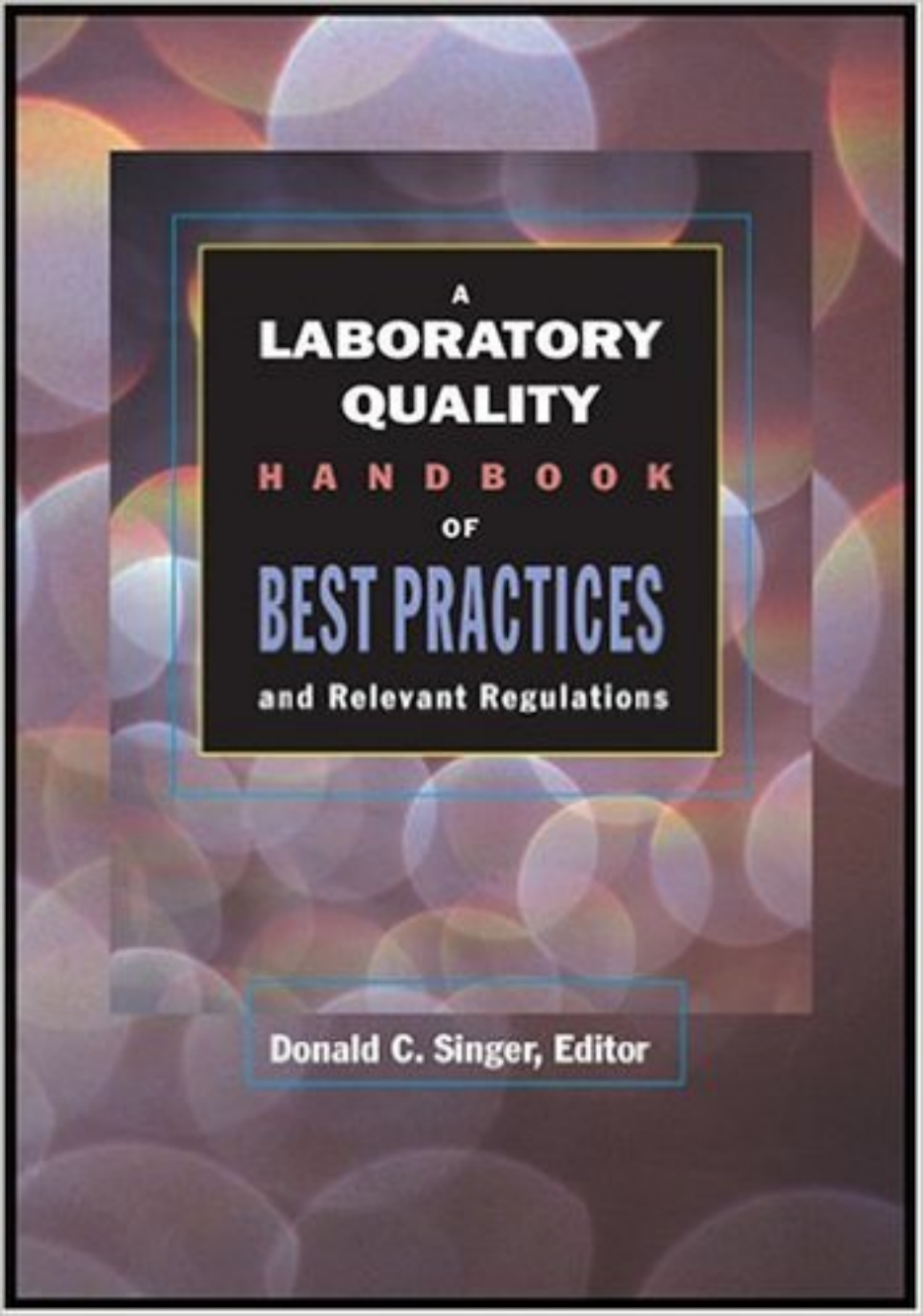
A
LABORATORY
QUALITY
HANDBOOK
OF
BEST PRACTICES
and Relevant Regulations
Donald C. Singer, Editor

A Laboratory Quality Handbook of Best Practices

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Donald C. Singer, Editor

ASQ Quality Press
Milwaukee, Wisconsin

A Laboratory Quality Handbook of Best Practices
Edited by Donald C. Singer

Library of Congress Cataloging-in-Publication Data

A laboratory quality handbook of best practices and relevant regulations / edited by Donald C. Singer.
p. cm.
Includes bibliographical references and index.
ISBN 0-87389-491-X (alk. paper)
1. Laboratories—Quality control—Handbooks, manuals, etc.. 2. Laboratories—Law and legislation—Handbooks, manuals, etc. I. Singer, Donald C., 1953–

R852.L25 2001
616.07'56'0685—dc21 2001022072

10 9 8 7 6 5 4 3 2 1

ISBN 0-87389-490-1

Acquisitions Editor: Annemieke Koudstaal
Production Administrator: Gretchen Trautman
Special Marketing Representative: David Luth

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Printed in the United States of America

Printed on acid-free paper

American Society for Quality
ASQ

Quality Press
P.O. Box 3005
Milwaukee, Wisconsin 53201-3005
Call toll free 800-248-1946
Fax 414-272-1734
www.asq.org
http://qualitypress.asq.org
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Dedication

To Sue and our children, Chelsea and Trevor;

and

To my dedicated laboratory team, Elise, Kathy, Crystal, Tony, Mike, and Bob.
"Life can be a Dreamcatcher. Keep reaching for those good dreams."

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Preface

I have been asked often, by a fellow scientist or by a student, which is the correct way to accomplish science in our laboratories and be compliant with regulations, such as the current good manufacturing practices (cGMP). I have learned over time that the answer is that there is no one correct way, but there is a best approach to accomplishing science and compliance. That approach is by following the science, in a laboratory setting, with as much scrutiny as possible, and then making sound, scientific-based decisions from the information generated. Many decisions will be judgments made with low to high risk. And the risk levels may differ from the perspective of the manager, the lab, and the company. It is the responsibility of a scientist or manager of scientists to make judgments based on sufficient facts or data. Not all decisions will be clear-cut. Some may be pretty close to a knowledgeable guess. But, there should always be some amount of practicality and sound scientific knowledge. With practicality and science as a basis for decisions, compliance should easily fall into place. A Food and Drug Administration inspector follows their agency guidelines, uses their own scientific education, and publishes standards to perform an audit of a laboratory. As we presently continue to see an increase in the reported number of noncompliant findings in laboratories, we should realize that the inspectors are just looking closer than ever before. And we should be prepared for that. We have access to the same guidelines and standards as inspectors do. We have many more scientists who have thorough education and training in the actual science of the laboratory work being performed. We have written all of the procedures and validated the instrumentation used in our laboratories. Should we be able to be compliant all the time? Yes, as long as we do what we say we do, and practice the way sound science is practiced. And that is the reason for this book. I have gathered together experts from across the laboratory science and quality assurance fields to share their knowledge. Each author provides their perspective on accomplishing good science or compliance in their area of expertise. They offer what are the best practices to meet compliance needs.

