series, No. 961, Annex 6, 2011; and GMP: Heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth report*. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961; https://iris.who.int/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1), Annex 5.

Further reading

- ISO 7218 (2007) *Microbiology of food and animal feeding stuffs — General requirements and guidance for microbiological examinations*.
- ISO 6887-1 (1999) *Microbiology of food and animal feeding stuffs — Preparation of test samples, initial suspension and decimal dilutions for microbiological examination — Part 1: General rules for the preparation of the initial suspension and decimal dilutions*.
- ISO Guide 30 (1992) *Terms and definitions used in connection with reference materials*.
- ISO 9000 (2008) *Quality management systems — fundamentals and vocabulary*.
- ISO Guide 99 (1993) *International vocabulary of basic and general terms in metrology (VIM)*.
- ISO (CIPM):1995. *Guide to the expression of uncertainty in measurements*.
- Draft ISO/DIS 16140. (1999) *Food microbiology. Protocol for the validation of alternative methods*.
- Draft ISO/FDIS (2003) 11133-2. *Microbiology of food and animal feeding stuffs. Guidelines on preparation and production of culture media. Part 2 — Practical guidelines on performance testing on culture media*.
- EN 12741 (1999). *Biotechnology — Laboratories for research, development and analysis — Guidance for biotechnology laboratory operations*.

Appendix 1

Examples of zones in which operations could be carried out

The zones are designed as the following grades, during the installation and monitoring can be carried out, e.g. through appropriate air supply.

Zone	Installation grade	Proposed
Sample receipt	Unclassified	Unclassified
Media preparation	Unclassified	Unclassified
Autoclave loading	Unclassified	Unclassified
Autoclave unloading, inside the sterility testing area	Grade B	ISO 5 (turbulent) and <10 cfu/m ³
Sterility testing — UDAF	Grade A	ISO 5 (UDAF) and <1 cfu/m ³
Sterility testing — background to UDAF	Grade B	ISO 5 (turbulent) and <10 cfu/m ³
Sterility testing — isolator	Grade A (NVP and microbiology only)	ISO 5 (UDAF) and <1 cfu/m ³
Sterility testing — background to isolator	Unclassified	Unclassified
Incubator	Unclassified	Unclassified
Enumeration	Unclassified ^a	Unclassified ^a
Decontamination	Unclassified	Unclassified

cfu, colony-forming unit.

^a Critical steps should be done under laminar flow.

Appendix 2

Examples of maintenance of equipment

This information is provided as an example and the frequency will be based on the need, type and previous performance of the equipment and on the recommendations in suppliers' manuals.

Type of equipment	Requirement	Suggested frequency
– Incubators – Fridges – Freezers, ovens	Clean and disinfect internal surfaces	– Monthly – When required (e.g. every 3 months) – When required (e.g. annually)
Water-baths	Empty, clean, disinfect and refill	– Monthly, or every 6 months if biocide used
Centrifuges	– Service – Clean and disinfect	– Annually – Each use
Autoclaves	– Make visual checks of gasket, clean/drain chamber – Full service – Safety check of pressure vessel	– Regularly, as recommended by manufacturer – Annually or as recommended by manufacturer – Annually
Safety cabinets unidirectional cabinets	Full service and mechanical check	Annually or as recommended by manufacturer
Microscopes	Full maintenance service	Annually
pH meters	Clean electrode	Each use
Balances, gravimetric diluters	– Clean – Service	– Each use – Annually
Stillts	Clean and descale	As required (e.g. every 3 months)
De-ionizers, reverse osmosis units	Replace cartridge/membrane	As recommended by manufacturer
Anaerobic jars	Clean/disinfect	After each use
Media dispensers, volumetric equipment, pipettes and general service equipment	Decontaminate, clean and sterilize as appropriate	Each use

Table *continued*

Type of equipment	Requirement	Suggested frequency
Spiral platers	– Service – Decontaminate, clean and sterilize	– Annually – Each use
Laboratory	– Clean and disinfect working surfaces – Clean floors, disinfect sinks and basins – Clean and disinfect other surfaces	– Daily and during use – Daily – Every 3 months

Appendix 3

Examples of calibration checks and intervals for different laboratory equipment

This information is provided as an example and the frequency will be based on the need, type, previous performance and criticality of the equipment.

Type of equipment	Requirement	Suggested frequency
Reference thermometers (liquid-in-glass)	Full traceable recalibration Single point (e.g. ice-point check)	Every 3 years Annually
Reference thermocouples	Full traceable recalibration Check against reference thermometer	Every 3 years Annually
Working thermometers and working thermocouples	Check against reference thermometer at ice-point and/or working temperature range	Annually
Balances	Full traceable calibration	Annually
Calibration weights	Full traceable calibration	Annually
Check weight(s)	Check against calibrated weight or check on balance immediately following traceable calibration	Annually
Volumetric glassware	Gravimetric calibration to required tolerance	Annually
Microscopes	Traceable calibration of stage micrometer (where appropriate)	Initially
Hygrometers	Traceable calibration	Annually
Centrifuges	Traceable calibration or check against an independent tachometer, as appropriate	Annually

Appendix 4

Examples of equipment qualification and monitoring

This information is provided as an example and the frequency will be based on the need, type, previous performance and criticality of the equipment.

Type of equipment	Requirement	Suggested frequency
Temperature-controlled equipment (incubators, baths, fridges, freezers)	– Establish stability and uniformity of temperature – Monitor temperature	– Initially, every 2 years and after repair/modification – Daily/each use
Sterilizing ovens	– Establish stability and uniformity of temperature – Monitor temperature	– Initially, every 2 years and after repair/modification – Each use
Autoclaves	– Establish characteristics for loads/cycles – Monitor temperature/pressure/time	– Initially, every 2 years and after repair/modification – Each use
Grade A areas used for sterility testing: • safety unidirectional cabinets • isolators	– Establish performance – Microbiological monitoring – Airflow monitoring – Test for integrity of HEPA filters	– Initially, every year and after repair/modification – Each use – 6-monthly – 6-monthly
Unidirectional cabinets	– Establish performance – Microbiological monitoring – Airflow monitoring – Test for integrity of HEPA filters	– Initially, and after repair/modification – Weekly – 6-monthly – 6-monthly
Timers	Check against national time signal	– Annually
Microscopes	Check alignment	Daily/each use
pH meters	Adjust using at least two buffers of suitable quality	Daily/each use
Balances	Check zero, and reading against check weight	Daily/each use

Table *continued*

Type of equipment	frequency and nature of use)	Suggested frequency
De-ionizers and reverse osmosis units	– Check conductivity – Check for microbial contamination	– Weekly – Monthly
Gravimetric diluters	– Check weight of volume dispensed – Check dilution ratio	– Daily – Daily
Media dispensers	Check volume dispensed	Each adjustment or replacement
Pipettors/pipettes	Check accuracy and precision of volume dispensed	Regularly (to be defined by taking account of the frequency and nature of use)
Spiral platers	– Establish performance against conventional method – Check stylus condition and the art start and end-points – Check volume dispensed	– Initially and annually – Daily/each use – Monthly
Colony counters	Check against number counted manually	Annually
Centrifuges	Check speed against a calibrated and independent tachometer	Annually
Anaerobic jars/incubators	Check with anaerobic indicator	Each use
Laboratory environment	Monitor for airborne and surface microbial contamination using, e.g. air samplers, settle plates, contact plates or swabs	Based on risk assessment, an appropriate environmental monitoring programme should be established

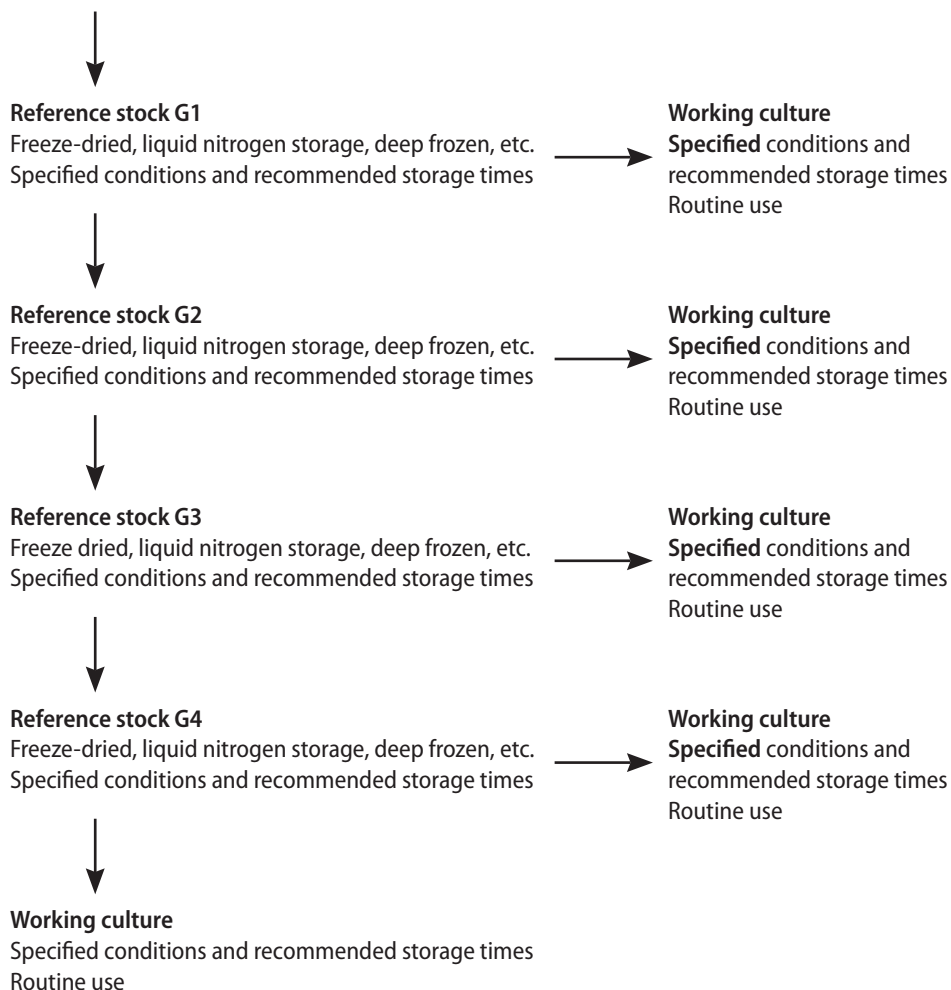
HEPA, high-efficiency particulate air.

Appendix 5

General use of reference cultures

Reference strain

from source recognized by accreditation body



All parts of the process should be fully documented and detailed records of all stages must be maintained. Purity checks and biochemical tests should be made as appropriate.

11.3 WHO guidelines for preparing a laboratory information file

Annex 13, WHO Technical Report Series, 961, 2011

Background

The WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted in its thirty-eighth report in 2003 the *Guidelines for preparing a laboratory information file* (WHO Technical Report Series, No. 917, 2003, Annex 5).

The content of these guidelines is closely related to *WHO guidelines on good practices for pharmaceutical quality control laboratories*, which have recently been revised (the revised version was adopted by the WHO Expert Committee at its forty-fourth meeting in 2009).

The WHO Expert Committee on Specifications for Pharmaceutical Preparations discussed the need for a revision of both sets of guidelines at its forty-third meeting in 2008 and recommended that if the *Guidelines for good practices for national pharmaceutical control laboratories* were revised, the *Guidelines for preparing a laboratory information file* should be revised accordingly.

On the basis of the above and following the usual consultation process, the following text will replace the previously published guidelines.

1. General information on the laboratory	1191
2. Quality management system	1192
3. Control of documentation and records	1192
4. Personnel	1192
5. Premises	1193
6. Equipment	1194
7. Materials	1194
8. Subcontracting of testing	1194
9. Handling of samples	1195
10. Validation of analytical procedures	1195
11. Investigation of out-of-specification results	1195
12. Stability testing (where applicable)	1195
13. Microbiological testing (where applicable)	1195

A laboratory information file (LIF) is a document prepared by the laboratory. It contains specific and factual information about the operations carried out at the named site and any closely integrated operations of the laboratory. If only some of the operations are carried out on the site, the LIF needs to describe only those operations, e.g. sampling, chemical analysis or stability testing.

An LIF should be written in English, succinct and, if possible, should not exceed 30 A4 pages, excluding appendices.

The laboratory should give a short description of its activities under each of the following headings. Policy or essential steps for each activity should be described and reference to a standard operating procedure (SOP) or other supporting documents should be given, where applicable. Where appropriate, supportive documentation should be appended.

1. General information on the laboratory

- 1.1 Brief information on the laboratory (including name, physical (location) and mailing address, contact details and brief history). If the laboratory is part of an organization or company, provide details of its position within the organization or company, including reporting lines (e.g. organizational chart).
- 1.2 Summary of all laboratory activities, including objectives of the laboratory, categories of customers, types of sample tested. In addition, state the relation (if any) to a manufacturing site.
- 1.3 Areas of expertise proposed for prequalification (list methods and tests, for examples see the List of Prequalified Quality Control Laboratories).¹

Type of analysis	Finished products	Active pharmaceutical ingredients
Physical/chemical analysis		
Identification		
Assay, impurities and related substances		
Microbiological tests		
Bacterial endotoxin testing (BET)		
Stability testing		

¹ <https://extranet.who.int/prequal/medicines/prequalified/quality-control-labs>.

- 1.4 Brief description of a policy for participation in proficiency testing schemes and collaborative trials and for the evaluation of the performance. Attach the list of tests in which the laboratory has participated in the last three years, including the organizer and results.

2. Quality management system

- 2.1 Short description of the quality management system implemented in the laboratory, including reference to the standard used (such as *WHO good practices for pharmaceutical quality control laboratories*, ISO 17025, good manufacturing practices) and existence of a quality manual.
- 2.2 Information on inspections carried out by national or regional authorities and external audits performed in the laboratory in the last three years, including reference to valid accreditation, certificate, authorization or licence.
- 2.3 Brief description of the procedures for internal audits, implementation of corrective and preventive actions and complaints.

3. Control of documentation and records

- 3.1 Brief description of the procedures for the control of and changes to documents that form a part of the quality documentation. Attach a list of valid SOPs.
- 3.2 Brief description of the procedures for the preparation, revision and distribution of necessary documentation for specifications, standard test procedures, analyst workbooks or worksheets.
- 3.3 Brief description of any other documentation related to product testing, including reports, records, arrangements for the handling of results (including laboratory information management systems (LIMS), where used).
- 3.4 Brief description of the procedures for release of certificates and analytical reports.

4. Personnel

- 4.1 Number of employees engaged in the following activities:

Activity	Number
Supervisors	
Chemical sector	
analysts	
technicians	
Microbiological sector	
microbiologists	
technicians	
Quality assurance staff	
Staff trained for sampling	
Other	
Total number of employees in the laboratory:	

- 4.2 Organization chart showing the arrangements, responsibilities and reporting lines in the laboratory.
- 4.3 Qualifications, experience and responsibilities of key personnel.
- 4.4 Outline of arrangements for initial and ongoing training and its recording.

5. Premises

- 5.1 Simple plan or description of the layout of the laboratory areas with an indication of scale (architectural or engineering drawings not required, but photographs may be submitted if available).
- 5.2 Nature of construction and finishing.
- 5.3 Brief description of ventilation systems including those for microbiological testing areas, storage areas, etc. (Include reference to air circulation and control of temperature and relative humidity.)
- 5.4 Brief description of special areas for the handling and storage of hazardous materials such as highly toxic (including genotoxic), poisonous and flammable materials.
- 5.5 Description of planned programmes for preventive maintenance of the premises and the system for recording maintenance activities.