A laboratory should work as a well-tuned race car engine. Each integral part depends on the action and result of the other. From sample tracking to accurate documentation, training to methods validation, maintenance to calibration, and out-of-specification responses to preparation for audits, a combination of people, instrumentation, and documentation must work in sync for high quality results. This handbook provides information that will help a laboratory achieve high quality results and compliance. Remember, accuracy, consistency, practicality, and sound science are keys to a successful laboratory.

Donald C. Singer

Acknowledgements

I would like to thank my scientist colleagues and the many other laboratory scientists that I have met who have contributed to this book by offering their insights and issues related to developing consumer trust and meeting regulatory compliance for their own laboratories.

The following individuals also contributed to specific chapters with recommendations or timely reviews:

Fred E. Burris	Chapter 7
Anthony P. Hart	Chapter 4
Boyd Montigney	Chapter 7
Christopher M. Riley	Chapter 7

Many of my fellow ASQ Food, Drug and Cosmetic Division members have been a constant source of knowledge in our highly regulated field of science.

The persistent drive and support of Annemieke Koudstaal of the American Society for Quality should not go without gratitude, and special thanks go to her for getting this book into your hands.

D. Singer

I.

Quality in the Laboratory

1

Quality Assurance in the Laboratory

As we enter the twenty-first century, advances in science are progressing rapidly. New technologies are leading the way to the discovery and implementation of improvements to the way we live and survive in a constantly changing biological and physical environment. These new technologies, initiated in laboratories around the world, have led to improved diagnostics, new medicines, more stable food sources, and improved cosmetics.

A strong global effort exists to provide safe and effective pharmaceuticals to the world population. The medical field requires diagnostics that are precise and consistent. Manufacturers of foods and cosmetics are becoming more scrutinized in their production and testing practices than ever before. The basis of most scientific decisions in all of these regulated industries is found in the laboratory. From discovery through final product manufacturing, the laboratory plays a crucial role. Soundness of scientific decisions is based on the consistency and accuracy of data generated from laboratories.

Performance of a laboratory must be measured periodically to identify areas that require improvement. A laboratory quality audit (Singer and Upton 1993) is the best way to accomplish this measurement and improvement process.

Since laboratories can and should be audited on a periodic basis, there are numerous guidelines and recommendations that can be used for references (see Appendices). Foremost, though, in the daily activity of any laboratory is a quality assurance approach. One definition of quality assurance (ASQC 1996) is "all those planned or systematic actions necessary to provide adequate confidence that a product or service will satisfy given needs." These include written procedures and documentation of training, analytical results, and any quality control practices. The infrastructure for quality assurance is comprised of experienced and knowledgeable individuals who can carry out and manage the quality assurance processes, including audits. Some regulations define the requirement for a quality assurance organization (21 CFR Part 820, FDA).

The Food and Drug Administration (FDA) regulations, good laboratory practices (21 CFR Part 58) state the requirement of a "quality assurance unit (QAU)," for nonclinical laboratory studies. The quality assurance unit has a responsibility to audit the laboratory study, and has a broad perspective of quality. It must not only oversee the personnel, instruments, and facilities where the studies are performed, but also review and audit the procedures and documentation generated from the studies.

Quality assurance is a separate organizational entity in most regulated companies. But the laboratory organization should have the responsibility for assuring quality in its own operation and practices. There is no substitute for quality when seeking confidence in scientific data.

Systems of documentation provide a means to review methods, instrumentation precision, and analytical data generation and calculations performed in a laboratory. It is this capability to review documentation that develops an environment where laboratory practices can be measured and improved, if necessary. The quality assurance processes also provide the proof that is required in most audits showing that practices in the laboratory are consistent and accurate.

Some laboratories are dedicated to specific industry testing, such as a quality control laboratory that is responsible for testing the environment, raw materials, and finished products produced by a food, pharmaceutical, or cosmetic manufacturer. Other laboratories may offer testing capabilities for all of the latter product types. And there are laboratories focused strictly in areas of discovery and development of new materials and products. Human activity, human judgment, instrumentation, and computers build an environment in a scientific laboratory where there is a crucial balance between accurate measurement and inherent error. Training, experience, and adequate management can minimize human error. Documentation of training and experience is well-justified to maintain good work practices and promote successful hiring. Proper instrumentation operation, maintenance, and calibration minimize excursions from precision and consistency. Documentation of preventative maintenance and calibrations on each laboratory instrument are aspects of the foundation of a useful quality assurance process.

Quality assurance processes and applicable instrument validation/qualification practices congruently support good laboratory practices (of which one small segment is the FDA-regulated good laboratory practices). Performing science in a laboratory utilizing practices that provide reproducibility and precision to generate trustworthy data enhances successful decision making.

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2

History of Regulation and the Laboratory

The general public in the United States has been legally protected from adulterated products since 1938, when the first version of the Food, Drug, and Cosmetic Act was written. Since then, the food, pharmaceutical, cosmetic, and medical device industries have been increasingly regulated and inspected by federal agencies (for example, Food and Drug Administration [FDA], Environmental Protection Agency, and United States Department of Agriculture) to develop assurance of safety for the general public. Good manufacturing practices (GMP) (21 CFR 210) were first written in 1978 to give general guidance to the pharmaceutical industry on how to manufacture, process, package, and hold drugs and prevent them from adulteration. Also written in 1978 were proposed guidelines for good laboratory practices for nonclinical laboratory studies (21 CFR Part 58). In 1979, good manufacturing practices guidelines were written for the food industry (21 CFR 110). The United States Environmental Protection Agency wrote good laboratory practice standards in 1983 for safety testing of agricultural and industrial chemicals in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (40 CFR Part 160) and the Toxic Substance Control Act (TSCA) (40 CFR Part 792). The U. S. Environmental Protection Agency also developed guidelines for automated laboratory systems (see Appendix A).

Most federal government agency guidelines were written to be very general in scope. This allowed the regulated industries to choose their own practices and prove, when inspected, their compliance to the guidelines and the laws. For laboratory scientists, adequate documentation of methods and data were the first areas routinely inspected by the FDA. Now, laboratories involved with development or with release testing of product for food, drug, medical device, and cosmetic manufacturers are inspected by the FDA periodically. Often an FDA inspection is a response to (Singer and Upton 1993):

1. Customer complaints or reported adverse reactions;
2. Voluntary recalls;
3. Deviations from product quality or product claim by the FDA product sampling program found;
4. Manufacturer problems with raw materials or packaging components;
5. Submission of a new drug application (NDA), biologic license, or premarket approval (PMA);
6. Current GMP inspections of manufacturing operations; or
7. Approval of a sterile product manufacturing operation.

Regulated firms increasingly use new technologies in the laboratory. There is a conscious effort to gain better control over new laboratory procedures. Common compendial methods are still followed where they are legally binding to a product (for example, United States Pharmacopoeia, European Pharmacopoeia, Japanese Pharmacopoeia). Noncompendial methods and alternatives to compendial methods are used when adequately and properly validated according to published guidelines (see Appendix B).

A few science-based organizations originating in the United States have been writing analytical methods for a good portion of the 20th century, and have provided additional sources of compendial methods, supported by expert reviewers and, in many instances, collaborative studies. The most well-recognized of these organizations are: AOAC International (Association of Official Analytical Chemists), American Society for Testing and Materials (ASTM), National Committee for Clinical Laboratory Standards (NCCLS), Association for the Advancement of Medical Instrumentation (AAMI), and the American Public Health Association (APHA) technical committees. It is also important to note that the FDA and EPA laboratories have developed and published methods of their own in relevant areas.

Good laboratory practices have already become international in scope. The leadership of the International Organization for Standardization (ISO) in publishing guidelines for accreditation (ISO Guide 25, ISO) has resulted in "an increasing trend towards the development of broad spectrum accreditation programs that apply the same principles of good laboratory practices to laboratories working in any field of science or technology" (Bell 1989).

All FDA-regulated pharmaceutical firms are closely following the developments of global guidelines from the International Conference on Harmonization (ICH), since most are competitors in the international marketplace. The harmonization of ISO Guide 25 and the ISO 9000 standards was completed during 2000, and resulted in ISO 17025 (see section IV).

The United States versus Barr Laboratories court case resulted in a landmark decision in 1993, providing a legal interpretation of the application of good manufacturing practices and the United States Pharmacopoeia to the operation of pharmaceutical quality control laboratories. Specific actions were prescribed by court for quality control

laboratories to follow in the event of certain occurrences, for example, out-of-specification results.

Measurement of compliance to regulation is accomplished by inspection. It became evident to regulated companies that GMP-type self-inspections were a way to keep abreast of their quality and compliance efforts. Performed by a quality assurance team (see chapter 1), internal GMP audits of laboratories, as well as manufacturing and packaging operations, have become routine during the past decade.

The increase in inspections of laboratories over the past 10 years has been significant. As regulatory agency inspectors became more knowledgable of laboratory operations, the number of laboratory-related findings considered "noncompliant" increased. In 1998, one of the most common citings in domestic and international drug preapproval inspections were problems with laboratory controls.

Even now, with the enhancements in communications, driven by the Internet, the FDA, EPA, and industry auditors and scientists are sharing more information than ever before. These efforts allow them to learn more and improve practices that assure product quality and safety.

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3

An Overview of Key Parameters for Evaluating a Laboratory

It is very proactive and, without a doubt, critically important to perform periodic evaluations of your own laboratory. An external evaluation team or an internal self-evaluation (self audit) team can seek areas of noncompliance in order to provide the first step towards correction. Identifying areas of noncompliance is the first step. Once identified, progress can begin towards improvement.

All audits start with an organized plan to measure laboratory compliance to recognized standards or guidelines. As noted in chapter 2, laboratory practice guidelines have evolved during the last 25 years. A quality control laboratory, a research and development laboratory, or a clinical laboratory have similar basic goals regardless of the type of product(s) tested. These goals are:

- Accurate test data;
- Timely reporting of data;
- Useful action plans to correct problems; and
- Well-trained analysts.

A working and written quality program should exist in a laboratory. This ensures that these goals are met. The quality program (Singer and Upton 1993) monitors and evaluates all laboratory procedures as well as the competence of the laboratory analysts.

Critical areas in a laboratory operation that must be evaluated and ascertained for compliance are described (summarized from Laboratory Quality Auditing 1993) in the following lists.

DOCUMENTATION

- written procedures, original or raw data recording
- instrument calibration and maintenance recordkeeping
- review and approval procedures
- data tracking and trending
- laboratory notebook use and storage
- automated versus manual data recording

PERSONNEL

- academic background and training of analysts
- up-to-date training records
- staff size

ORGANIZATIONAL STRUCTURE

- written, up-to-date chart of organization reporting relationships
- flow of communication for problem resolution
- review and approval responsibilities
- fit of quality assurance team

FACILITY

- maintenance, sanitation, and housekeeping
- usage of space
- adequate utilities for laboratory operation
- waste management

SAMPLE CONTROL

- documentation and tracking
- storage conditions

- written sampling procedures
- expiration dating
- automated systems (for example, Laboratory Information Management [LIM] systems)

SUPPLIES ORGANIZATION

- documented procurement process
- vendor audits, if necessary for certification
- expiration dating system
- identification confirmation
- inventory usage (for example, first-in, first-out, FIFO)

EQUIPMENT QUALIFICATION

- installation and documentation
- operation validation, where appropriate
- written procedures for use
- process qualification, where appropriate

INSTRUMENT CALIBRATION

- training of personnel performing calibrations
- written procedures
- data recordkeeping

INSTRUMENT MAINTENANCE

- written procedures
- training of personnel performing maintenance
- preventative maintenance program
- change control recordkeeping

LABORATORY WATER SYSTEM

- quality attributes and user requirements
- maintenance and calibration

LABORATORY TESTING

- written methods and specifications
- validation of methods
- analysts performing tests
- data recording
- review of data
- written plan for response to out-of-specification results

PROFICIENCY TESTING

- control of positive and negative controls
- accreditation of sample source laboratory

LABORATORY HEALTH AND SAFETY

- written policy
- periodic safety inspections
- normal working conditions and design of laboratory, to protect analysts

Benchmarking other companies in the same industries, or in different industries, and networking with peers has increased the speed of technology development. It has also increased knowledge of activities in other laboratories as well as sharing of results from recent agency inspections. Benchmarking has become a critical, useful tool and resource for determining what are best laboratory practices for compliance.

II.

Critical Laboratory Operations

4

Training in the Laboratory

by Graham Bunn*
GB Consulting

OVERVIEW

This chapter describes the various types of training and provides some examples of training plans and matrixes. Individual training requirements may be developed from the models described.

Remember:

- "I have read and understood SOP #" is rarely acceptable training.
- Training is dynamic.
- Define and maintain the requirements.
- Make individuals responsible and accountable for their own training.
- Training is more than meeting regulatory requirements.
- Motivation, company loyalty, and ownership can be created from adequate training.

KEY WORDS

- Training
- Standard Operating Procedure (SOPs)
- Job description
- Training content

*The author appreciates the contribution of Mr. A. P. Hart in reviewing this chapter.

The most valuable asset of a company is not necessarily the products or services that it provides, but the staff it employs. A company may have the latest product at a competitive price or provide a value-for-money service, but both are worth nothing without the people to produce/provide them. Companies spend large amounts of resources in developing and producing products to meet regulatory expectations but may neglect employee training. The only alternative may be to contract out the work, which may not be practical or cost effective. The output and benefits from investing in people is difficult to assess. However, getting it right the first and every time must be cost effective for the company and become a matter of pride to the staff. Having attained a highly trained and motivated workforce, the knowledge, expertise, and skills of this resource may be equally difficult to replace.

Training is a dynamic and constantly changing process. Some companies' training involves the operators reading a standard operating procedure (SOP) and having some practical demonstrations. The SOP reading may be documented, but any practical application is probably not described in any detail and the training lacks structure. There is no definition of expectations from this form of training or any evaluation of the ability of the operator to satisfactorily perform the required function. Ability to operate a piece of equipment is more than reading the procedure and being shown how to use it. There must be hands-on training, under supervision, before competence in a practical situation is achieved.