- 5.6 Brief description of the procedures for cleaning of areas and equipment.
- 5.7 Short description of the storage areas (size, location) including arrangements for the storage of materials and retention samples.

6. Equipment

- 6.1 Brief description of the main equipment used in the laboratory. Attach a list of equipment in use, in tabular form, indicating the equipment and its brand model and date of installation.
- 6.2 Brief description of the planned programme for the preventive maintenance of equipment and the system for recording the maintenance activities.
- 6.3 Brief description of arrangements and status for qualification of equipment (installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ)) as well as calibration of measuring equipment, including the recording system.
- 6.4 Brief description of computer system and its validation and data integrity management, including access to data and frequency of back-up.

7. Materials

- 7.1 Brief description of general policy for purchasing and handling of materials (including chemicals and reagents and availability of safety data sheets) and for handling of waste. Brief description of the procedure for selection and evaluation of suppliers.
- 7.2 Brief description of the water system in the laboratory, its qualification and arrangements for the sampling and testing of the water.
- 7.3 Brief description of the system for purchasing, preparation, handling and storage of reference substances and reference materials.

8. Subcontracting of testing

- 8.1 List of activities contracted out to other laboratories, including names and addresses of subcontractors of subcontractors. Description of the way in which the compliance with standards for activities contracted out is assessed.

9. Handling of samples

- 9.1 Brief description of general policy for sampling. If the laboratory is responsible for sampling describe briefly the procedures used and standards applied.
- 9.2 Brief description of the procedures for handling of samples from their receipt to storage after completion of testing. Where possible, flow charts describing important steps and work allocation in the laboratory should be supplied.

10. Validation of analytical procedures

- 10.1 Brief description of general policy for validation of analytical methods, including verification of pharmacopoeial methods or analytical procedures validated by manufacturers

11. Investigation of out-of-specification results

- 11.1 Brief description of the procedure for recording and investigation of out-of-specification results.

12. Stability testing (where applicable)

- 12.1 Brief description of the stability testing procedure.
- 12.2 Brief description of the conditions under which samples are kept, the arrangements for monitoring and the equipment used.

13. Microbiological testing (where applicable)

- 13.1 Brief description of the activities for microbiological testing.
- 13.2 Brief description of preparation and control of media and types of media used.
- 13.3 Brief description of the procedure in place for positive and negative controls.
- 13.4 Brief description of validation policy.
- 13.5 Brief description of arrangements for waste disposal.

11.4 Good pharmacopoeial practices

Annex 1, WHO Technical Report Series, 996,
2016

1. Background	1692
2. Purpose and scope of good pharmacopoeial practices	1693
3. Glossary	1693
4. Benefits of good pharmacopoeial practices	1694
5. Implementation	1694
6. Monograph development	1694
6.1 General considerations	1695
6.1.1 Adoption of pharmacopoeial standards	1696
6.1.2 Open and transparent process	1696
6.1.3 Harmonization	1697
6.1.4 Legal recognition	1697
6.1.5 Compliance with a pharmacopoeial monograph	1697
6.1.6 Analytical requirements	1697
6.1.7 Acceptance criteria	1698
6.2 Technical guidance	1698
6.2.1 Monographs for pharmaceutical substances	1698
6.2.2 Monographs for finished pharmaceutical products	1703
7. Analytical test procedures and methods	1707

1. Background

A pharmacopoeia's core mission is to protect public health by creating and making available public standards to help ensure the quality of medicines. Pharmacopoeia standards support regulatory authorities in controlling the quality of pharmaceutical substances, their finished pharmaceutical products (FPPs) and related materials and will provide a tool with which the user or procurer can make an independent judgement regarding quality, thus safeguarding the health of the public.

Today there are 49 pharmacopoeias in the world (according to the World Health Organization (WHO) list of pharmacopoeias, 2015). There are differences between these pharmacopoeias, including the use of technology reflected in each pharmacopoeia as well as the breadth of medicines and other articles included. Pharmacopoeias are embedded in their respective national or regional regulatory environment and reflect specifications approved by the regulatory body.

Efforts towards pharmacopoeial harmonization started more than a century ago. When WHO was created in 1948, this was included in its mandate. This led to the creation of *The International Pharmacopoeia*, which was the first global pharmacopoeial activity. Many others followed.

Pharmacopoeial harmonization has been defined by the Pharmacopoeial Discussion Group (PDG) as “when a pharmaceutical substance or product tested by the document's harmonized procedure yields the same results and the same accept/reject decision is reached”.

Developments in science and medical practice, globalization and the presence of spurious/falsified/falsely labelled/counterfeit (SFFC) products require pharmacopoeias to continuously revise their monographs and other text. Harmonization and reinforced collaboration among pharmacopoeial committees and regulators, supported by adequate interaction with industry, will assist in facing new challenges and resource constraints.

The first initiative to reopen the discussion on international harmonization of quality control specifications on a global scale was taken in a side meeting of the 10th International Conference of Drug Regulatory Authorities (ICDRA) entitled: “Pharmacopoeial Specifications – Need for a Worldwide Approach?” in China, Hong Kong SAR on 24 June 2002. This led to further discussions among regulators during the 11th ICDRA meeting held in Madrid in 2004. Other international events during the following years enabled discussions with and among pharmacopoeias on this topic.

The main suggestion emerging from all these events was the development of good pharmacopoeial practices (GPhP) to encourage harmonization, facilitated by WHO.

It was agreed to develop the GPhP under the auspices of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, benefiting from its well-established international standard-setting processes and procedures. These processes include an international consultation process, which enables the participation of all stakeholders and users in the development process. The final guidance would then be presented, in line with the procedure, to WHO's 194 Member States and pharmacopoeial authorities.

2. Purpose and scope of good pharmacopoeial practices

The primary objective of the GPhP guidance is to define approaches and policies in establishing pharmacopoeial standards with the ultimate goal of harmonization.

These GPhP describe a set of principles that provide guidance for national pharmacopoeial authorities (NPAs) and regional pharmacopoeial authorities (RPAs) that facilitates the appropriate design, development and maintenance of pharmacopoeial standards.

Although the principles may also apply to other products, the focus of these good practices is pharmaceutical substances and FPPs.

3. Glossary

Terms in this document are used in accordance with WHO terminology, while recognizing that individual pharmacopoeias may apply their own nomenclature policies.

active pharmaceutical ingredient. Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

dosage form. The form of the completed pharmaceutical product, e.g. tablet, capsule, elixir, suppository or injection.

excipient. A substance or compound, other than the active pharmaceutical ingredient and packaging materials, that is intended or designated to be used in the manufacture of a pharmaceutical product.

finished pharmaceutical product. A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling.

period of use. Utilization period of multidose products after opening, reconstitution or dilution of a solution.

pharmaceutical substance. Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials. This includes active pharmaceutical ingredients and pharmaceutical excipients.

shelf life. The period of time during which a pharmaceutical product, if stored as indicated on the label, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf life is used to establish the expiry date of each batch.

4. Benefits of good pharmacopoeial practices

GPhP are designed to facilitate collaboration among pharmacopoeias, leading to possibilities for work-sharing, harmonization of standards and the recognition of published standards between NPAs and RPAs.

In addition to the above, the establishment of GPhP may result in the following:

- 1) strengthening of global pharmacopoeial cooperation;
- 2) providing stakeholders with a better understanding of how pharmacopoeial standards are developed and maintained in a transparent manner;
- 3) improving cooperation between NPAs/RPAs and stakeholders (e.g. regulators, pharmaceutical industry) with a view to facilitating the harmonization of pharmacopoeial standards and reducing duplication of work;
- 4) increasing access to and the availability of affordable, quality medicines.

By establishing common practices, GPhP can facilitate adoption or adaptation of the standards from one pharmacopoeia by another pharmacopoeia, proactively harmonizing the requirements with considerably less effort than is currently needed.

GPhP should ultimately enable harmonization of pharmacopoeial standards.

5. Implementation

While the implementation of the GPhP by NPAs and RPAs is voluntary, it is recommended and encouraged, as a high level of participation will result in greater benefit to the stakeholders and ultimately to patients.

6. Monograph development

Development of a monograph requires consideration of information and candidate materials. This information may come from donors, literature, various publicly available sources, from other pharmacopoeias, or may be generated within the laboratory resources of a pharmacopoeia and/or of a competent authority (such as an official medicines control laboratory). The draft text should be displayed for public comments with sufficient time allowed for review and input by stakeholders.

Pharmacopoeias are encouraged to conform, where possible, to the work of harmonization initiatives (e.g. WHO, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the PDG)).

6.1 General considerations

Pharmacopoeial monographs provide an important tool for assurance of the quality of marketed pharmaceutical ingredients and products through testing of their quality. They generally cover chemical, biological and herbal FPPs and their ingredients, which have either been approved by national regulatory authorities or are otherwise legally marketed. Some pharmacopoeias also include standards for items such as natural products, nutritional products and medical devices. The principles of GPhP apply equally to substances and products used in both human and veterinary medicine. It is recognized that different requirements may be applied to human and veterinary medicines, such as those included in the ICH and the corresponding Veterinary International Conference on Harmonization (VICH) requirements.

Specifications in pharmacopoeias are one facet of the overall control of the quality of FPPs and their ingredients (active pharmaceutical ingredients (APIs) and excipients). Monographs provide publicly available standards that a product or a component of a product is expected to meet during its shelf life. Thus, a substance should be able to demonstrate compliance with a pharmacopoeial monograph up to the point at which it is used to prepare an FPP. An FPP should demonstrate compliance with a monograph, if available, throughout its shelf life. Pharmacopoeial specifications are used within pharmaceutical product marketing authorization systems and by manufacturers, suppliers, purchasers and those acting on behalf of patients.

Before developing a monograph it is important to consider the specifications (tests and acceptance criteria) needed to assure the quality of a given pharmaceutical substance or FPP. Specifications that limit market access by, for example, favouring one manufacturer to the exclusion of others should be avoided.

The ICH guideline Q6A (*Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances*), for example, could be used as a basis. Whenever possible, specifications should be applied consistently in monographs across all participating pharmacopoeias, regardless of whether the requirements are specified in the specific monograph or are incorporated in general monographs. However, there may be situations where different acceptance criteria are required depending on the national or regional regulatory authorities. Additional tests might be added by NPAs and RPAs, depending on national or regional regulations.

Pharmacopoeial standards allow independent testing and are a critical part of the “safety net” of standards that help ensure the quality, safety and efficacy of FPPs. They are closely allied with good manufacturing practice (GMP) standards.

Pharmacopoeial standards should be available for FPPs and their APIs and associated materials at an appropriate time to support and benefit patients through the availability of medicines with consistent quality. They are usually based on the shelf-life specifications approved by regulatory authorities¹ or on the specifications of unlicensed

¹ In the case of *The International Pharmacopoeia* this relates to the shelf-life specifications evaluated by the WHO Prequalification Team.

products (e.g. compounded and other preparations, as defined by national or regional regulations).

The monographs may employ various validated analytical procedures for the tests that are designed to be suitable for a competent analyst to perform using established technologies and facilities.

Pharmacopoeial standards are public standards that are science-based and data-driven and based on sound analytical measurement and accompanying validation data.

Pharmacopoeias respect the intellectual property of donors and recognize the importance of maintaining the confidentiality of proprietary third-party information. Pharmacopoeias endeavour to work collaboratively with regulators (including medicines regulatory authorities, official medicines control laboratories and inspectorates), the pharmaceutical industries (including manufacturers and trade associations), academia, health-care professionals and patient advocacy groups (as appropriate), and other stakeholders in the development of public standards.

6.1.1 Adoption of pharmacopoeial standards

- (a) Text in a pharmacopoeial monograph or general chapter is approved by an expert body of the pharmacopoeia, following publicly available rules and procedures. This includes public consultation and the application of conflict of interest and confidentiality rules.
- (b) Reference standards cited in a pharmacopoeia are also approved by a pharmacopoeial expert body.

6.1.2 Open and transparent process

Pharmacopoeial standards are based on current scientific knowledge and reflect the quality of pharmaceutical substances and FPPs available.

Pharmacopoeias ensure openness and transparency throughout the development and revision of monographs and other texts, which includes:

- i. engaging stakeholders in the routine development and revision of pharmacopoeial standards through adequate and timely public notice and comment;
- ii. engaging stakeholders in the timely development and revision of standards to address major public health concerns;
- iii. general transparency of the pharmacopoeial approaches, including making work programmes publicly available;
- iv. good communication with stakeholders through forums, workshops and other interactions;
- v. timely response to user enquiries;

- vi. opportunities for user training and education on the pharmacopoeial process and finalized standards;
- vii. rapid correction of errors published in compendial text, when necessary;
- viii. timely and appropriate revision and/or withdrawal of compendial standards, when necessary. (The legal status of monographs that have been withdrawn will depend on the national regulatory framework.)

6.1.3 Harmonization

Pharmacopoeias should harmonize standards wherever possible through monographs and general chapters. Harmonization may occur through several processes including, but not limited to: adoption or adaptation² of existing standards; development of a new standard through coordinated consideration (prospective harmonization); revision of a standard between two or more pharmacopoeias (bilateral or multilateral harmonization); and creation or revision of standards through a harmonization initiative (e.g. PDG).

6.1.4 Legal recognition

Pharmacopoeial monographs may acquire legal status and then provide a basis for enforcement depending on applicable national or regional requirements.

6.1.5 Compliance with a pharmacopoeial monograph

Any pharmaceutical substance or FPP subject to a monograph must comply with all of the mandatory requirements within the pharmacopoeia, throughout its period of use or shelf life.

The assays and tests described are the official methods upon which the standards of the pharmacopoeia depend. The analyst may not be precluded from employing alternative methods depending on national and regional legislation. A validation of the alternative analytical procedure should be done to show at least an equivalent performance to the analytical procedure described in the monograph. Subject to regulatory approval an alternative method of analysis may be used for routine analytical purposes. In this case it is necessary to provide a rationale for its inclusion, validation data and data comparing results obtained using the pharmacopoeial method and the alternative method.

In case of doubt or dispute, the official pharmacopoeial methods prevail and are alone authoritative.

6.1.6 Analytical requirements

Pharmacopoeial procedures and acceptance criteria are set with the intention that they should be used as compliance requirements and not as requirements to guarantee total quality assurance.

² The source of the text should be indicated.

To achieve maximum benefit from the examination of a product, the recommended approach is that, wherever possible, a variety of different analytical techniques should be employed, considering the feasibility and affordability of the methods.

6.1.7 Acceptance criteria

Acceptance criteria are numerical limits, ranges or other suitable measures for acceptance of the results of analytical testing to allow determination of pass/fail criteria. Acceptance criteria indicated in a pharmacopoeial monograph allow for analytical error, for unavoidable variations in manufacturing processes and for deviations to an extent considered acceptable under practical storage conditions. They provide standards with which pharmaceutical substances or FPPs must comply throughout their shelf life or period of use.

6.2 Technical guidance

The technical guidance provided in this section shall be considered as the minimum requirements agreed between the participating pharmacopoeias. They do not preclude national or regional pharmacopoeias from supplementing such requirements in their monographs in accordance with national or regional regulations.

6.2.1 Monographs for pharmaceutical substances

Prior to the preparation of any monograph it is essential to gather as much information as possible on the substance in question.