The accumulation of many years' investments is focused in the pharmaceuticals industry on approval to market the drug. A Food and Drug Administration investigator may conclude that the conditions under which the product are to be made are not in compliance with current good manufacturing practices (cGMPs) and recommend withholding approval of the application. Lack of documented evidence that people have adequate training who are involved in producing the product may be one of the reasons for the withholding.

There are other legal reasons to have training. These include the health and safety standards adopted and enforced in private workplaces by the Occupational Safety and Health Administration. The Right to Know Act requires the employer to provide safety data on the materials handled by their operators. Failure to comply can result in individual and company fines. From a business viewpoint, a company needs to invest in its people, to involve them, and also provide them with a rewarding career pathway. Loyalty to the company can be established and people will want to stay with the company. External responses to job postings can equally benefit from the reputation that is built up when the company becomes known as the place to work. Safety training, aside from being a legal requirement, also means that operators work in a safe environment. This leads to less time off due to injury or work related sickness. The company benefits from the time taken to adequately train people and also from maintaining productivity.

The following training suggestions should be interpreted and adapted for each individual company. The principles and goals of the training program are still the same no matter which regulated industry is applying them. The suggestions can be adapted equally for a relatively small number of employees using a paper and file system, or larger organizations having a computer-based tracking program for training. The

amount of resources required to maintain tracking of training in a paper system reaches a point at which the investment in a computer-based program becomes justified.

Training is one of the key areas in a company that requires senior management support, resources, and maintenance for the company to be successful in a regulated industry. There are some companies who like to run operations on a minimum budget and commitment. It is only a matter of time before regulatory agencies or external auditors/visitors identify their weaknesses. Either way, the company stands to lose business by not meeting customer expectations through quality, production, or delivery problems. It may be as simple as a lost order, but bad news always travels faster than good. Approval for a regulated product may be withheld, and ultimately senior management has to answer to the company board and possibly to the shareholders. Loss of public image has probably the greatest impact, which is difficult to assess and, naturally, not easy to correct. The public is aware of the products and services of companies and relies on their reputation for the quality of the product/service. The trust that this image portrays can easily be lost through adverse publicity originating from a poor regulatory inspection or action.

The critical and essential role of the employee to company performance has now been established. Management cannot run a successful business without the confidence, support, and reliability of its employees. Likewise, the chairman of the company cannot run a company without the confidence, support, and reliability of its senior management team. Training is a requirement for all levels of employees from the janitor to the senior management. The only difference is the type of training that is required in order to meet the needs and responsibilities of the position. If each employee is going to be able to perform their job function successfully then they must be trained, and trained properly. Failure to clean a warehouse can result in an inspection observation just as easily as management not meeting their responsibilities under the law or company SOP.

Training in isolation will not be totally effective if the employee does not understand why they are required to follow certain procedures or how their decisions and actions could have an impact on customer satisfaction. Failure of management to provide a suitable compliant environment and lead by example may also undermine the confidence of the employee in the company standards.

Every department in a regulated industry should have a published structure and each person employed should have a current job description. They should know where they fit into the organization and what their responsibilities are. In the laboratory there is a broad range of jobs which need to be identified. Each job title is linked to a description of the responsibilities for that position and the requirements (educational and experience) of the individual. The requirements usually list the minimum qualifications and experience that the position requires. An individual may have outstanding academic qualifications but lack the necessary experience to apply the knowledge. Alternatively, an individual may have both the academic qualifications and experience but lack the required skills to implement the knowledge base. Skill levels need to be assessed so that an individual training plan can be developed to meet the position responsibilities.

A company has the flexibility to design the training program to meet their business needs. The program and its implementation must be documented in an SOP and have

the complete support of management for the resources required. Trainers must be employed to perform the different types of training. It is not acceptable to identify someone who has been doing an operation for several years and assign them responsibility as a trainer. Trainers have specific verbal and written communication skills. They may also have an in-depth knowledge of particular operations or processes which support their eligibility to become a trainer. Designation as trainer is not automatic and must fulfill defined criteria to ensure that training is effective. There must be documentation to support the designation of trainers. There are a variety of courses and programs specifically designed to provide training for trainers.

The laboratory training model in attachment 1 (Analyst Training Plan), located at the end of this chapter, may be useful in forming the basis to develop programs for the different regulated industries. It should be adapted for the individual requirements so that it can be described and decisions justified during an inspection by a regulatory agency. Training may be divided into different stages:

- Site and company orientation;
- Laboratory curriculum (general operations and safety);
- Analyst curriculum (specifically related to the position responsibilities); and
- Training development specific to the analyst for career development.

As shown in Figure 4.1, the complexity and scope of the training content are more focused the closer the training is to actual laboratory operations requirements.

It makes no difference if a new analyst has two or 22 years experience in the industry when it comes to site orientation. Although site safety and other regulations (for example, cGMPs) will be basically the same for two companies, the interpretation and, hence, expectations can be different. Companies will handle a wide range of different chemicals, have different emergency phone numbers and emergency assembly points which the new employee must know. There is no basis for exempting an experienced new employee from orientation when it relates to safety and regulatory expectations. The SOPs covering laboratory safety and basic cGMPs will undoubtedly be different in content and hence must be taught and understood before training can be approved. This

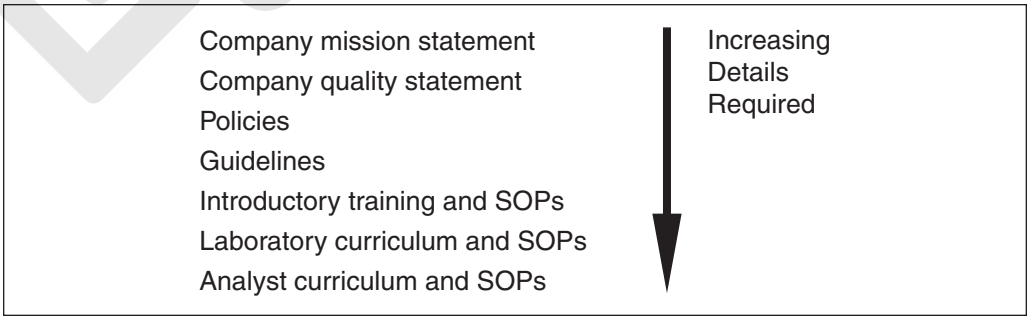

Figure 4.1 Scope of the training content.

principle is true for any procedure that the new analyst performs. While the theory remains constant, the practice may vary. The supervisor must make an evaluation of the skills of the analyst to identify the type and determine the amount of training that is required. This does not mean that all analysts must follow the same training program irrespective of their previous experience. Instead the program can be adapted for the individual and the rate of progression through the program will depend on assessment of the analyst skills by the trainer.

SITE AND COMPANY ORIENTATION

Most companies have an introduction session to explain company policies and other human resources related items. Safety and general introduction to the regulations specific to the industry are also covered in the first few days of employment. When a facility or site is operated under government regulations, all employees are usually required to attend a general introduction to the regulations. This will ensure that all new employees have the same introduction to the company interpretation of the regulatory expectation. Additional, more in-depth regulatory training will be performed at the department level for the requirements specific to the department operations. This applies equally to the mechanic responsible for the maintenance of the validated water for injection system, the forklift operator in the finished product warehouse, and manufacturing personnel. All have a responsibility to follow the SOPs that affect their operations but they still require a general understanding of supporting regulatory requirements. These introductory sessions are all part of the training records and therefore must be documented by the trainer and trainee.

Laboratory Curriculum

The laboratory curriculum covers the SOPs and other basic requirements relating to the laboratory operations. There will be basic training and orientation requirements, which must be completed before any new hire can enter the laboratory. These are generally safety related and are a necessity for the analyst's safety, and to protect the company to a degree, if an emergency should arise during the first day in the laboratory. Disposal of hazardous wastes are covered by federal regulations under the Resource Conservation Recovery Act and some local or state regulations. Correct use of safety equipment is necessary to maintain a safe working environment for all personnel. Training in "Hazard Communication" is a requirement for employees handling or being exposed to potential chemical hazards. Material safety data sheets provide safety labeling, handling, and precautions. The company should assign responsibility for safety and ensure that all training requirements are met. Reporting requirements and documentation relating to incidents/accidents should also be covered.

All other SOPs relating to the general operation of the laboratory should be prioritized according to the analyst's responsibilities. These may include qualification of instruments, calibration, out-of-specification results, reagent preparation, and change

control. It is not necessary to initially train all analysts in all the SOPs, as their job function may not immediately require it. This is the reason for the manager/supervisor of the area to develop the laboratory curriculum for the individual's specific requirements in relation to the job function. Laboratory personnel must be trained in the SOP that covers hosting an FDA or other regulatory inspection. This should not only be performed for new hires but also every time an inspection is scheduled. An abbreviated session may be suitable before the inspection and the opportunity to interact on this level should be taken with internal auditors. It is better to train with a company auditor than during an inspection. Feedback and learning are all part of the preparation, which will hopefully result in a successful inspection.

Analyst Curriculum

The manager/supervisor responsible for the laboratory must approve all laboratory and analyst curriculums. Without these predefined criteria the supervisor has no means of determining if the analyst has completed all the necessary requirements.

Once an individual is identified as suitable for a position, a training matrix can be assigned. The job description will define the roles and responsibilities of the position. Each position will have a specific matrix, which lists the training requirements to meet the job responsibilities. This is a living document and will change as new SOPs are issued and the job requirements also change. The changes must be controlled, documented, and approved by management. A mentor may be assigned to support the new analyst in basic laboratory orientation and procedures. The mentor may be responsible for some of the training and resolution of questions.

DEVELOPMENT, PERFORMANCE REVIEW, AND RETRAINING

General performance topics including career development, personnel management, teamwork, innovation, and communication skills will impact on and may be included in the individual's development plan. This plan should be reviewed about every six months and be part of the employee's yearly objectives. The objectives must not replace the requirement for frequent evaluation of the employee's training status. Both employees and supervisors have a responsibility to ensure that training is current.

The practical application of training should include an assessment of the analyst's competency in the instruments and techniques that are covered by the job description. This does not mean however that the person has to be immediately trained in all the instruments. Instead there should be a defined program, which enables the analyst to progress with increasing capabilities and responsibilities in the test methods. Previously analyzed products can be used and analyzed by the analyst following the test method and instrument procedure. Acceptance criteria must be defined before the training is initiated and the exercise documented as part of the training program. It is proactive and in everyone's interest to identify any areas requiring additional training before actual products are analyzed.

A quality investigation may conclude in the follow-up action that an analyst requires retraining. In this case, management should be prepared to answer any questions from a regulatory investigator or external auditor relating to the retraining. An example of a question is, "If this analyst required retraining, at what time were they untrained and what analyses were performed from that point to date?" This is a very difficult question to answer.

At what point in time is an analyst in complete compliance with their training requirements? This is another difficult question to answer because, as with any regulated industry, the expectations are constantly changing. When this is linked to the changing daily environment of the company the complexity of the changes is multiplied many times. New products, people, evolution of processes/systems, and the general development of the company all influence the compliance requirements at any point in time. The goal is to have all employees meet their training requirements at all times. In practice this is not always achievable, but the training program must be in a state of control so that product quality and patient safety are not at risk.

The current GMPs require that employees are trained at sufficient frequency to assure that they remain familiar with the regulations. The current part of the regulations is derived from several sources, including regulatory actions, conferences, FDA guidelines, and industry standards. Suitably qualified people in the company should screen information from these sources and disseminate the revised status to the appropriate people through training sessions, information bulletins, or other suitable means. Any information or changes in procedures, which results in training, must be documented.

Temporary employees may be necessary in the laboratory when there is an increased workload or a special project requiring additional resources. The basic requirements, particularly including safety, for these employees is no different than those of the permanent employees. There must be a defined and approved introductory training with a matrix determined by the position responsibilities. Where training is required—in specific techniques or retraining at defined intervals—it is important to ensure that the temporary employee meets all the requirements. There should be no difference in the training requirements between temporary and permanent employees for the same operation. To have a difference highlights to an investigator a dual standard which may not be easily explained.

Consultants used in the pharmaceutical industry are specifically covered in 21 CFR 211.34. Evidence is required of adequate education, training, and experience for the subjects being advised upon. It is advisable to document any specific training that was given in order for the consultant to completely meet the requirements of their contract. This is particularly important when the consultant is retained for a project covering the facility operations and which may include following specific SOPs.

Training Media

There are several different means by which to train employees. As previously discussed, these include self-paced reading, verbal instruction, demonstration, and on-the-job training. Self-paced training has a limited application for background reading and

preparation for practical applications. Assessment by the use of questioners independently or in a classroom setting should be approached with caution so as not to introduce any bias into the assessment. Predetermined passing levels may be defined and revision with reevaluation performed for those trainees not meeting the passing levels. Choice of media is determined by the trainer to be the most effective for the particular training being performed. A video linked to slides can be effective for general training where there is no requirement for on-the-job experience or in preparation for a practical demonstration. There are multiple resources and companies specializing in training presentations, which may be found useful for a particular application. An external presenter could be hired to present training for which there is insufficient expertise within the company. Alternatively some of the manufacturers of laboratory equipment may offer in-house training but this is usually offered when purchasing new equipment. This should still be adequately documented as training with the trainers and trainees signatures. If the equipment/process is entirely new to the laboratory, then this training should form the basis of the first SOP and those trained, when judged competent, act as the future trainers for the laboratory.

Computer-based training is becoming more available and can be provided as a self-paced tutorial to a wide audience. Data from tests can be used to determine if further training is required. The disadvantage from this type of learning is that it cannot accommodate all the possible variations in trainees and the possibility for guessing the answers exists. While this application has its uses, there should still be a separate evaluation by a trainer who then documents that the trainee is competent to perform the operation in a hands-on situation.