In particular it is necessary to ascertain:

- the origin of the substance;
- the method(s) of preparation of the substance, if needed;
- whether the substance is a mixture or a single entity;
- whether different entities (e.g. acid, base or salt) are available;
- the physicochemical characteristics of the substance that contribute to its identity and classification, for example, solubility or optical rotation;
- whether there are differences in physical form, for example, crystallinity or polymorphism, since these properties may affect the behaviour of the substance;
- whether a single optical isomer (e.g. enantiomer) as well as mixtures of isomers (e.g. racemate) are available;
- whether anhydrous or different hydrates or solvates are available.

Substances that are to be described in a monograph may be members of a group of very similar substances. A general monograph may be drafted stating the attributes

common to all members of the group and that can be used to identify single members of the group.

6.2.1.1 Monograph title

The International Nonproprietary Name (INN) or modified INN (INNM) established by WHO should be considered for use wherever it is available, while recognizing that individual pharmacopoeias may apply their own nomenclature policies.

6.2.1.2 General information to define the pharmaceutical substance

A pharmacopoeial monograph includes information regarding the pharmaceutical substance, such as:

- graphic formula;
- empirical/molecular formula and relative molecular mass (the latter is calculated based on the figures of the International Table of Relative Atomic Masses considering, where appropriate, the degree of hydration);
- Chemical Abstracts Service (CAS) registry number, if available;
- chemical name;
- the possible existence of isomers, so as to be able to specify either which isomer is present or to state that the substance is a mixture of isomers;
- in the case of an optical isomer, the absolute configuration is given by the R/S system at the asymmetrical centre(s) or any other appropriate system (e.g. for carbohydrates and amino acids);
- state of hydration or solvation, where relevant, ascertaining the state of hydration or solvation by an appropriate technique in order to distinguish clearly between substances which are well-defined hydrates and solvates and those that contain variable quantities of water or solvent(s):
 - for well-defined hydrates or solvates, water or solvent content ranges are specified;
 - for substances containing variable amounts of water or solvents, only a maximum content is given;
 - where substances exist as both non-hydrated (or non-solvated) and hydrated (or solvated) forms, and if all these forms are used and can be clearly distinguished, they may be treated as individual substances depending on the regulatory approach prevailing in the country or region.

In therapeutics, well-defined chemical combinations or even mixtures are sometimes used. In such cases it is necessary to specify precisely each component of

the combination or mixture, with its chemical structure and the proportion in which it is present.

6.2.1.3 Content

Assay limits are specified between which the content must fall. In certain instances the content may be given only as a lower limit. The assay limits take account of the precision of the method as well as the acceptable purity of the substance. Assay limits are normally expressed with reference to the dried, anhydrous and/or solvent-free substance.

In setting limits for the API content, account is taken of:

- the method of preparation, which determines the degree of purity that may be reasonably required;
- the precision and accuracy of the analytical method;
- where a separation technique is employed both for the test for related substances and the assay, content limits are set taking into account the maximum permitted amount of impurities and the analytical error;
- the evaluation of the extent of degradation during storage (since the limits are intended to apply throughout the shelf life of the substance and not just at the time of release testing);
- a sufficient number of experimental results obtained on several batches (at least three), if possible, of different origins and ages.

6.2.1.4 Qualitative properties of the pharmaceutical substance

The statements under this heading are not to be interpreted in a strict sense and are not to be regarded as analytical requirements. Caution statements may be included here.

The principal characteristics that may be referred to are:

- appearance;
- solubility;
- stability factors;
- hygroscopicity;
- solid-state properties;
- other characteristics, as necessary.

6.2.1.5 Identification

The tests given in the identification section are not designed to give a full confirmation of the chemical structure or composition of the substance. They are intended to give confirmation, with an acceptable degree of assurance, that the substance is the one stated on the label. The specificity of the identification should be such that pharmaceutical

substances exhibiting similar structures can be distinguished. When an identification series is being investigated it is desirable that other similar substances, whether or not they are the subject of monographs of the pharmacopoeia, are examined at the same time to ensure that a particular combination of tests within a series will successfully distinguish one similar substance from another. False-positive reactions caused by the presence of known impurities should be avoided.

Some of the purity tests in a monograph may also be suitable for identification purposes, possibly in a modified form. A system of cross-references to the section(s) can be exploited. This is particularly relevant in cases where distinction between closely related materials depends on properties that are also parameters in purity or composition control. In some cases an organic impurity procedure may be introduced to differentiate the analyte from similar, common, dangerous adulterants.

In the case of monographs for similar pharmaceutical substances, identification of the type of substances may be supplemented by selective but discriminating tests to identify individual members of the group.

6.2.1.6 Impurities and other tests

Certain tests may apply to special grades (e.g. parenteral preparations, dialysis solutions) or a test may have a special limit for a particular use: the particular application of a test/limit is indicated within the test.

6.2.1.6.1 Organic impurities

This section is principally directed at limiting impurities in chemical substances.

In the interests of transparency, information may be included on the impurities controlled by a test and the approximate equivalent (e.g. percentage or parts per million) of the prescribed limit in terms of the defined impurities or class of impurities.

Monographs should include tests and acceptance criteria for impurities that are likely to occur in substances used in approved medicinal products, insofar as the necessary information and samples (substance and impurities) are available from the producers.

Monographs on organic chemicals usually have a test entitled “Related substances” (or a test with equivalent purpose under a different title), designed to control related organic impurities. Impurities to be controlled include intermediates and by-products of synthesis, co-extracted substances in products of natural origin and degradation products.

Monographs on pharmaceutical substances should take account of the principles defined in ICH guideline Q3A (R2) (*Impurities in new drug substances*), or comparable guidelines, and follow regulatory decision-making. Products of fermentation and semi-synthetic products derived therefrom should be limited applying the same principles, but should be covered by thresholds considered appropriate for these substances. The same principle applies to excipients.

Unusually potent or toxic impurities. In addition to the above-mentioned requirements, impurities that are unusually potent or produce toxic or unexpected pharmacological effects need to be specifically considered. In this context, requirements for genotoxic impurities may be followed.

Monographs frequently have to be designed to cover different impurity profiles because of the use of different synthetic routes and purification procedures.

For pharmacopoeial purposes the objective of a purity test using a separation method will usually be the control of impurities derived from one or more known manufacturing processes and decomposition routes. However, the experimental conditions, especially the detection system, are chosen for the test so as not to make it unnecessarily narrow in scope.

Where monographs include a chromatographic method, this should provide a reliable means of locating all specified impurities on the chromatogram.

6.2.1.6.2 Inorganic impurities

Inorganic impurities include reagents, ligands and catalysts, elemental impurities, inorganic salts and other materials such as filter aids (where relevant).

Where known impurities are present, these are typically covered by specific tests.

6.2.1.6.3 Residual solvents

When applicable, residual solvents need to be controlled, for example, as outlined in the ICH guideline Q3C (Impurities: guideline for residual solvents).

6.2.1.6.4 Other tests

The following tests should be considered, but are not limited to:

- foreign anions and/or cations;
- loss on drying;
- semi-micro determination of water (Karl Fischer);
- micro determination of water (colorimetric titration);
- sulfated ash/residue on ignition;
- residue on evaporation;
- sterility;
- microbiological quality;
- bacterial endotoxins.

6.2.1.7 Assay

Assays are included in monographs unless, for example:

- all the foreseeable impurities can be detected and limited with sufficient precision;

- certain quantitative tests, similar to assays, are carried out with sufficient precision;
- the tests performed are sufficient to establish the quality of the substance (usually a non-active ingredient, for example, ethanol and water).

In certain cases more than one assay may be necessary, for example, when the substance to be examined consists of a combination of two parts that are not necessarily present in absolutely fixed proportions, so that the assay of only one of the two constituents does not make it possible to determine correctly the content of the substance as a whole.

In the case of well-defined salts, the assay of only one of the components, preferably the pharmacologically active component, is generally considered sufficient.

6.2.2 Monographs for finished pharmaceutical products

General tests and acceptance criteria that are applied to a specific pharmaceutical dosage form (and are not specific to a particular formulation) may be grouped together, for example, uniformity of mass/content, friability and disintegration as applied to tablet testing. These tests may be included in a general monograph for a pharmaceutical dosage form, in this example, tablets, as the test procedures are the same for all tablets.

Specific tests group together those procedures that are required to provide evidence that an FPP is of a suitable quality, and are specific to a particular pharmaceutical dosage form. As an example, tests described in tablet monographs may include identification, related substances, assay and dissolution. Specific tests are designed to control the purity, composition and release; these tests are dependent on the pharmaceutical substance.

Prior to the preparation of any monograph it is essential to gather as much information as possible on the product in question. In particular it is necessary to ascertain:

- if the FPP contains a mixture or a single pharmaceutical substance;
- if the FPP can be prepared from different entities (e.g. acid, base or salt);
- in cases where the pharmaceutical substance exhibits polymorphism, if the crystallographic form of the entity should be identified in the FPP monograph;
- if the FPP is available in different strengths, whether all strengths can be controlled under one monograph.

6.2.2.1 Monograph title

The titles of monographs for FPPs combine the name of the pharmaceutical substance and the pharmaceutical dosage form.

The pharmaceutical substance name should be based on the INN or national name, wherever it is available (the common name should be used where an INN or national name is not available). It is supplemented, when required, by the INN^M. The name is followed by the nationally or regionally accepted pharmaceutical dosage form taxonomy (or published standard term).

For FPPs containing more than one pharmaceutical substance (“combination products”), the individual INNs should be used where possible. Combination Names (Co-names) may exist in national pharmacopoeias for prescribing purposes.

6.2.2.2 General information to define the finished pharmaceutical product

Such information may include elements relating to the API, an expression of the content and other essential features of the dosage form. An appropriate reference to the relevant general monographs may be included.

The following should be observed:

- the pharmaceutical substance will be referred to in this section; it is not necessary to reproduce the defining information found in the pharmaceutical substance monograph within this section of the FPP monograph (e.g. the chemical name);
- any reference to producing a salt of the active moiety in situ during the manufacture of the FPP should be made in this section;
- the definition only refers to the name of the pharmaceutical substance; where the content is expressed in terms other than those described in the title of the monograph, the limits stated under “Content” (see 6.2.2.3) should reflect the label claim.

6.2.2.3 Content

Assay limits are specified between which the content of the pharmaceutical substance in the FPP must fall. Limits for each pharmaceutical substance (if more than one) or individual component are included. The assay limits must take account of the precision of the method as well as the strength of the FPP. Assay limits are normally expressed with reference to the active moiety or the label claim in accordance with the national or regional requirements.

Limits should be justified and account should be taken of:

- the strength of the FPP;
- the stability of the pharmaceutical substance in a specific FPP.

In the case of antibiotics determined by microbiological assay, the content limit is expressed in International Units (IU); where these exist a content limit is given in terms of a range, for example:

“The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. The upper fiducial limit of error is not less than 97.0% and the lower fiducial limit of error is not more than 110.0% of the stated number of IU”.

6.2.2.4 *Identification*

The tests given in the identification section are not designed to give a full confirmation of the chemical structure or composition of the API in the product. They are intended to give confirmation, with an acceptable degree of assurance, that the API(s) in the product is/are the one(s) stated on the label. Special attention must be given to the sample preparation to ensure that the API is adequately extracted from the sample matrix.

The minimum number of tests should be included, commensurate with providing adequate assurance of identity. For example, the monograph may contain at least two procedures to identify the API(s) in a pharmaceutical dosage form; one test per API may be sufficient if the technique used is considered to be a fingerprint of the active moiety (e.g. infrared absorption spectrophotometry).

6.2.2.5 *Impurities and other tests*

This section should include all of the specific tests that are required to prove the quality of the specific FPP.

The “Tests” section is intended to:

- limit the impurities within the FPP. This includes degradation impurities throughout the shelf life of the FPP and impurities that occur due to the manufacturing process. In certain circumstances it is necessary to control FPP impurities resulting from the synthesis of the pharmaceutical substance;
- ensure the homogeneity of the API(s) from dose to dose within the FPP;
- take account of the potential for the sample matrix to restrict the release of the active moiety in the FPP (i.e. a dissolution test in a monograph for tablets);
- limit the pyrogenic content of a parenteral FPP (i.e. a test for bacterial endotoxins or a monocyte activation test).

6.2.2.5.1 *Impurities: title of test(s)*

Where the test is intended to control specified and unspecified impurities, the title of the test should be “related substances” or “related compounds”, or similar, in line with national or regional practices.

Where the test is intended to control one or a limited number of specified impurities the title of the test should indicate the impurity or impurities controlled.

6.2.2.5.2 *Related substances (or related compounds)*

Further to the section on pharmaceutical substance monographs, the following should be considered for related substances tests specified in FPP monographs:

- specific, quantitative techniques (i.e. high performance liquid chromatography (HPLC)) are preferred;
- non-specific or non-quantitative techniques should be used only if a specific method is not available or is unsuitable;
- methods should be developed with the aim of controlling degradation products and impurities. In certain circumstances it is necessary to control impurities from synthesis of the pharmaceutical substance in the FPP (for example, when they are detected in the test for related substances at a level greater than the limit for unspecified impurities);
- impurities being controlled at a level above the limit for unspecified impurities should be identified using a reference standard or other suitable techniques.

The principles outlined in, for example, ICH guideline Q3B (R2) (*Impurities in new drug products*) could be used as a starting point.

6.2.2.6 *Performance testing*

Depending on the dosage form, adequate performance testing may need to be included in the monograph. Such tests may include, but are not limited to, dissolution or deposition of the emitted dose.

6.2.2.7 *Uniformity*

Pharmaceutical preparations presented in single-dose units should comply with the test(s) as prescribed in the specific dosage form monograph.

Acceptance criteria will be specified regionally for a specific product or pharmaceutical form.

6.2.2.8 *Other tests*

The following tests should be considered, but are not limited to:

- sterility;
- bacterial endotoxins;
- microbiological quality;
- if necessary, tests for excipients such as antioxidants and antimicrobial agents.

6.2.2.9 *Products of natural origin*

Attention needs to be paid to the requirements in the different regions for minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.

6.2.2.10 *Assay*

The assay quantifies the amount of API in the FPP. It may also quantify certain excipients, such as preservatives, depending on national and regional legislation. Where possible the method used should be harmonized with that in the pharmaceutical substance monograph, but this may not be possible because of the sample matrix.

Assays are included in all FPP monographs unless certain quantitative tests, similar to assays, are carried out with sufficient precision (for example, uniformity of content, where a mean of individual results could be considered an accurate assay).

In certain cases more than one assay may be necessary, for example, where the FPP contains two or more APIs.

For products such as antibiotics, the results of the quantitative tests may not fully represent the therapeutic activity, in which case a microbiological assay and a test for composition are included.

Specific assays should be used where possible, for example, liquid or gas chromatography. Specific assays remove interference from excipients (formulation matrix) which could lead to significant errors when using non-specific assays.

Whenever possible, a stability-indicating procedure should be used for the assay. Generally, chromatographic procedures are preferred. When a non-stability-indicating assay is proposed, a separate stability-indicating impurity procedure should be provided.

7. Analytical test procedures and methods

Analytical test procedures and methods are employed to establish quality aspects such as identity, purity and content of pharmaceutical substances and FPPs. An analytical method and/or technique specified in a pharmacopoeia should be robust, reliable, accurate, precise, sensitive, specific and use readily available materials and equipment.

A pharmacopoeia provides different types of methods, mainly physical, physicochemical or chemical methods and microbiological tests, for the analysis of pharmaceutical substances and FPPs. The type of method applied for analysis depends on the nature of the substance or product.

The principles of method validation apply to all types of analytical procedures in a pharmacopoeia. However, it is the responsibility of the user to verify that a particular method is valid for the particular pharmaceutical substance or FPP being tested.