DOCUMENTATION REQUIREMENTS

Once the required training has been performed as determined by the syllabus and tracked by a system it must be documented. At a minimum the record must contain a brief description of the training, date, length of time, employee's signature and unique identification number, and trainer's signature. Training materials used can be attached to the attendance record or cross-referenced as a specific module (for example, Regulations #1). The original attendance record must be filed securely. The training record may also be recorded in a validated computer tracking database program and/or copies placed in the employee's training files according to company policy. The employee should always have access to their files and be in agreement with their contents. The files should also contain a current job description, curriculum vitae, and evidence (for example, certificates) of attendance at external courses. The contents should be reviewed regularly to ensure that the records are current, accurate, and complete. Personal appraisals, salary histories, and other nontraining documents should be stored in a separate location, usually human resources.

Ongoing training is required to keep the analyst informed of new and emerging regulatory requirements and industry trends. New methods, SOPs, or changes to existing documents also trigger some degree of retraining. Failure to ensure that this retraining is

performed before the analyst performs the procedure or method could be detected in records, and further questions asked during an inspection. Figure 4.2 illustrates the results of continuing training. Steep increases in knowledge/skill levels will be recorded at key stages having direct, often hands on, employee involvement, for example, orientation, and job-specific and equipment-practical training. Unfortunately, the graph will trend downwards with time and the continual change that all industries experience. Training must be adequate to meet regulatory expectations but the company also has a vested interest to maintain trained, skilled employees. Regulatory expectations should not be driving the training program. A company must determine its own needs and the needs of its employees and ensure that these are compatible with regulatory expectations.

A company that allocates adequate resources to training its people will have a better chance of retaining them. In turn, the company will prosper through low personnel turnover, fewer days lost from accidents relating to inadequate training, and, in turn, compliance with regulatory expectations (safety and manufacturing).

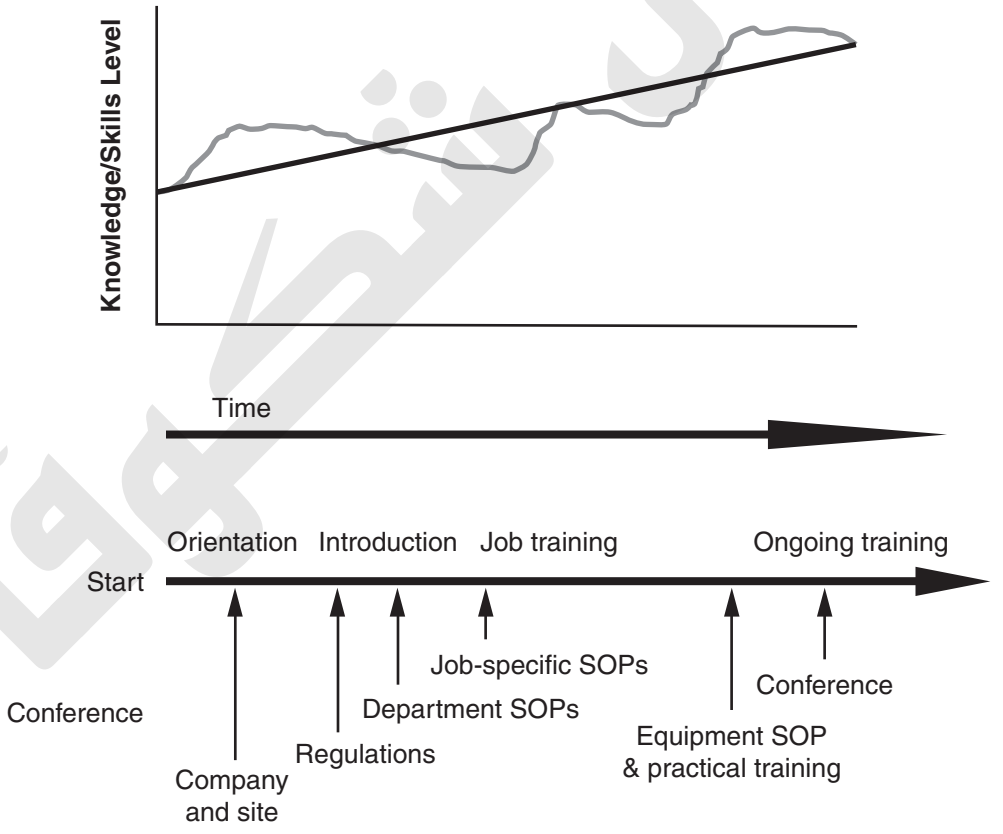

Figure 4.2 Training information source.

Attachment 1

Analyst Training Plan for

_____

Approved By:

Date:

Training Element	Responsibility	Schedule	Employee signature /date	Trainer signature /date
General orientation				
New hire orientation	Human Resources	Day 1		
Overview of company	Manager	Day 2		
Overview of site operations	Manager	Day 2		
Review of job responsibilities	Manager	Day 2		
Review of products	Manager	Day 2		
Site GMP training	GMP trainer	Week 1		
Site safety training	Safety trainer	Week 1		
Laboratory Orientation/SOPs				
General safety	Supervisor	Week 1		
Operation of the laboratory water system				
Preparation of reagents				
Out-of-specification results				
Sample handling				
Instrument qualification				
Laboratory calibration program				
Laboratory documentation				
Analytical methods maintenance				
Job-Specific Orientation				
HPLC analysis SOPs and related SOPs (List)	Manager or Mentor	Before performing analysis		
Interface with other departments				
Meet with manufacturing manager	Employee	1 month		
Meet with QA manager	Employee	1 month		
Meet with				
Orientation training program completed	Employee	1 month		

(continued)

Training File	Responsibility	When	Performed By/Date
Establish employee training file	Manager	Week 1	
File current CV	Employee	Week 1	
File job description	Manager	Week 1	
File specimen signature	Employee	Week 1	
File orientation training plan	Employee	1 month	
Develop 6 month training plan	Manager	1 month	

5

Laboratory Documentation and Data

by Graham Bunn*
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OVERVIEW

This chapter examines the different types of documentation used in the laboratory, its control, traceability, usage, and maintenance. Ideas, tools, and information discussed may be applied to other areas with suitable modifications. Good documentation practices are at the core of FDA-regulated industries. Failure to ensure adequate retrieval of documents or explanation for changes could lead to regulatory results, which are not in the interest of the company.

Remember:

- Keep it clear, accurate, and simple.
- Leave nothing open to interpretation.
- Cross-reference other documents to provide a secure paper trail.
- Clearly identify who did what and when.
- Define what signatures mean.
- Only the facts on paper/electronic media count.
- Rumors and thoughts mean nothing.

KEY WORDS

- Document control
- Data
- Logbooks
- Standard operating procedure
- Raw data

*The author appreciates the contribution of Mr. A. P. Hart in reviewing this chapter.

In any regulated industry, documentation can provide evidence of conformance with regulatory authorities' expectations. As with all complex operations, the completeness and accuracy of the documentation content is paramount in maintaining daily work in compliance. The sheer number of procedures and methods involved and data/information generated in the laboratory from one analysis may amount to several pages. The supporting documentation, for example, calibration and maintenance of an instrument and analysts training records, add further complexity to the traceability of all information. This chapter will review the overall control and generation of documentation in a laboratory and provide suggestions for good documentation practices.

Document control must be fully supported by the company through management allocation of adequate resources with time, financing, and people. Implementation of procedures establishing company standards must have the full support of management and be monitored through regular internal audits. Noncompliance relating to documentation identified through audits should be assessed and the root cause(s) corrected, while also determining if any other areas are affected. A proactive program should frequently monitor conformance and identify opportunities for improvement. Inadequate cross-referencing, incorrect filing of documentation, or inadequate explanation for a correction may have detrimental effects. This is particularly visible during a regulatory inspection if either the required documentation is not retrieved within a suitable time frame or an adequate explanation cannot be given for errors or corrections that are detected.

The boxed exhibit shows some examples of the types of documentation found in laboratories. These documents will be discussed in general terms with specific references where necessary for clarification.

1. Standard operating procedures (SOPs)
2. Guidelines
3. Policies
4. Protocols
5. Qualification and calibration
6. Calibration records
7. Equipment logbooks
8. Equipment maintenance records
9. Specifications
10. Testing methods
11. Laboratory notebooks (LNB)
12. Computer printouts
13. Certificates of analysis
14. Charts
15. Forms
16. Memos
17. Out-of-specification investigations
18. Quality investigations

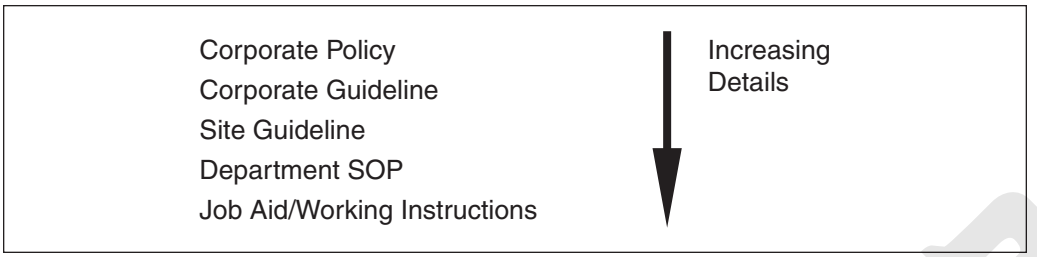

Figure 5.1 Change in the types of documents and their content detail.

Documentation is only as good as the procedures and training that support it. A company needs to have a standard operating procedure (SOP) which describes in suitable detail the writing, issuance, and maintenance of documents. In larger companies there is usually a corporate document (policy) that describes, in general terms, documentation commonly found, but this is usually based on legal, patent, and business requirements. The corporate quality organization may issue a guideline with the general requirements for the standard and content of documentation, which is used in regulatory applications or in regulated industries. This usually contains the minimum requirements and describes the expectations in very general terms. Laboratory management may decide to issue their own SOP covering specific documentation, but it should not repeat or be in conflict with other SOPs in other departments. Too often SOPs are written in isolation and either repeat, or worse, contradict other publications, or do not adequately cross-reference other SOPs. During any inspection of the laboratory by internal compliance, external client auditors, or even a regulatory investigator, the SOPs are the one document reviewed extensively. They are also a reflection of the importance the company places to ensure that they are accurate, complete, and reflect current practices.

The corporate policy sets the overall philosophy of the company, and any guidelines define requirement, but not how to attain them. SOPs define the actual steps to be taken and may be supported by job aids/working instructions.

SOPS

SOPs must, of course, be controlled and administered through an approved system for the administration of SOPs. This is usually administered from a central location that may cover multiple departments, but more than one system may exist in very large and complex pharmaceutical companies, for example, research and development or manufacturing departments. The challenge for the company is to ensure that the systems are compatible, and not in conflict or setting dual standards. An auditor performs assessments to determine if the SOPs are meeting their requirements and are being followed. If the laboratory is responsible for its own SOPs then their format, approval, and control must be defined in a specific SOP. There are probably as many different ways to administer an SOP system as there are different formats of the SOP. There is no one format or procedure that fits all

situations. Some ideas have been discussed in a previous publication.[1] There must be no question as to the validity of the SOP. It is unquestionably a management mandate that either must be followed or requires suitable approved documentation with justification to deviate from it. A quality function and the management of the area(s) having responsibilities defined in the procedure must approve all SOPs.

Key points of the SOP controlling SOPs are:

- Use a standard format/template;
- Have a unique identity and version number;
- Be written in the active voice;
- Describe the objectives and scope;
- Define definitions;
- Describe any safety requirements;
- Define management responsibilities;
- Include any references;
- Describe any appendices (diagrams, flow charts);
- Describe the process of writing and approving SOPs;
- Define approvals;
- Clarify who has control of official copies;
- Identify revision procedures, including review period;
- Explain deviation approval process; and
- Include document history.

Keep SOPs simple, concise, accurate, workable and complete. A procedure that reads well but is not practical is worth no more than one that is functional but so complicated and/or poorly written that no one can follow it.

One of the key SOPs of any laboratory or any regulated department covers documentation principles. This simple but essential document is often overlooked because it is assumed to be common sense and that everyone knows what is expected. Experience has shown otherwise. What may be usual and routine to one analyst may not be the same for a second analyst, and could be forgotten by others. The need for such an SOP is evidenced by the variations in quality and quantity of data and information recording, corrections, and cross-referencing. There is a legal and patent basis for defining the recording of research data, which is usually covered by a company document and may also be described in every laboratory notebook. This is outside the scope of this chapter and the reader is strongly advised to check with senior management or the company attorney for further information.

DATA RECORDING

The following sections will describe key points of the SOP content covering documentation principles. *Data* will be used as a general term to describe information, results, values, and readings.

Data must be clear, complete, accurate and recorded at the time they are generated. They must be clearly identified by the person recording them with the date and time if necessary. Data cannot be pre- or postdated. Accidental omission of the author/date/time at the time of the data recording can be subsequently corrected by clearly marking the document: "recorded 'by' 'date' 'at.'" The date and signature can then be added with a note that the information was omitted at the time of entry. There should be no doubt that the entry was made after the data were originally recorded. Data entered on different days must be clearly identified as such. Where data are entered by different analysts due to shift changes, this must be clearly defined with dates, signatures, and explanations when necessary. Repeated occurrences of data and information corrections indicate that there is another underlying problem, such as lack of training, or that there are inadequate controls to prevent these reoccurrences. If documentation was reconstructed using data from other sources at a later date than actually performed, then there must be an explanation and supporting evidence. Suspicions are aroused when it appears that a problem was identified and the data reconstructed to appear that everything was entered at the same time.