The validation of analytical procedures described in monographs should comply with the requirements as laid down, for example, in the *WHO Supplementary guidelines on good manufacturing practices: validation, Appendix 4 on Analytical method validation*, in WHO Technical Report Series, No. 937, 2006, Annex 4, and ICH guideline Q2 (R1) (*Validation of analytical procedures: text and methodology*).

11.5 Good pharmacopoeial practices: Chapter on monographs for compounded preparations

Annex 6, WHO Technical Report Series, 1010, 2018

Background

Following the fiftieth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, the guidance on good pharmacopoeial practices (GPhP) was published as Annex 1 to the report.¹ The primary objective of the GPhP is to define approaches and policies in establishing pharmacopoeial standards with the ultimate goal of harmonization. In line with this objective, this guidance on monographs for compounded preparations has been developed outlining the structure and contents of such monographs.

1. Introduction

Compounded preparations² involve the preparation, mixing, assembling, altering, packaging and labelling of a medicine or drug-delivery device, in accordance with a licensed practitioner's prescription, medication order or initiative based on the relationship between the practitioner, patient, pharmacist and compounder in the course of professional practice.

This section of the GPhP helps define good practices for developing pharmacopoeial monographs for compounded preparations, which will help ensure the quality of these preparations.

2. Monograph development

Pharmacopoeial monographs for compounded preparations are generally developed by a pharmacopoeia and its expert committees rather than by donation from a manufacturer. Monographs for compounded preparations may include a stability-

¹ Good pharmacopoeial practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 1 (WHO Technical Report Series, No. 996).

² The term "compounded preparations" is used throughout this document. This term encompasses medicines that are (i) prepared extemporaneously, under the supervision of a pharmacist, for a specific patient and (ii) those that are prepared in advance in appropriate facilities (also known as stock preparations).

indicating assay and acceptable limits for the active pharmaceutical ingredient(s) (API(s)). Where required, a beyond-use date (BUD) or assigned shelf life³ is included, based on suitable stability studies. Typical sources of pharmacopoeial monographs for compounded preparations include:

- laboratory-conducted method development, validation and stability studies;
- peer-reviewed literature, evaluated based on stringent criteria;
- donated scientific data.

3. Quality of ingredients

Ingredients specified in the definition and/or used in the formula in pharmacopoeial monographs for compounded preparations comply with relevant monographs for pharmaceutical substances and general monographs, if available.

4. Monograph title

The titles of monographs for compounded preparations will follow national naming conventions, but should include the name of the pharmaceutical substance and the dosage form. Some pharmacopoeias may use the following naming convention for compounded preparations that are used for both humans and animals:

- [medicine name] dosage form;
- [medicine name] compounded [route] [dosage form];
- [medicine name] compounded [route] [dosage form], veterinary (for animals only).

5. Sections of the compounded preparation monograph

Compounded preparation monographs may include the following sections:

- Definition and content
- Assay
- Compounding procedures
- Identification tests
- Specific tests
- Additional information
- Stability information and BUD

³ The term “beyond-use date” (BUD) is used throughout this document synonymously with “assigned shelf life”.

5.1 Definition and content

Assay limits provide the acceptable range of the labelled amount of the API(s). The assay limits should take into account the precision and accuracy of the method, the strength of the preparation and the stability of the pharmaceutical substance in the specific preparation. Assay limits are normally expressed with reference to the active moiety or the label claim, in accordance with national and regional requirements.

5.2 Assay

The assay quantifies the amount of API in the compounded preparation. It may also quantify certain excipients, such as preservatives, depending on national and regional legislation. In certain cases more than one assay method may be necessary, for example, where the preparation contains more than one API.

Where required, the compounded preparation should be tested for strength and potency. The purpose of strength or potency testing is to establish or verify the concentration of the pharmaceutical substance(s) in the compounded preparation.

Where possible, a validated stability-indicating assay method is described. Methods used generally include high-performance liquid chromatography or gas chromatography, among others. Other methods include titration and microbiological assays, which are sometimes used to test antibiotics.

The routine testing of each batch may not be feasible.

5.3 Compounding procedures

The monograph may contain a formula for the preparation which lists all of the ingredients and their quantities. Compounding procedures may include all of the steps necessary to accurately and reproducibly prepare the preparation.

5.4 Identification tests

The tests given in the identification section are not designed to give a full confirmation of the chemical structure or composition of the API(s) in the compounded preparation. They are intended to give confirmation, with an acceptable degree of assurance, that the API(s) in the compounded preparation is/are the one(s) stated on the label.

5.5 Specific tests

In addition, specific tests may be included, as appropriate. Examples are included in the following list, which is neither exhaustive nor comprehensive:

- pH;
- sterility;
- bacterial endotoxins;

- uniformity of dosage units;
- particulate matter;
- antimicrobial effectiveness;
- impurities or related substances;
- other tests, as appropriate.

5.6 Additional information

▪ *Packaging and storage information*

For containers and container-closure system materials it is preferable to reference pharmacopoeial monographs, if available. The container system is chosen to prevent contamination and minimize degradation.

Storage conditions, which are necessary to assure the quality of the product until the BUD, should be included.

▪ *Labelling information*

Pharmacopoeial labelling requirements are not comprehensive, and only those statements that are necessary to demonstrate compliance with the monograph are mandatory. National and international requirements for licensed products may not apply to compounded preparations and specific guidance on compounded preparations should be available.

5.7 Stability information and beyond-use dating for compounded preparations

Where specified in a monograph, BUDs should be assigned conservatively, taking note of the following:

- the nature of the medicine and its degradation mechanism;
- the dosage form and its components;
- the method of sterilization, if applicable;
- the potential for microbial proliferation in the preparation;
- the container in which it is packaged;
- the expected storage conditions;
- the intended duration of therapy.

When an authorized or licensed product is used as the source of the API for a compounded preparation, the compounder should refer to the manufacturer for stability information and to the literature for information on stability, compatibility and degradation of ingredients as well as using his or her compounding education and experience.

Compounded preparations should be stored under conditions that prevent contamination and minimize degradation. The chemical, physical and microbiological stability until the BUD should be assured.

■ *Additional considerations*

For compounded preparations it is preferable to include a BUD based on laboratory-derived stability data in the pharmacopoeial monograph.

Susceptible preparations should contain suitable antimicrobial agents to protect against bacteria, yeast and mould contamination inadvertently introduced during or after the compounding process. When antimicrobial preservatives are contraindicated in susceptible compounded preparations intended for multiple use, storage of the preparation in a refrigerator is necessary and this should be stated in the monograph. Appropriate patient instruction and consultation is essential to ensure proper storage and handling of such compounded preparations by the patient or caregiver.

For sterile compounded preparations, it is preferable to include laboratory-derived stability and sterility information in pharmacopoeial monographs for such preparations. The laboratory-derived sterility information should evaluate the suitability of the sterilization method (for example, filtration, steam or dry heat) and container-closure integrity.

11.6 Good pharmacopoeial practices: Chapter on monographs on herbal medicines

Annex 7, WHO Technical Report Series, 1010, 2018

Background

Following the fiftieth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, the guidance on good pharmacopoeial practices (GPhP) was published as Annex 1 to the report.¹ The primary objective of the GPhP is to define approaches and policies in establishing pharmacopoeial standards with the ultimate goal of harmonization. In line with this objective, this guidance for monographs on herbal medicines has been developed outlining the structure and contents of a herbal medicine monograph.

1. Introduction

Pharmacopoeial monographs for herbal medicines should contain information in the definition that is consistent with the monograph title, followed by specifications for quality including identity, purity and content. Individual monographs describe test procedures, together with the corresponding specifications. The monograph may include:

- an official title;
- a definition;
- a production section;
- an identification section;
- a test section covering, for example, physicochemical tests and, where appropriate, tests on contaminants;
- an assay section on determining constituents with known therapeutic activity, active or analytical markers.

Further sections providing information on labelling and storage may also be provided.

¹ Good pharmacopoeial practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 1 (WHO Technical Report Series, No. 996).

2. General chapter

The general testing methods and other specifications that are common for herbal medicines may be described in a General chapter.

3. Individual monographs on herbal medicines

3.1 Monograph title

The title of the monograph may include the Latin name, or the well-established common local name and English common name. This may be followed by the name of relevant plant part(s) or plant material (e.g. resin, gum-resin) and, where applicable, its state and the type of herbal preparation (e.g. liquid extract, dry extract) and its dosage form (e.g. tablet, capsule or other form). Individual pharmacopoeias may apply their own nomenclature policies that meet regulatory needs and reflect the common names in commerce, as appropriate.

3.2 Definition

The definition provides details about the subject of the monograph and includes: the Latin binomial name and the taxonomic authority (abbreviations, if used, should be according to internationally accepted rules); the plant family name, if required by national legislation; the well-established common local name and English common name may be provided in addition to the scientific name, together with well-recognized synonyms. This section also provides details about the plant part(s) (i.e. aerial parts, root, leaves, flowers, rhizome, etc.), plant material (e.g. resin, gum-resin) and, where applicable, its state and the type of herbal preparation (e.g. liquid extract, dry extract) and its dosage form (tablet, capsule, etc.). When necessary, as dictated and supported by data, the definition also states the season or period in which plant material should be harvested according to *Good agricultural and collection practices (GACP) for medicinal plants*.² If more than one species is covered by the monograph, the definition should include, for each of the species, the requirements listed above. The definition should include the names and molecular formulae of relevant known constituents for which there is a specified range or minimum content, in percentages, usually calculated on the basis of the dry weight of the herbal medicine. Where a monograph applies to the herbal medicine in different states or stages of processing, this is stated in the definition.

3.3 Identification

The purpose of the Identification section is to ensure that the herbal medicine under examination is the one stated on the label. It is only necessary to include those techniques

² WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants. Geneva: World Health Organization; 2003.

that are applicable for the identification of specific herbal medicines. Macroscopic and microscopic descriptions may be supported by illustrations. Identification tests should be specific for the herbal medicine under examination. Typically, several identification tests, using independent approaches, are required in order to confirm the identity. The tests given in the Identification section are not designed to give a full confirmation of the chemical structure or composition of the herbal medicine. They are intended to give confirmation, with an acceptable degree of assurance, that it is the one stated on the label.

Test methods should be able to detect substitutes or adulterants that are likely to be found.

3.3.1 Macroscopic characteristics

The important macroscopic botanical characteristics of the herbal materials are specified to enable a clear identification. Where two or more species of a genus or subspecies are included in the definition, the differences, if any, between them should be indicated.

3.3.2 Microscopic characteristics

The microscopic examination of herbal materials is useful in determining their identity. Histological characteristics, such as microscopic characteristics of a transverse or longitudinal section may support the identification. For herbal materials for which macroscopic identification cannot be performed (for example, powdered herbal materials), the microscopic characteristics are important to determine their identity.

3.3.3 Chemical tests

Chemical tests can also be useful in determining the presence of substitution, adulteration or other foreign matter. Nonspecific chemical tests should be avoided. Phytochemical screening tests that recognize general classes of compounds such as alkaloids, flavonoids, terpenes, steroids, saponins and tannins, among others, should be avoided unless they provide a means of identifying potential adulteration due to species substitution or adulteration.

3.3.4 Fingerprinting

Chromatographic or spectroscopic patterns, often referred to as “fingerprints”, may be used for identification. The fingerprints should ideally be able to distinguish the herbal material under examination from other species that constitute both intentional and unintentional adulterants.

Fingerprints may be obtained, for example, by thin-layer chromatography (TLC), high-performance thin-layer chromatography (HPTLC), high-performance liquid chromatography, ultra-high-performance liquid chromatography, capillary

electrophoresis or gas chromatography methods. The methods should include all of the information required to perform the test, for example, preparation of sample and reference solutions, nature of plates or columns, testing conditions, mobile phase preparation, flow rate, and method of detection/detectors.

The results of such testing should contain a description of the critical features of the fingerprint chromatograms, such as the presence of specific peaks, bands or spots, retention time or relative retention values, retardation or retention factor (RF or Rf), their order of elution and, where applicable, their relative abundance. A colour image of a typical reproducible TLC fingerprint and/or table presentation may be provided as a guide for users. Pharmacopoeias may consider providing reference standards (RS) to be used for fingerprint testing.

3.3.5 DNA-based tests

DNA-based tests, such as polymerase chain reaction and DNA sequencing, can be useful in identifying specific herbal materials or detecting adulteration with either related or unrelated species that are difficult to detect using other methods.

3.4 Tests for contaminants/impurities

3.4.1 General

Tests for the following may be included and limits specified, as appropriate:

- foreign matter;
- elemental contaminants or impurities (for example, toxic metals such as lead, cadmium, mercury and arsenic);
- microbiological quality: individual pharmacopoeias may consider specifying requirements for total aerobic microbial count and total combined yeast/moulds count as well as for specified microorganisms, for example, bile-tolerant Gram-negative bacteria, *Escherichia coli* and *Salmonella*;
- mycotoxins;
- toxic and harmful substances (such as pesticide residues, radioactive contaminants and natural toxins);
- residual solvents.

3.4.2 Specific

An individual herbal medicine may require specifications that are peculiar to that item, especially when patient safety is an issue. Limits should be set for certain constituents of the herbal medicines that may be considered undesirable “negative markers”, negative botanical characteristics or histological parameters.

For some individual herbal medicines, there could be a risk of adulteration by herbal medicines that have a related morphological appearance or are marketed under similar common names. In such cases, additional tests may be specified, as appropriate, to detect and determine such adulterants. Where appropriate, tests for compounds that may affect the safety of the herbal medicines (such as alkaloids or cardiotonic steroids, among others) may be included in the monograph.

3.5 Assay

Where the constituent(s) responsible for the therapeutic activity of the herbal medicine is/are known, its/their quantitative determination should be included. Where the chemical constituent(s) responsible for the known therapeutic activity is/are not known, the pharmacopoeia may include testing for determination of the chemical constituent(s) that act as analytical or active marker(s).

Where an assay of one or more chemical constituents is carried out, assay limits are specified for each constituent either as a minimum content or as a percentage content range. Where the herbal medicine contains constituents that are known to degrade (e.g. due to improper drying, storage under high temperatures or extended storage), those constituents may be used as analytical markers to control the quality of the herbal medicine.

Stability-indicating chromatographic procedures that are validated for routine quality control work should be used, where possible. Pharmacopoeial procedures should be validated in accordance with accepted scientific practice and current recommendations on analytical validation. Assay methods developed through a collaborative process involving several laboratories, or using other suitable approaches, may be adopted.

3.6 Physicochemical tests

Physicochemical tests can serve as a valuable source of information and provide appropriate characterization standards to establish the quality of herbal medicines. Such evaluations may include:

- water and/or alcohol extractable matter;
- total ash content;
- water-soluble ash;
- alcohol-soluble ash;
- acid-insoluble ash;
- loss on drying;
- water content;
- volatile oils, etc.

3.7 Other tests

The following tests may be included, as appropriate:

swelling index;

bitterness values;

particle size;

any other test(s) specific to the particular herbal medicine.

Reference to taste and/or odour in the definition or the test procedures may be inappropriate due to safety reasons and should be avoided.

3.8 Additional information

3.8.1 Packaging, labelling and storage

Labelling requirements consistent with applicable national or regional legislation may be provided. Storage conditions may be provided when considered necessary to prevent contamination and/or to minimize possible deterioration. Guidance statements specifying the packaging may be included, where applicable, for example, in monographs for oils or oleoresins or distilled oils.

3.8.2 Reference standards

Pharmacopoeias may describe the use of RS in the analysis of individual herbal medicines. RS may be pure substances or extracts of herbal materials or powdered herbal materials used for comparison. The RS established by individual pharmacopoeias are suitable for their intended purpose.

Glossary

To comply with national and regional legislation, the definitions given in the individual pharmacopoeias may deviate from those provided below.

Adulterant is herbal material, a herbal constituent or other substance that is either deliberately or non-intentionally (through cross-contamination or contamination) added to a herbal material, herbal preparation or finished herbal product.

Herbal dosage forms are the physical form (liquid, solid, semi-solid) of herbal products produced from herbs, with or without excipients, in a particular formulation (such as decoctions, tablets and ointments). They are produced either from herbal materials (such as dried roots or fresh juices) or herbal preparations (such as extracts).

Herbal medicines include herbs and/or herbal materials and/or herbal preparations and/or finished herbal products in a form suitable for administration to patients.

Note: In some countries herbal medicines may contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (e.g. animal and mineral materials, fungi, algae or lichens).

Herbs include crude plant materials such as leaves, flowers, fruit, seed, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.

Herbal materials³ include, in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries these materials may be processed by various local procedures, such as steaming, roasting or stir-baking with honey, alcoholic beverages or other plant materials.

Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey or in other materials.

Finished herbal products consist of one or more herbal preparations made from one or more herbs (i.e. from different herbal preparations made from the same plant as well as herbal preparations from different plants. Products containing different plant materials are called “mixture herbal products”).

Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture herbal products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be “herbal”.

Medicinal plant materials: see Herbal materials

Medicinal plants are plants (wild or cultivated) used for medicinal purposes.

State of the herbal material means whole, fragmented, peeled, cut, fresh or dried.

³ The participants of the third WHO consultation on quality control, held in China, Hong Kong SAR, from 4 to 6 September 2017, recommended that latex and exudates can be included.

11.7 Good chromatography practices

Annex 4, WHO Technical Report Series, 1025,
2020 (new)

1. Introduction and scope	1722
2. Glossary	1722
3. Chromatographic systems	1724
4. Qualification, validation, maintenance and calibration	1724
5. Access and privileges	1725
6. Audit trail	1726
7. Date and time functions	1726
8. Electronic systems	1726
9. Solvents, buffer solutions and mobile phases	1727
10. Column management	1727
11. Sample management and sample set	1728
12. Chromatographic methods (acquisition and processing)	1729
13. Peak integration	1730
14. Data management	1731
References	1732
Further reading	1732

1. Introduction and scope

- 1.1 The use of chromatography methods such as high-performance liquid chromatography, also referred to as high-pressure liquid chromatography (HPLC), and gas chromatography (GC) in quality control laboratory analysis has increased significantly in recent years. Observations during inspections have shown that there was a need for a specific good practices (GXP) document.
- 1.2 HPLC and GC methods are used in, for example, the identification of materials and products, for determination of assay and related substances in materials and products, as well as in validation such as process validation and cleaning validation. *Note:* Although thin-layer chromatography methods are also used, this approach is not specifically addressed in detail in this document.
- 1.3 Owing to the criticality of the results obtained through chromatography, it must be ensured that the data acquired meet ALCOA+ principles (i.e. attributable, legible, contemporaneous, original and accurate, with additional emphases [see Glossary]).
- 1.5 This document provides information on GXP to be considered in the analysis of samples when chromatographic methods and systems are used. The principles should be applied in the analysis of, for example, raw materials, starting materials, intermediates, in-process materials and finished products.
- 1.6 The principles contained in this guideline are applicable to general chromatographic analysis used in, for example, assay determination, testing for related substances and impurities, process validation, cleaning validation, cleaning verification and stability testing.

2. Glossary

The definitions given below apply to the terms used in this guideline that are not defined in existing WHO terms and definitions databases. They may have different meanings in other contexts. *Note:* For general definitions relating to chromatography, see the relevant pharmacopoeia recognized by the national medicines regulatory authority.

ALCOA. A commonly used acronym for “attributable, legible, contemporaneous, original and accurate”.

ALCOA+. A commonly used acronym for “attributable, legible, contemporaneous, original and accurate” that puts additional emphasis on the attributes of being complete, consistent, enduring and available – implicit basic ALCOA principles.

audit trail. A form of metadata that contains information associated with actions that relate to the creation, modification or deletion of GXP records. An audit trail provides for

secure recording of life-cycle details such as creation, additions, deletions or alterations of information in a record, either paper or electronic, without obscuring or overwriting the original record. An audit trail facilitates reconstruction of the history of such events relating to the record, regardless of its medium, including the “who, what, when and why” of the action.

back-up. A copy of one or more electronic files created as an alternative in case the original data or system are lost or become unusable (for example, in the event of a system crash or corruption of a disk). It is important to note that back-up differs from archival, in that back-up copies of electronic records are typically only temporarily stored for the purposes of disaster recovery and may be periodically overwritten. Such temporary back-up copies should not be relied upon as an archival mechanism.

calibration. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

data. All original records and true copies of original records, including source data and metadata and all subsequent transformations and reports of these data, that are generated or recorded at the time of the good manufacturing practices (GMP) activity and allow full and complete reconstruction and evaluation of the GMP activity. Data should be accurately recorded by permanent means at the time of the activity. Data may be contained in paper records (such as worksheets and logbooks), electronic records and audit trails, photographs, microfilm or microfiche, audio- or video-files, or any other media whereby information related to GMP activities is recorded.

data integrity. The degree to which data are complete, consistent, accurate, trustworthy and reliable and to which these characteristics of the data are maintained throughout the data life-cycle. The data should be collected and maintained in a secure manner, such that they are attributable, legible, contemporaneously recorded, original or a true copy and accurate. Assuring data integrity requires appropriate quality and risk management systems, including adherence to sound scientific principles and good documentation practices.

metadata. Data about data that provide the contextual information required to understand those data. Metadata necessary to evaluate the meaning of data should be securely linked to the data and subject to adequate review. Examples of metadata include the time/date stamp of an activity, the operator identification (ID) of the person who performed an activity, the instrument ID used, processing parameters, sequence files, audit trails and other data required to understand data and reconstruct activities.

qualification. Documented evidence that premises, systems or equipment are able to achieve the predetermined specifications, are properly installed, and/or work correctly, and lead to the expected results.

sample set. The combination of samples, standards and blanks prepared for analysis, which includes the specified sequence to be injected or analysed.

source data. Original data obtained as the first-capture of information, whether recorded on paper or electronically.

validation. The action of proving and documenting that any process, procedure or method actually and consistently leads to the expected results.

3. Chromatographic systems

- 3.1 Chromatographic systems should meet regulatory and GXP requirements. This should include, for example, ensuring that data are acquired, processed and stored in accordance with ALCOA+ principles (see Glossary).
- 3.2 Supplier selection and vendor qualification should ensure that hardware and software are suitable for their intended application.
- 3.3 Valid agreements should specify the respective responsibilities between the purchaser and supplier and include arrangements for after-sales services.
- 3.4 Chromatographic systems selected, installed and qualified should be appropriate for their intended use.
- 3.5 The environment in which such systems are placed should be appropriate to support their performance. This may include, for example, control of temperature and relative humidity in the area.

4. Qualification, validation, maintenance and calibration

- 4.1 The scope and the extent of validation and qualification of chromatographic systems should be determined based on risk management principles. This includes hardware and software.
- 4.2 The approach to, and execution of, validation and qualification should be described in an authorized document such as a validation master plan.
- 4.3 All stages of qualification should be considered and may include, for example, user requirement specifications (URS), design qualification (DQ), factory acceptance

test (FAT), site acceptance test (SAT), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

- 4.4 Validation and qualification should be described in protocols and recorded in reports. Reports should contain documented evidence and include, for example, screenshots, printouts or other source data and metadata of tests executed as part of validation and qualification.
- 4.5 The data should provide evidence of the consistency of performance of the system and reliable and accurate results.
- 4.6 Parameters such as, but not limited to, password control, audit trail, access and privileges should be described and verified during validation and qualification.
- 4.7 Maintenance, preventive maintenance and calibration of chromatographic systems should be done in accordance with written procedures. Records should be maintained.
- 4.8 Root cause analysis, impact assessment and risk assessment should be done when any calibration parameter is found to be out of calibration or not meeting the predefined limits. Appropriate corrective and preventive action should be taken and documented.

5. Access and privileges

- 5.1 There should be a standard operating procedure (SOP) for the creation and deletion of user groups and users of the chromatographic system, indicating the relevant privileges allocated to each user. Records should be maintained.
- 5.2 An up-to-date record of user groups and users should be maintained.
- 5.3 Users in each group should be appropriately qualified for the responsibility and privileges allocated.
- 5.4 Where required, justification should be provided for privileges granted to user groups or users, including all exceptions.
- 5.5 User privileges reflected in written procedures should be a true reflection of the privileges allocated electronically.
- 5.6 Administrator access rights should not be given to other users on the system.

6. Audit trail

- 6.1 Chromatographic systems should have an audit trail(s) which reflect(s), for example, users, dates, times, original data and results, changes and reasons for change.
- 6.2 Full audit trails should be enabled from the time of installation of software.
- 6.1. Audit trails should remain enabled throughout the life-cycle of a chromatographic system.
- 6.3 Audit trails should be reviewed in accordance with an SOP and include systems and project audit trails. There should be evidence of regular review of an audit trail (for example, each sample sequence or sample set in chromatographic analysis) and of periodic review of audit trails. (Periodic review should be done at specified intervals, based on risk management principles.)
- 6.4 Audit trails are part of metadata and should be stored as part of the data set for all chromatographic analyses.

7. Date and time functions

- 7.1 Chromatographic systems should have date and time functions enabled from the time of installation of the software.
- 7.2 The date and time function should be locked, and access to change the date and time should be controlled. (This includes changes to time zone setting.)
- 7.3 All GMP actions on chromatographic systems should be date- and time-tracked.

8. Electronic systems

Note: This includes computerized systems.

- 8.1 Written procedures should be followed when a new electronic system is taken into use. Procedures should also be followed for the removal of a system from use. Records should be maintained.
- 8.2 Software selected, installed and applied for acquisition, processing and calculation of results should be suitable for its intended use, validated, and render results meeting regulatory, GXP and ALCOA+ principles.
- 8.3 It is preferable that all chromatographic systems be linked to a network system where data are stored and managed on a centralized server.

- 8.4 Stand-alone systems should be appropriately managed. Risk assessment should be done to ensure that sufficient controls are in place to eliminate the risks associated with stand-alone systems. These include, but are not limited to, access, privileges, date and time function, audit trail, data back-up and data management.
- 8.1. Electronic data management systems (EDMS) should be considered for the appropriate management of data, including acquisition, processing and storage of data. EDMS should be appropriate for their intended use and ensure the accuracy and reliability of data acquired and processed.

9. Solvents, buffer solutions and mobile phases

- 9.1 Solvents, buffer solutions and mobile phases should be prepared, stored and used in accordance with authorized specifications and procedures and a relevant pharmacopoeia recognized by the national medicines regulatory authority. These should be used within appropriate, scientifically justifiable timelines.
- 9.2 Records for their preparation and use should be maintained.
- 9.3 Chemicals, reagents and other materials used should be of appropriate grade and quality.
- 9.4 Liquid mobile phases should be filtered, degassed and pressurized when required.
- 9.5 Carrier gases used for gas chromatography should have the appropriate purity and be suitable for their intended use.

10. Column management

- 10.1 Columns used in chromatography should be appropriate for their intended use.
- 10.2 Columns should be purchased from approved suppliers.
- 10.3 Columns should be verified on initial receipt and checked for their suitability as part of the chromatographic system, prior to use in analysis.
- 10.4 Tubing and fittings should be appropriate to ensure that the system performs as expected.
- 10.5 The number of theoretical plates (column efficiency) should be monitored to ensure efficiency is obtained for acceptable chromatography.
- 10.6 Columns should be equilibrated before the analysis. The column oven (and column) temperature should be controlled when specified in the analytical procedure.

- 10.7 The required flow rate should be specified in relevant test procedures. It should be appropriate for the column to be used, to ensure optimal chromatographic separation without exceeding recommended maximum backpressure.
- 10.8 The use of columns should be recorded in a traceable manner. This includes, for example, the unique column identification number, number of injections and washing of the column.
- 10.9 Columns should be washed (cleaned or flushed) according to defined procedures describing the steps and parameters, such as sequence, temperature, flow rate and time.
- 10.10 Columns should be stored in a manner that ensures that they are not damaged.

11. Sample management and sample set

Note: Inappropriate management of samples may result in errors during analysis. Written procedures should be followed to avoid such risks.

- 11.1 Sample management in the laboratory (including the receipt and preparation of samples) should be considered an important aspect in good chromatography practices.
- 11.2 Samples received for analysis should be entered in an appropriate record that ensures the traceability of the sample detail and analysis.
- 11.3 Samples should be stored under appropriate conditions.
- 11.4 Samples (as well as blank and standard solutions) should be prepared in accordance with the authorized specifications and standard test procedures. Records for the preparation should be maintained.
- 11.5 Official, secondary or working standards used should be traceable to the records maintained for their purchase, preparation and storage.
- 11.6 Standard and sample solutions prepared for use in chromatography should be used within defined timelines derived from analytical procedure validation and stability data, as appropriate.
- 11.7 The sample set should be defined. The vials with standard solution(s), sample solution(s) and blank solution(s) should be verified to ensure the correct sequence of injections in the chromatographic system before starting the sequence of injections.
- 11.8 Where carry-over or interference in analysis is relevant, suitable precautions should be taken, such as the inclusion of a blank in the sequence of injections.

- 11.9 The use of “trial injections”, “system check injections”, or other injections that are not specified as part of a sample set, is not recommended. In exceptional cases where this is done, authorized procedures should clearly describe this approach. (Normally, only standard solutions may be used for this purpose, unless otherwise needed and justified e.g. biologics). The electronic record of results in such cases should be saved and stored, together with the results of the sample set for analysis.
- 11.10 A system suitability test (SST) should be part of the sample set. The SST should be performed as described in the respective pharmacopoeia monograph or validated in-house specification and standard test procedure. The SST should meet the predefined acceptance criteria, before samples are injected and throughout the analysis.
- 11.11 Acceptance criteria should be set for the SST, bracketing standards, deviation from relative retention and any other aspect that may be deemed necessary for the chromatographic analysis. This includes acceptability of peak shapes.
- 11.12 Bracketing standards (standard solution injections) should be included in the sample set, at defined intervals, where appropriate. The number of bracketing standards included in a sample set should be defined. Compliance with the defined acceptance criteria should be verified.
- 11.13 Where blank interferences are detected, these should be within predefined limits.

12. Chromatographic methods (acquisition and processing)

- 12.1 Chromatographic methods should be suitable for their intended use. Appropriate acceptance criteria should be specified for parameters such as selectivity (resolution and/or peak-to-valley ratio), sensitivity (signal-to-noise ratio), peak symmetry, repeatability and integration conditions (if applicable).
- 12.2 Where non-pharmacopoeia methods are to be used, these should be developed, validated and described in detail in standard procedures. These procedures should be followed by qualified, trained, experienced personnel.
- 12.3 It is preferable that methods are created and saved in the chromatographic system by authorized personnel. The method selected for analysis from the saved methods should not be modified, unless approved for the intended purpose by authorized personnel.
- 12.4 Data acquisition and processing software should be appropriately validated or verified as being suitable for use. Methods selected for acquisition and processing should be traceable and reflected in the audit trail.

- 12.5 Methods should be proven to remain in a validated state throughout their life-cycle.
- 12.6 Chromatographic conditions (such as the composition of the mobile phase, pH, column dimensions) may be adjusted, within specified limits and in accordance with written procedures, to obtain the separation required. The adjustments made should be within the limits specified (such as defined in the design space of the analytical procedure). The SST requirements (e.g. resolution, symmetry, repeatability) should be met, and retention times and relative retention should be similar.

13. Peak integration

- 13.1 Peak areas in chromatograms should be accurately and consistently integrated in a scientifically sound manner.
- 13.2 Where possible, HPLC and GC instruments should be interfaced with computerized chromatographic data-capturing and processing systems that are capable of applying the integration parameters set, automatically and consistently.
- 13.3 To facilitate the accurate integration of chromatographic peaks, it is preferable that all of the peaks are fully separated. However, when quantitative data are to be obtained from unresolved peaks, the laboratory should have clear policies as to how such peaks should be integrated. This should include a description of the type of integration to be used, with a justification for its use, including, for example:
 - tangential skim;
 - exponential skim;
 - exponential curve fitting;
 - straight line skim;
 - front peak skim;
 - rear peak skim;
 - peak-to-valley ratio; and
 - valley height ratio.
- 13.4 Validated methods, specified chromatographic conditions and good chromatography practices should facilitate obtaining symmetrical peaks. Where atypical peak shapes are observed, these should be investigated and appropriate action taken.
- 13.5 Where manual integration has to be done, authorized procedures should be followed. Records should be maintained and include the authorization and justification for manual integration.

- 13.6 Using a procedure to integrate peak height or area by manually setting the baseline using chromatographic software should only be allowed in exceptional cases. Only trained, experienced users should be granted privileges to do so. Records and justification should be given when this procedure is followed.
- 13.7 Where smoothing is applied, the type of “filter” used and the extent of smoothing should be justified.

14. Data management

- 14.1 Chromatographic data should be managed in accordance with this guideline and other related guidelines (1–3).
- 14.2 Procedures should be followed for timely processing and review of data and reporting of results.
- 14.3 Data should be backed up according to procedures, and records maintained as proof thereof. Special care should be taken to ensure frequent back-up of data from stand-alone systems, to prevent loss of data.
- 14.4 Data should be safely stored in a way that includes control over access to data. Backed-up data should be stored at a separate location. Some data should be randomly selected for restoration and verification, at defined intervals, in accordance with a written procedure.
- 14.5 Where appropriate, paper printed records (including data and metadata) may be retained as part of the analytical report reflecting analyses performed.
- 14.6 Procedures should be in place to allow for recovery of chromatographic data in case of disasters such as instrument failure, viruses, hardware or software failure and power failure.
- 14.7 Complete data should be retained for appropriate periods of time, to allow for data verification, inspection, registration or other reasons.

Note: See other guidelines addressing computerized systems (1), data integrity (2) and good documentation practices (3).

References

1. Good manufacturing practices: guidelines on validation. Appendix 5. Validation of computerized systems. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; <https://iris.who.int/bitstream/handle/10665/312316/9789241210287-eng.pdf?sequence=1&isAllowed=y>, accessed 29 January 2020).
2. Guideline on data integrity. Draft for comments. Geneva: World Health Organization; 2019 (Working document QAS/19.819).
3. Guidance on good data and record management practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 5 (WHO Technical Report Series, No. 996; <https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>, accessed 4 November 2019).

Further reading

- The International Pharmacopoeia, 9th ed. Geneva: World Health Organization; 2019 (<https://apps.who.int/phint/en/p/docf/>, accessed 4 November 2019).
- European pharmacopoeia (Ph. Eur.), 9th edition. Strasbourg: Council of Europe; 2019.
- United States Pharmacopoeia (<https://www.usp.org/>, accessed 5 December 2019).
- Good manufacturing practices: guidelines on validation. Appendix 6. Guidelines on qualification. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (<https://iris.who.int/bitstream/handle/10665/312316/9789241210287-eng.pdf?sequence=1&isAllowed=y>, accessed 29 January 2020).
- WHO good practices for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 1 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y, accessed 5 December 2019).

11.8 Model certificate of analysis

Annex 4, WHO Technical Report Series, 1010, 2018

It has been recommended in various forums that the World Health Organization (WHO) should establish a model certificate of analysis (CoA) for use by quality control laboratories (QCLs) and in trade in starting materials and finished pharmaceutical products (FPPs). The model for such a certificate was first published in 2002 (1) and the current model is shown in Appendix 1. The items included are based on *WHO good practices for pharmaceutical quality control laboratories* (2) and *WHO good manufacturing practices for pharmaceutical products* (3). In addition, requirements of the International Standard ISO/IEC 17025 (4) and recommendations of the International Pharmaceutical Excipients Council (5) have been taken into account. Any specific legal requirements existing in the country of issue or importation should also be considered when issuing the certificate. This guidance is essentially designed for QCLs not related to manufacturers since the QCLs of manufacturers may have some of the information listed below in other quality system documents and therefore not necessarily included in the CoA.

The format and organization of the information on the CoA is at the issuing laboratory's discretion. The CoA can be printed on letterhead with the logo of the issuing laboratory.

According to *WHO good practices for pharmaceutical quality control laboratories* (2) the CoA lists tests performed on a particular sample with the results obtained and the acceptance criteria applied, followed by an indication of whether or not the sample complies with the specification. A CoA is usually prepared for each batch of a substance or product and should include the following information:

- the name and address of the laboratory issuing the CoA;
- the identification number of the CoA and on each page an identification, the page number and the total number of pages to ensure that every page is recognized as a part of the certificate;
- the name, address and contact person representing the originator of the request for analysis;
- the number assigned to the sample by the laboratory during registration upon receipt;
- the date on which the sample was received in the laboratory and the quantity of sample (number of units or packages);
- the name, description (for example, active ingredient, dosage form, strength, package size in the case of FPPs; grade in the case of starting

materials; type and material of the primary packaging), batch number (used by the original manufacturer and repacker or trader) of the sample for which the certificate is issued, the expiry date (or retest date, where applicable) and date of manufacture (if available);

- the name and address of the original manufacturer; in addition, if supplied by repackers or traders, the certificate should show the name and address of the repacker or trader;
- specifications for testing and a reference to the test procedure(s) used, including the acceptance criteria (limits);
- the results of all tests performed on the sample for which the certificate is issued (in numerical form, where applicable) and a comparison with the established acceptance criteria (limits); results of tests performed by subcontractors should be identified as such;
- any comments, observations or information on specific test conditions, where these are necessary for the interpretation of the results;
- a conclusion as to whether or not the sample was found to be within the limits of the specification;
- the date and signature of the head of the laboratory or other authorized person approving the certificate.

If the sampling plan and procedures used by the laboratory or other bodies are relevant to the validity or interpretation of the results, they should be referenced in the CoA.

Where relevant to the validity or application of the results, or if required by a customer, a statement on the estimated uncertainty of measurement should be included. However, it should be borne in mind that pharmacopoeial content limits are set taking into account the uncertainty of measurement and the production capability, and acceptance criteria for an analytical result should be predefined. Under currently applicable rules, neither the pharmacopoeias nor the medicines regulatory authorities require the value found to be expressed with its associated expanded uncertainty for compliance testing.

In the case of testing under contract, a customer may also request other information to be specified in the CoA.

If appropriate, the CoA may include a photograph(s) of the packaging and/or product tested.

If new certificates are issued by or on behalf of repackers or traders, these certificates should show the name and address of the laboratory that performed the tests and the name and address of the original manufacturer. A copy of the CoA generated by the original manufacturer should be attached.

When the certificate is used in trade it may also include a statement of the expected conditions for shipping, packaging, storage and distribution, deviation from which would invalidate the certificate.

QCLs with accreditation to the International Standard ISO/IEC 17025 should include in the CoA a reference to the accreditation, if related to the specific analysis.

References

1. Model certificate of analysis. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-sixth report. Geneva: World Health Organization; 2002: Annex 10 (WHO Technical Report Series, No. 902; https://iris.who.int/bitstream/handle/10665/42424/WHO_TRS_902.pdf?sequence=1&isAllowed=y).
2. Good practices for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 1 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y).
3. WHO good manufacturing practices for pharmaceutical products. Geneva: World Health Organization (<https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/guidelines>, accessed 29 December 2017).
4. General requirements for the competence of testing and calibration laboratories. Geneva: International Organization for Standardization; 2005 (ISO/IEC 17025:2005).
5. Certificate of analysis guide for pharmaceutical excipients. Brussels: International Pharmaceutical Excipients Council; 2013.

Appendix 1

Model certificate of analysis for starting materials and finished pharmaceutical products

This model is intended to serve as an example and not to be prescriptive.

Header:

Logo of the laboratory or company issuing the certificate (if applicable)

Identification no. of the CoA

page X of Y

Name and address of the laboratory

issuing the CoA: _____

Identification no. of the CoA: _____

Name, address and contact person representing the originator

of the request for analysis: _____

Registration no. of the sample: _____

Date received: _____ Quantity received: _____

Name of the product (International Nonproprietary

Name (INN), brand name, etc.): _____

Dosage form, strength, package size (if applicable): _____

Type and material of the primary packaging: _____

Batch number: _____

Date of manufacture (if available): _____

Expiry date/retest date: _____

Name and address of the original manufacturer: _____

Phone: _____ Email: _____

Name and address of the repacker and/or trader (if applicable): _____

Phone: _____ Email: _____

Specifications for testing: _____

11.9 WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines

Annex 1, WHO Technical Report Series, 1003, 2017

1. Introduction	1739
1.1 Background	1739
1.1.1 Preparation of the document	1740
1.2 Objectives	1740
1.3 Glossary	1741
1.3.1 Terms related to herbal medicines	1741
1.3.2 Terms related to constituents of herbal medicines	1742
1.3.3 Terms related to standardization and quality control of herbal materials and herbal preparations	1743
2. Selection criteria for substances of herbal origin relevant for standardization and quality control of herbal medicines	1744
2.1 General considerations in the standardization and quality control of herbal materials, herbal preparations and herbal medicines	1744
2.2 Purpose and expected functions of relevant marker substances	1745
2.2.1 Marker substances of constituents with known therapeutic activity	1745
2.2.2 Marker substances of constituents with recognized pharmacological activities	1746
2.2.3 Marker substances of characteristic constituents	1747
2.2.4 Marker substances for toxic constituents	1748
2.3 Use of reference materials	1749
3. Analytical methods for substances of herbal origin in herbal medicines	1750
3.1 General considerations regarding the test methods to be employed	1750
3.2 Monographs	1751
References and bibliography	1751

1. Introduction

1.1 Background

With the constant increase in the use of herbal medicines worldwide and the rapid expansion of the global market for them, the safety and quality of herbal materials and finished herbal products has become a major concern for health authorities, pharmaceutical industries and the public. The safety and efficacy of herbal medicines largely depend on their quality. Requirements and methods for quality control of finished herbal products, particularly for mixture herbal products, are far more complex than for chemical medicines. The quality of finished herbal products is also influenced by the quality of the raw materials used.

The World Health Assembly resolution on traditional medicine (WHA56.31), adopted in May 2003, requested WHO to provide technical support to develop methodology to monitor or ensure the quality, efficacy and safety of herbal products.

The International Conference of Drug Regulatory Authorities (ICDRA) in 2002 and 2004, as well as the Meetings of National Centres Participating in the WHO Programme of International Drug Monitoring (in 2000, 2001, 2002 and 2003) requested WHO to develop and continuously update the technical guidelines on quality, safety and efficacy of herbal medicines. One of the challenges in analysing the cause of adverse events reported in connection with use of herbal medicines is the lack of expertise in identifying and testing ingredients and constituents of suspect herbal products at the national pharmacovigilance centres, and/or national quality control laboratories.

To reduce the proportion of adverse events attributable to poor quality of herbal medicines, WHO has committed to developing new guidelines on quality assurance and control of herbal medicines, as well as to updating existing ones.

As a follow-up to the WHO Informal Meeting on Methodologies for Quality Control of Finished Herbal Products, held in Ottawa, Canada in July 2001, WHO decided to develop four new documents to provide technical guidance at the key stages where quality control is required in production of herbal medicines:

- (1) *WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants* (published in 2003) (1);
- (2) *WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues* (published in 2007) (2);
- (3) *Good processing practices for herbal materials* (in preparation); and
- (4) *Analytical methods for chemical identification of ingredients/constituents for quality control of herbal medicines* (originally proposed title).

In 2006, WHO revised the *Good manufacturing practices (GMP) supplementary guidelines for manufacture of herbal medicines* (3) to take into account the recent

update of the WHO core GMP and the fact that many Member States were considering establishing specific GMP for herbal medicines. Subsequently the WHO guidelines on *Good manufacturing practices (GMP) for herbal medicines* were published in 2007 (4).

WHO also revised the *Quality control methods for medicinal plant materials* (5) updating several chapters relating to determination of major contaminants and residues (e.g. microbial contaminants, toxic heavy metals and pesticide residues) and published it under the title *Quality control methods for herbal materials* (6).

1.1.1 Preparation of the document

The original title suggested for these guidelines was *Analytical methods for chemical identification of ingredients/constituents for quality control of herbal medicines*, as mentioned above. In February 2004, WHO convened a working group meeting on quality control of herbal medicines with financial support from Health Canada, in Vancouver, Canada. During this meeting, a brainstorming session was held on how to approach the issue of marker substances in quality assurance and control of herbal medicines. Subsequently, a WHO Consultation on quality control of herbal medicines, held in Abu Dhabi, United Arab Emirates, in July 2005, provided the forum to discuss the working draft of these guidelines. After wide global reviews of subsequent versions of the draft guidelines, the final draft guidelines were reviewed and discussed at the 2nd WHO Consultation on quality control of herbal medicines held in China, Hong Kong SAR, in November 2014. In October 2016, the finalized guidelines were submitted to the fifty-first meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations; the Committee endorsed and adopted the guidelines for publication as an annex to the report of the fifty-first meeting and as an independent WHO publication.

1.2 Objectives

The objectives of this document are to:

- 1) provide selection criteria for marker substances of herbal origin for quality control of herbal medicines;
- 2) identify methods and techniques for the identification and assay of these substances;
- 3) provide examples of selected marker substances in selected herbal materials;
- 4) contribute to the technical guidance on methodologies for quality control of herbal materials, herbal preparations and finished herbal products, in order to meet the quality control requirements;
- 5) promote the safety and efficacy of herbal medicines by contributing to consistent and reproducible quality.

1.3 Glossary

The terms used in this document are defined below. Additional terms that may be used in pharmaceutical texts referring to herbal medicines are also included. These terms and their definitions have been selected and adapted from other WHO documents and guidelines that are widely used by the WHO Member States. The citation numbers in parentheses following a term refer to the publication, as listed in the reference list, from which the term has been derived.

These definitions may differ from those included in national regulations, and are therefore provided for reference only.

1.3.1 Terms related to herbal medicines

Medicinal plants are plants (wild or cultivated) used for medicinal purposes (1, 3, 4).

Medicinal plant materials: see *Herbal materials*

Herbal medicines include *herbs* and/or *herbal materials* and/or *herbal preparations* and/or *finished herbal products* in a form suitable for administration to patients (Box A1.1).

Note: In some countries herbal medicines may contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (e.g. animal and mineral materials).

Box A1.1

Definition of herbs, herbal materials, herbal preparations and finished herbal products

Herbs are crude plant material which may be entire, fragmented or powdered. Herbs include, e.g. the entire aerial part, leaves, flowers, fruits, seeds, roots, bark (stems) of trees, tubers, rhizomes or other plant parts.

Herbal materials include, in addition to herbs, other crude plant materials. Examples of these other plant materials include gums, resins, balsams and exudates.

Herbal preparations are produced from herbal materials by physical or biological processes.

These processes may be extraction (with water, alcohol, supercritical carbon dioxide (CO₂)), fractionation, purification, concentration, fermentation and other processes. They also include processing herbal materials with a natural vehicle or steeping or heating them in alcoholic beverages and/or honey, or in other materials.

The resulting herbal preparations include, among others, simply comminuted (fragmented) or powdered herbal materials as well as extracts, tinctures, fatty (fixed) or essential oils, expressed plant juices, decoctions, cold and hot infusions.

Box A1.1 continued

Finished herbal products consist of one or more herbal preparations made from one or more herbs (i.e. from different herbal preparations made of the same plant as well as herbal preparations from different plants. Products containing different plant materials are called “mixture herbal products”).

Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture herbal products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be “herbal”.

Substitute is a herbal material or herbal preparation that is replaced by another, appropriately labelled herbal material, or herbal preparation consistent with the national pharmacopoeia, or traditional (or complementary and alternative) medicine practice.

Adulterant is herbal material, a herbal constituent or other substance that is either deliberately or non-intentionally (through cross-contamination or contamination) added to a herbal material, herbal preparation, or finished herbal product.

1.3.2 Terms related to constituents of herbal medicines

Constituents are chemically defined substances or group(s) of substances found in a herbal material or herbal preparations.

Therapeutic activity refers to the successful prevention, diagnosis and treatment of physical and mental illnesses. Treatment includes beneficial alteration or regulation of the physical and mental status of the body and development of a sense of general well-being as well as improvement of symptoms.

Active ingredients refer to constituents with known therapeutic activity, when they have been identified. Where it is not possible to identify the active ingredients, the whole herbal medicine may be considered as one active ingredient.

Constituents with known therapeutic activity are substances or group(s) of substances which are chemically defined and known to contribute to the therapeutic activity of the herbal material or of a preparation (3, 4).

Constituents with recognized pharmacological (biological) activities are characteristic constituents (substances or group(s) of substances) which are chemically defined and where the relevance of the pharmacological (biological) activities for the therapeutic or toxicological effects of the herbal material or herbal preparation has not yet been fully established.

Characteristic constituents are chemically defined substances or group(s) of substances that are specific for one medicinal plant or for certain plant species, families or genera.

Toxic constituents are substances or group(s) of substances that are chemically defined and their toxic property is predominant, although they may contribute to the therapeutic activities of the herbal material or herbal preparation.

1.3.3 Terms related to standardization and quality control of herbal materials and herbal preparations

Reference substances are chemically defined molecular entities (appropriate for intended uses in standardization or quality control of herbs and herbal materials).

Markers (marker substances) are reference substances that are chemically defined constituents of a herbal material. They may or may not contribute to the therapeutic activity. However, even when they contribute to the therapeutic activity, evidence that they are solely responsible for the clinical efficacy may not be available.

Primary chemical reference substances are substances that are widely acknowledged to have the appropriate qualities within a specified context, and whose assigned content when used as a (mostly as an assay) standard is accepted without requiring comparison to another chemical substance (7).

Secondary chemical reference substances (also called *working standards*) are substances whose characteristics are assigned and/or calibrated by comparison with a primary chemical reference substance.

The extent of characterization and testing of a secondary chemical reference substance may be less than for a primary chemical reference substance (7).

International Chemical Reference Substances (ICRS) are primary chemical reference substances established on the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

They are supplied primarily for use in physical and chemical tests and assays described in the specifications for quality control of medicines published in *The International Pharmacopoeia* or proposed in draft monographs. The ICRS may be used to calibrate secondary standards (7).

Certified reference substances are primary reference substances certified by regulatory bodies.

Pharmacopoeial reference substances (standards) are primary reference substances established and distributed by pharmacopoeial authorities following the general principles of the *ISO Guide 34* (8).

Note: a different approach is used by the pharmacopoeial authorities to give the user the information provided by certificate of analysis and expiration dates (7).

Reference materials refer to materials other than substances appropriate for intended uses in standardization or quality control of herbs and herbal materials. Reference materials include, among others, herbarium samples, authentic specimens of herbal materials (such as extracts and their fractions), herbal reference preparations and authentic spectra or fingerprints.

2. Selection criteria for substances of herbal origin relevant for standardization and quality control of herbal medicines

2.1 General considerations in the standardization and quality control of herbal materials, herbal preparations and herbal medicines

Herbal materials, herbal preparations and finished herbal products are very complex. This can make the identification and quantification of herbal medicines very difficult and the detection of adulteration is very challenging.

It should be emphasized that the identification of herbal medicines using markers, and quantification of marker substances in herbal medicines are not in themselves sufficient to guarantee the quality of herbal medicines. Quality control must cover all steps of their production and must be complemented by good agricultural and collection practices (GACP) and good manufacturing practices (GMP) (such as those described in references 1 and 4), as appropriate.

Criteria for the selection of reference substances and quality control of herbal medicines should take into account that various ingredients may have different levels of influence on the final quality, safety and efficacy. For this reason, the order of selection of the substances for identification and quantification should follow the rules presented below.

- 1) If **constituents with known therapeutic activity (activities)** have been identified, they should be used as markers.
- 2) If 1. is not the case, but **constituent(s) with recognized pharmacological activity (activities)** is (are) **known**, they should be used as markers.
- 3) If the above cases are not applicable, the identity and quantity of herbal materials, preparations and medicines may be established by the production process and by analysing marker substance(s) containing other characteristic constituent(s).

Note that identification of herbal materials, and also to some extent herbal preparations and finished herbal products, may be done or may be complemented by microscopic, macroscopic or DNA analytical methods using appropriate reference materials and descriptions.

2.2 Purpose and expected functions of relevant marker substances

Markers used as chemical reference substances should be international chemical or pharmacopoeial reference substances. If others are used, markers for quantitative determination should be of high purity as required by national regulations, determined by validated analytical methods, including physical and chemical ones. These analytical methods may be different from those employed for quantifying herbal materials. For markers used for identification, lower purity may be suitable.

The general requirements for markers are:

- identity, specificity and selectivity using the specified analytical method(s);
- should be present in traceable quantity for identification or sufficient quantity for assay;
- should be easily obtained,¹ stable under specified storage conditions;
- should be easily detected and quantified analytically.¹

2.2.1 Marker substances of constituents with known therapeutic activity²

PURPOSE AND FUNCTION

Markers of constituents with known therapeutic activity should serve their appropriate purpose (identification or quantification).

SELECTION CRITERIA

The criteria for selection of a marker substance of constituents with known therapeutic activity are as follows:

- The marker must be readily available (for example, as an international or pharmacopoeial reference substance). New markers may only be selected if no such reference substance is available. In that case, detailed documentation should be provided on the identity and properties of the selected markers.
- It should be relatively easy to separate or distinguish the marker analytically from other structurally similar herbal constituents.

¹ This does not apply to substances described under 2.2.4.

² They could also be named "reference substances". However, taking the complex nature of all kinds of herbal medicines into account, it is unlikely that one single compound would be solely responsible for the therapeutic action. Thus, substances of constituents with known therapeutic activity are generally also called "markers".

- Markers should be detectable and quantifiable with available analytical instrumental methods (such as thin-layer chromatography (TLC), high-performance thin-layer chromatography (HPTLC), gas chromatography (GC) or high-performance liquid chromatography (HPLC)).
- Different marker substances may be selected for the same herbal medicines depending on the analytical instrumental methods available.

Notes

- Derivatives of the naturally occurring markers may be used where the latter are not easy to detect, are not stable or are not easily obtained.
- Different marker substances may be selected for the same herbal materials depending on the different forms of herbal preparations or finished herbal products.
- A group of markers may be selected if a single marker is not sufficient to identify and evaluate the herbal materials or finished herbal products.

2.2.2 Marker substances of constituents with recognized pharmacological activities

PURPOSE and FUNCTION

Markers of constituents with recognized pharmacological activities should serve as qualitative and quantitative measures in herbal medicines.

SELECTION CRITERIA

The criteria for selection of a marker substance of constituents with recognized pharmacological activities are as follows:

- They occur naturally in sufficient quantities in herbal materials.
- *Markers for quantification*: should be representative of the main therapeutic or pharmacological profiles of the herbal materials and finished products.
- *Markers for identification*: should be specific for one plant or for certain plant species and genera. If not, other marker(s) should be selected for specific identification.
- They should be detectable and quantifiable by available instrumental analytical methods (such as TLC, HPTLC, HPLC, GC) or by another relevant analytical method.
- Different substances may be selected for the same herbal materials depending on the different forms of the herbal preparations (including different, e.g. aqueous and alcoholic extracts) or different therapeutic indications.

- A group of substances may be selected if a single one is not sufficient to evaluate the herbal material or finished herbal product.

2.2.3 Marker substances of characteristic constituents

PURPOSE and FUNCTION

The main purpose of markers of characteristic constituents is identification and quantification of herbal materials in herbal preparations and finished herbal products.

SPECIFIC REQUIREMENTS

Markers for identification:

- The marker should be specific for one plant. If not, the marker should be specific for a certain plant species, genus and family.

Note: a plant family may contain many classes of biologically diverse species and chemically diverse ingredients, but the plants in the same genus are normally genetically close and contain structurally similar secondary metabolite constituents.

- If not specific for one plant, the marker should be specific at least for one herbal material or preparation in a mixture herbal preparation or herbal medicines.
- The marker should consist of one substance or group of substances, or characteristic pattern of substances.

Note: A pattern of substances characteristic for a specific herb may replace a single substance.

Markers for quantification:

- The marker for quantification should be available in sufficient quantity for assay.

SELECTION CRITERIA

The criteria for selection marker substances of characteristic constituents are as follows:

- They should occur naturally in sufficient quantities in herbal materials.
- An authentic reference should be available.
- Spectral data on the substance should be recorded in an available library or database.
- TLC chromatogram pattern or other analytical identification should be illustrated in an available source.
- A simple identification and quantification test should be described for the substance or its chemical class.

- There should be adequate experimental evidence that the substance or group of substances is characteristic of the given herbal medicine.

2.2.4 Marker substances for toxic constituents

PURPOSES AND FUNCTION

Marker substances for toxic constituents are used to define maximum acceptable concentrations of toxic constituents in herbal materials, herbal preparations or finished herbal products.

REQUIREMENTS

- As a consequence of the composition of the herbal material or product, such a limit test is needed.
- There should be a defined upper tolerable limit for the mode of application and posology intended (e.g. oral, topical, inhalation, short-term, subchronic or chronic application).
- A toxicological evaluation is required, but experience with traditional use should be taken into account.
- Genotoxicity, mutagenicity and carcinogenicity should also be considered when establishing toxicity criteria.
- An analytical detection procedure for the established tolerable limits should be available.
- These requirements should always be met by the finished herbal product destined for human use, since processing and conservation may alter toxicity.

SELECTION CRITERIA

- An appropriate reference substance should be available.
- For identity, specificity and selectivity are important characteristics.
- Limit of detection and limit of quantitation values for the target herbal medicines should be specified.
- Highly sensitive instrumental analytical methods (such as TLC, HPTLC, GC, HPLC, GC/mass spectrometry (MS), liquid chromatography (LC)/MS) should be available for detection of toxic substances.
- Simple identification tests for groups of toxic substances, such as alkaloids or terpenoids should be available.

Note: The criteria used for selecting marker substances for toxic constituents apply to detection of a toxic substance specific to a particular herbal material. To ensure its safety for human consumption, the toxic constituents of a herbal material, its herbal preparation or its finished herbal product should be identified accurately.

The toxicity may be assessed for control by the absence of a constituent or by establishing and testing allowable tolerable limit(s) for the toxic constituents using selected marker(s) and analytical methods. For example, the absence of thiaminase enzyme activity in horsetail (*Equisetum arvense*) as well as a method for the detection of kavalactone (a hepatotoxic agent) in kava kava (*Piper methysticum*) should be required.

If it is not possible to exclude the toxic effect, e.g. because there is no appropriate marker constituent or because of the lack of an analytical method or specific method of preparation, the herbal material or its herbal preparation should not be used in finished herbal products.

2.3 Use of reference materials

Various types of herbal reference materials are used as complements to analytical methods that were performed using markers and especially when no reference substances for the above-mentioned markers are available. They may also be used when markers are available, but are not adequate for identification of the herbal materials, preparations or finished products.

For example, herbal medicines may contain a group of specified constituents or constituents with recognized pharmacological activities, such as flavonoids, alkaloids and saponins. There are also cases (e.g. well-identified extracts) when the reference material might be more stable than single ingredients with a high degree of purity (primary or secondary reference standards).

PURPOSE AND FUNCTION

Identification and quantification of herbs, herbal materials and herbal medicines.

REQUIREMENTS

- Botanical reference materials and/or herbal preparations should be described by national pharmacopoeias or materia medica (e.g. those of China, Indonesia and Japan).
- Herbarium samples and authentic herbal material for microscopic and macroscopic comparison should be developed in cooperation with botanists for systematic authentication.
- If herbal preparations are used as the reference standard, full documentation on the preparation needs to be submitted to allow full traceability.
- Reference materials should be prepared following methods described in guidelines on validation.

SELECTION CRITERIA

- Herbal reference extracts should be prepared in accordance with standard operating procedures and the characteristic and/or active

constituents should be well demonstrated on chromatograms (obtained by instrumental analytical methods such as TLC, high-performance thin-layer chromatography (HPTLC), HPLC, GC) and spectra (such as nuclear magnetic resonance (NMR) or MS) under specified conditions.

- The herbal reference extracts or herbal reference preparations and their main constituents should be stable and identifiable using available analytical instruments and analytical methods.
- There should be predetermined in-house criteria on how to use herbal reference preparations for identification of specified finished herbal products produced by manufacturers.

3. Analytical methods for substances of herbal origin in herbal medicines

This section describes testing methods employed for quality control.

3.1 General considerations regarding the test methods to be employed

Analytical methods used for quality control of herbal materials, herbal preparations and finished herbal products are generally based on:

- 1) chemical reactions;
- 2) chromatographic procedures (such as TLC, HPTLC, GC and HPLC), including fingerprinting;
- 3) spectroscopic and spectrometric methods;
- 4) a combination of b) and c); and
- 5) others.

Test methods should be specific and selective for the selected substances in the herbal materials, herbal preparations or finished herbal products. Test methods must be validated. It might be necessary to revalidate the method if the substance is tested at different stages of the production process (e.g. herbal preparations such as extracts and finished herbal products) because other substances, e.g. excipients may influence the analytical procedures.

Test methods, if applicable, should be able to detect substitutes or adulterants that are likely to be present in the sample.

- *Herbal materials, herbal preparations or finished herbal products with constituents with known therapeutic activity*

The analytical methods used for quality control should be capable of detecting and quantifying the constituents with known therapeutic activity. The use of reference substances for the therapeutically important constituents in the analysis is recommended.

- *Herbal materials, herbal preparations or finished herbal products with constituents with recognized pharmacological activities*

The analytical methods used for quality control should be capable of detecting and quantifying the constituents with recognized pharmacological activities. The use of reference substances for the therapeutically important constituents in the analysis is recommended.

- *Herbal materials, herbal preparations or finished herbal products with characteristic constituents (whose pharmacologically or therapeutically active constituents are unknown)*

When the pharmacological and the therapeutically active constituents are unknown, the identification and assay procedures should be based on characteristic constituents (markers) and fingerprint chromatograms, or on characteristic microscopic or macroscopic features of the herbal materials, herbal preparations or finished herbal products. Reference samples should be used in the analysis, where available.

Where the local laboratory has limited capacity, the use of dependable but simple basic technical and testing methods is recommended. However, the producer should not be discouraged from developing and applying more sophisticated methods for testing products intended for export.

3.2 Monographs

It is recommended that pharmacopoeial monographs prepared by national or regional authorities should incorporate substances and constituents for quality control of herbal materials, herbal preparations or finished herbal products.

References and bibliography

References

1. WHO Guidelines on good agricultural and collection practices (GACP) for medicinal plants. Geneva: World Health Organization; 2003.
2. WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues. Geneva: World Health Organization; 2007.

3. Good manufacturing practices: supplementary guidelines for the manufacture of herbal medicines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fortieth report. Geneva: World Health Organization; 2006: Annex 3 (WHO Technical Report Series, No. 937; https://apps.who.int/iris/bitstream/handle/10665/43443/WHO_TRS_937_eng.pdf?sequence=1).
4. WHO guidelines on good manufacturing practices (GMP) for herbal medicines. Geneva: World Health Organization; 2007.
5. Quality control methods for medicinal plant materials. Geneva: World Health Organization; 1998.
6. Quality control methods for herbal materials. Geneva: World Health Organization; 2011.
7. General guidelines for the establishment, maintenance and distribution of chemical reference substances. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-first report. Geneva: World Health Organization; 2007: Annex 3 (WHO Technical Report Series, No. 943; https://iris.who.int/bitstream/handle/10665/43632/WHO_TRS_943_eng.pdf?sequence=1&isAllowed=y).
8. General requirements for the competence of reference material producers. ISO 17034:2016. Geneva: International Organization for Standardization; 2016.

Bibliography

- Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms. Geneva: World Health Organization; 1998.
- General guidelines for methodologies on research and evaluation of traditional medicine. Geneva: World Health Organization; 2000 (WHO/EDM/TRM/2000.1).
- Good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986; https://iris.who.int/bitstream/handle/10665/112733/WHO_TRS_986_eng.pdf?sequence=1&isAllowed=y).
- The International Pharmacopoeia, sixth edition. Geneva: World Health Organization; 2016.
- National policy on traditional medicine and regulation of herbal medicines: Report of a WHO global survey. Geneva: World Health Organization; 2005.
- Quality assurance of pharmaceuticals. WHO guidelines, good practices, related regulatory guidelines and GXP training materials. Geneva: World Health Organization; 2016.
- Regulatory situation of herbal medicines: a worldwide review. Geneva: World Health Organization; 1998 (WHO/TRM/98.1).
- WHO monographs on selected medicinal plants commonly used in the Newly Independent States (NIS). Geneva: World Health Organization; 2010.
- WHO monographs on selected medicinal plants. Volume 1, Geneva: World Health Organization; 1999.
- WHO monographs on selected medicinal plants. Volume 2, Geneva: World Health Organization; 2002.
- WHO monographs on selected medicinal plants, Volume 3. Geneva: World Health Organization; 2007.
- WHO monographs on selected medicinal plants, Volume 4. Geneva: World Health Organization; 2009.

Further reading

- World Health Organization/United Nations Population Fund Prequalification Programme guidance for contraceptive devices: male latex condoms, female condoms and intrauterine devices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. WHO Technical Report Series No. 1025, Annex 9. Geneva: World Health Organization; 2020 (<https://iris.who.int/bitstream/handle/10665/331814/9789240001824-eng.pdf?sequence=1>, accessed 9 April 2024).
- World Health Organization/United Nations Population Fund technical specifications for male latex condoms. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. WHO Technical Report Series No. 1025, Annex 10. Geneva: World Health Organization; 2020 (<https://iris.who.int/bitstream/handle/10665/331814/9789240001824-eng.pdf?sequence=1>, accessed 9 April 2024).
- World Health Organization/United Nations Population Fund specifications for plain lubricants. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. WHO Technical Report Series No. 1025, Annex 11. Geneva: World Health Organization; 2020 (<https://iris.who.int/bitstream/handle/10665/331814/9789240001824-eng.pdf?sequence=1>, accessed 9 April 2024).
- World Health Organization/United Nations Population Fund Recommendations for condom storage and shipping temperatures. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fifth report. WHO Technical Report Series No. 1033, Annex 5. Geneva: World Health Organization; 2021 (<https://iris.who.int/bitstream/handle/10665/340323/9789240020900-eng.pdf?sequence=1>, accessed 9 April 2024).
- World Health Organization/United Nations Population Fund Guidance on testing of male latex condoms. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fifth report. WHO Technical Report Series No. 1033, Annex 6. Geneva: World Health Organization; 2021 (<https://iris.who.int/bitstream/handle/10665/340323/9789240020900-eng.pdf?sequence=1>, accessed 9 April 2024).
- WHO/UNFPA guidance on natural rubber latex male condom stability studies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-sixth report. WHO Technical Report Series No. 1044, Annex 9. Geneva: World Health Organization; 2022 (<https://iris.who.int/bitstream/handle/10665/365397/9789240063822-eng.pdf?sequence=1>, accessed 9 April 2024).
- WHO/UNFPA technical specification for TCu380A intrauterine device. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-sixth report. WHO Technical Report Series No. 1044, Annex 10. Geneva: World Health Organization; 2022 (<https://iris.who.int/bitstream/handle/10665/365397/9789240063822-eng.pdf?sequence=1>, accessed 9 April 2024).
- WHO/UNFPA female condom generic specification. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-seventh report. WHO Technical Report Series No. 1052, Annex 5. Geneva: World Health Organization; 2024 (<https://iris.who.int/bitstream/handle/10665/376607/9789240091030-eng.pdf>, accessed 3 May 2024).

Revision history

No.	Document and reference	Publication date	Revision history (changes to the 9 th edition)
1. Pharmaceutical development			
1.1	Pharmaceutical development of multisource (generic) finished pharmaceutical products: points to consider. Annex 3, WHO Technical Report Series, 970	2012	No change
1.2	Development of paediatric medicines: points to consider in formulation. Annex 5, WHO Technical Report Series, 970	2012	No change
2. Marketing authorization: quality			
2.1	Guidelines on submission of documentation for a multisource (generic) finished product: quality part. Annex 6, WHO Technical Report Series, 986	2014	No change
2.2	Guidelines for the registration of fixed-dose combination medicinal products. Annex 5, WHO Technical Report Series, 929	2005	No change
2.3	Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. Annex 10, WHO Technical Report Series, 1010	2018	No change
2.4	Guidelines on packaging for pharmaceutical products. Annex 9, WHO Technical Report Series, 902	2002	No change

No.	Document and reference	Publication date	Revision history (changes to the 9 th edition)
2. Marketing authorization: quality <i>continued</i>			
2.5	Recommendations for quality requirements when plant-derived artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients. Annex 6, WHO Technical Report Series, 992	2015	No change
2.6	Recommendations on risk of transmitting animal spongiform encephalopathy agents via medicinal products. Annex 1, WHO Technical Report Series, 908	2003	No change
3. Marketing authorization: bioequivalence			
3.1	Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Annex 8, WHO Technical Report Series, 1052	2024	Replaces - Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability, Annex 6, WHO Technical Report Series, 1003; 2017
3.2	Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. Annex 8, WHO Technical Report Series, 992	2015	No change
3.3	WHO guideline on Biopharmaceutics Classification System-based biowaivers. Annex 7, WHO Technical Report Series, 1052	2024	New guideline

No.	Document and reference	Publication date	Revision history (changes to the 9 th edition)
3. Marketing authorization: bioequivalence <i>continued</i>			
3.4	WHO Biowaiver List: proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms Annex 6, WHO Technical Report Series, 1052	2024	Replaces - Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms - Annex 8, WHO Technical Report Series, 937; 2006
3.5	Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver Annex 4, WHO Technical Report Series, 1019 (under revision)	2019	New guideline
4. Regulatory standards: general guidance			
4.1	Good regulatory practices in the regulation of medical products. Annex 11, WHO Technical Report Series, 1033	2021	New guideline
4.2	Good review practices: guidelines for national and regional regulatory authorities. Annex 9, WHO Technical Report Series, 992	2015	No change
4.3	WHO guideline on the implementation of quality management systems for national regulatory authorities. Annex 13, WHO Technical Report Series, 1025	2020	New guideline

No.	Document and reference	Publication date	Revision history (changes to the 9 th edition)
4. Regulatory standards: general guidance <i>continued</i>			
4.4	Quality management system requirements for national inspectorates. Annex 5, WHO Technical Report Series, 1025	2020	Replaces - WHO Quality systems requirements for national good manufacturing practice inspectorates. Annex 8, WHO Technical Report Series, 902; 2002
4.5	WHO guidelines on quality risk management. Annex 2, WHO Technical Report Series, 981	2013	No change
4.6	Guideline on data integrity. Annex 4, WHO Technical Report Series, 1033	2021	Replaces - Guidance on good data and record management practices. Annex 5, WHO Technical Report Series, 996; 2016
4.7	WHO general guidance on variations to multisource pharmaceutical products. Annex 10, WHO Technical Report Series, 996	2016	No change
4.8	WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation. Annex 3, WHO Technical Report Series, 917	2003	No change
4.9	Guidelines on the implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. Annex 9, WHO Technical Report Series, 1033	2021	Replaces – Guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. Annex 10, WHO Technical Report Series, 863; 1996

No.	Document and reference	Publication date	Revision history (changes to the 9 th edition)
5. Contract research organizations			
5.1	Guidance for organizations performing in vivo bioequivalence studies. Annex 9, WHO Technical Report Series, 996	2016	No change
5.2	Guidelines for the preparation of a contract research organization master file. Annex 7, WHO Technical Report Series, 957	2010	No change
5.3	Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. Annex 3, WHO Technical Report Series, 850	1995	No change
6. Prequalification			
6.1	Guidelines on submission of documentation for a multisource (generic) finished product. General format: preparation of product dossiers in common technical document format. Annex 15, WHO Technical Report Series, 961	2011	No change
6.2	Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products. Annex 4, WHO Technical Report Series, 953	2009	No change
6.3	Guidelines on active pharmaceutical ingredient master file procedure. Annex 4, WHO Technical Report Series, 948	2008	No change

No.	Document and reference	Publication date	Revision history (changes to the 9 th edition)
6. Prequalification <i>continued</i>			
6.4	Procedure for prequalification of pharmaceutical products. Annex 10, Appendix 1, WHO Technical Report Series, 961	2011	No change
6.5	Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality parts. Annex 4, WHO Technical Report Series, 970	2012	No change
6.6	Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities. Annex 5, WHO Technical Report Series, 986	2014	No change
6.7	WHO guidelines on variations to a prequalified product. Annex 3, WHO Technical Report Series, 981	2013	No change
6.8	Guidelines on the requalification of prequalified dossiers. Annex 6, WHO Technical Report Series, 957	2010	No change
6.9	Prequalification of quality control laboratories: procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies. Annex 3, WHO Technical Report Series, 1003	2017	No change

No.	Document and reference	Publication date	Revision history (changes to the 9 th edition)
7. Regulatory standards: collaborative procedures and reliance			
7.1	Good reliance practices in the regulation of medical products: high level principles and considerations. Annex 10, WHO Technical Report Series, 1033	2021	New guideline
7.2	Good practices of national regulatory authorities in implementing the collaborative registration procedures for medical products. Annex 6, WHO Technical Report Series, 1019	2019	New guideline
7.3	Collaborative procedure between the World Health Organization (WHO) Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines. Annex 8, WHO Technical Report Series, 996	2016	No change
7.4	Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities. Annex 11, WHO Technical Report Series, 1010	2018	No change
7.5	Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. Annex 9, WHO Technical Report Series, 1010	2018	No change

No.	Document and reference	Publication date	Revision history (changes to the 9 th edition)
8. Storage, distribution and supply			
8.1	Guidelines on import procedures for medical products. Annex 5, WHO Technical Report Series, 1019	2019	Replaces - Guidelines on import procedures for pharmaceutical products - Annex 12, WHO Technical Series, 863; 1996
8.2	Points to consider for setting the remaining shelf-life of medical products upon delivery. Annex 8, WHO Technical Report Series, 1044	2022	New guideline
8.3	Model quality assurance system for procurement agencies. Annex 3, WHO Technical Report Series, 986	2014	No change
8.4	Good trade and distribution practices for pharmaceutical starting materials. Annex 6, WHO Technical Report Series, 996	2016	No change
8.5	Good storage and distribution practices for medical products. Annex 7, WHO Technical Report Series, 1025	2020	Replaces - Guide to good storage practices for pharmaceuticals, Annex 9, WHO Technical Report Series, 908; 2003
8.6	Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products. Annex 9, WHO Technical Report Series, 961	2011	No change
8.7	Technical supplements to Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products. Annex 5, WHO Technical Report Series, 992	2015	No change

No.	Document and reference	Publication date	Revision history (changes to the 9 th edition)
9. Good pharmacy practices			
9.1	Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services. Annex 8, WHO Technical Report Series, 961	2011	No change
9.2	FIP–WHO technical guidelines: Points to consider in the provision by health-care professionals of children-specific preparations that are not available as authorized products. Annex 2, WHO Technical Report Series, 996	2016	No change
10. Post-market surveillance			
10.1	Guidelines on the conduct of surveys of the quality of medicines. Annex 7, Appendix 1, WHO Technical Report Series, 996	2016	No change
10.2	WHO guidelines for sampling of pharmaceutical products and related materials. Annex 4, WHO Technical Report Series, 929	2005	No change
10.3	Considerations for requesting analysis of medicines samples. Annex 3, WHO Technical Report Series, 1010	2018	No change
10.4	WHO guidance on testing of “suspect” falsified medicines. Annex 5, WHO Technical Report Series, 1010	2018	No change

No.	Document and reference	Publication date	Revision history (changes to the 9 th edition)
11. Quality control			
11.1	WHO good practices for pharmaceutical quality control laboratories Annex 4, WHO Technical Report Series, 1052	2024	Replaces - WHO good practices for pharmaceutical quality control laboratories, Annex 1, WHO Technical Report Series, 957; 2010
11.2	WHO good practices for pharmaceutical microbiology laboratories. Annex 2, WHO Technical Report Series, 961	2011	No change
11.3	WHO guidelines for preparing a laboratory information file. Annex 13, WHO Technical Report Series, 961	2011	No change
11.4	Good pharmacopoeial practices. Annex 1, WHO Technical Report Series, 996	2016	No change
11.5	Good pharmacopoeial practices: Chapter on monographs for compounded preparations. Annex 6, WHO Technical Report Series, 1010	2018	No change
11.6	Good pharmacopoeial practices: Chapter on monographs on herbal medicines. Annex 7, WHO Technical Report Series, 1010	2018	No change
11.7	Good chromatography practices. Annex 4, WHO Technical Report Series, 1025	2020	New guideline
11.8	Model certificate of analysis. Annex 4, WHO Technical Report Series, 1010	2018	No change

No.	Document and reference	Publication date	Revision history (changes to the 9 th edition)
11. Quality control <i>continued</i>			
11.9	WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines. Annex 1, WHO Technical Report Series, 1003	2017	No change
	Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms	1998	Withdrawn - <i>Withdrawn or obsolete guidelines should not be used as they do not represent the current thinking of WHO</i>



Norms and Standards for Pharmaceuticals
Department of Health Products Policy and Standards
World Health Organization

20 Avenue Appia

1211 Geneva 27

Switzerland

Email: nsp@who.int

Website: <https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals>

ISBN 9789240099425