Auditors will track the date chronology of events to ensure that they are a true record and are in a logical time sequence. Errors associated with data, time, and date should be identified and corrected during the checking and approval process. If something looks too good to be true (for example, the pH or assay result is always exactly the same for all batches) then clarification and more information will be requested. If an auditor has any doubt concerning the authenticity of information, this must be clarified by other mechanisms before any conclusions are made. It is therefore critical to preserve any supporting evidence in the form of equipment printouts, charts, photographs, video, etc., carefully identified, dated, and authorized for future reference. Evidence of intentional misleading information and data is a serious occurrence and as such should be handled appropriately. The United States Code Title 18, Part I, Chapter 47 Fraud and False Statements, Sec. 1001. covers the submission of false, fictitious, or fraudulent statements to the United States government and the penalties. The Application Integrity Policy (CPG 7150.09) describes the action that the Food and Drug Administration (FDA) takes when it finds that a new drug application or abbreviated new drug application applicant has compromised the government's product application review process. It covers fraud, untrue statements of material facts, bribery, and illegal gratuities. Fraud has no place in FDA regulated industries.

Entries must always be made using an indelible pen. This is perhaps an obvious statement but the author has seen pencil being used in logbooks during 2000. Historically, the use of black ink was directed to ensure that copying was complete. Other colors are now also acceptable as they are copied completely with newer equipment. Some

companies require the use of inks other than black to denote an original signature, especially for approvals by the quality function. Be aware that the use of liquid ink will seep through the page and may obliterate data on the reverse side or become illegible.

The identity of the individual making the entries must be traceable and unambiguous at all times. When initials of individuals are used in regulatory documentation they should be registered/cross-referenced to their respective signatures. Sometimes this is done at the time of the operation, as in the case of batch manufacturing records with the initials and signature "registered" at the beginning of the record, and only the initials used thereafter. In the laboratory this may be easily managed in the index of the laboratory notebook or other suitable document.

Accidental damage to documents may be cause for concern but can be easily managed. If there is any chance that a liquid spill may cause further damage, the affected page(s) must be copied as soon as possible. The incident must be documented on the damaged page(s) and cross-referenced to the copies with appropriate verification signature and date. The signature verifies that the copy is an exact replica of the original. The damaged pages must be retained wherever possible, including their remains in a plastic bag if necessary.

Corrections

Corrections must be made with a single line through the information/data that does not obliterate the original entry. When correcting numerals, the entire number should be corrected and not just a single figure. Corrected information/data should be entered close to the original with initials/signature and current date. If this is not possible, a forward and backward page cross-referencing should be entered to facilitate location and checking. A brief explanation of the reason for the change is required if the change is not obvious. If there is any question or doubt concerning the correction, an explanation must be given. There should be no ambiguity of who made what correction on which date when different people make multiple corrections on the same page. Use of correction fluid is not permitted on any regulated document because it hides the original entry. If data entries in the logbook are not continuous, then a forward and backward cross-referencing to specific pages should also be used.

The use of dittos should not be permitted, which may be later overwritten with other data/information. It is, however, a best documentation practice to re-enter the data to avoid any misunderstanding. It is good practice to line out, with initials/date, all unused spaces, as there will be no question that the space was not used. Some companies require the entry of "N/A" for "Not Applicable." If data is requested, an entry, including "zero," is made. A blank space or a dash is not acceptable, as this leaves the reader to interpret if there should be any data present. It also offers the opportunity for subsequent data entry masquerading as an original entry.

Date Format

With continued company mergers involving different countries, the relatively simple date format can become a burden and has, in more than one case, caused major concerns with expiration dates. Three digital formats that have been seen are 2/3/99, 3/2/99, and

99/2/3. They all denote exactly the same day (the third of February 1999). In America the format is MM/DD/YY, the British use DD/MM/YY, and the Swedish reverse the British format with YY/MM/DD (Y: year, M: month, D: day). This may not be a problem unless you are British and working for a Swedish company in America. There are occasions when it requires a moment of thought to remember exactly which day is being documented. There are other countries that also may use variations of these formats. To prevent confusion a company may decide that the date will always be DD/MMM/YY or even DD/MMM/YYYY. The use of the two digits for the day and month serve to "lock" that date in time so that it cannot be altered. The "MMM" in this case is the month as text, for example, JAN, FEB, etc. A refinement is to encourage the use of upper-case letters to avoid any potential confusion through poor handwriting of months such as Jan/Jun, Mar/May, etc. Is it absolutely necessary? No. Is it good practice? Emphatically, yes! It could save multiple problems and miscommunications at a later date. Until an incident occurs with the date format that has a significant impact (for example, delaying product shipment), then superficially there appears to be no problems with the dates.

Photocopiers are an opportunity for a decimal point to be added or moved on the new copy and, without checking, could go undetected with potentially catastrophic consequences. The need for checking in these cases is illustrated in the preamble to 21 CFR 211.188. This section requires the checking of the master production record (directions for the manufacturing of a drug product) with the photocopy (the batch record) to ensure that it is an accurate reproduction of the original (master production record). The same is also true in the laboratory when photocopies are made from master documents. Some quality organizations stamp copies of release documents, including certificates of analysis, with a verification notice that the copy is a true, complete copy of the original.

Recording Raw Data

Recording of raw data must be covered in an SOP. Data must always be entered directly onto the paper that is being used for the recording of the event. It must not be written on scrap paper, napkins, the back of the analyst's hand, or even on the laboratory coat sleeve. Raw data also may be captured in uniquely numbered bound laboratory notebooks with preprinted numbered pages. The pages may also have "triggers" for signatures and dates. Use of forms/sheets for the recording of raw data must be controlled by an SOP to ensure that only the issued document can be used. This may be achieved by generating the sheets from a computer system with a unique tracking number and colored ink or other means to identify originality. Alternatively the documents may be preprinted with colored ink and unique page numbers before issuing to analysts. A log tracks the allocated page numbers to each analyst. All sheets issued must be accounted for with the author's signature and date. The procedure of issuance and the appearance of the documents are defined by each company.

The original entry of the data is the *raw data* and there is only one entry of raw data. This is equally applicable to the electronic capture of data from equipment and the recording of data and information by pen onto paper. It may be captured directly from

the analytical instruments into a validated management computer system, for example, Laboratory Information Management System. Interpretation of the requirements of the regulations for electronic records and electronic signatures (21 CFR 11) is outside the scope of this chapter. It is recommended that the reader obtain the regulations and preamble for interpretation by an expert for their company. Each page of data/information must be signed and dated by the analyst and by another person who checks the data for completeness and correctness. If the data is patentable, then a witness not directly involved in the project, but who is competent to understand the meaning of the work, should also sign the page.

The reader is encouraged to obtain advice from a patent expert concerning the legality of the data in research and development activities. Raw data cannot be selectively recorded either by deliberate removal of unwanted data or ignoring values from an instrument until a "true" value is seen. Control of the documents through procedure, training, and uniqueness is required. The FDA "Guide to Inspections of Pharmaceutical Quality Control Laboratories"[2] issued in July 1993 has a section covering records and documentation. The guide provides key areas and points which an FDA investigator or a customer auditor could examine equally. The laboratory manager is encouraged to use the guide to ensure that all areas, including documentation, are adequately maintained to meet current regulatory expectations. Nonpharmaceutical laboratories can benefit equally from the guide by adapting the information for their individual laboratories. The principles and practices are basically independent of the regulations covering the specific laboratory operations.

Documentation of analysis in a laboratory notebook must contain sufficient information and data, for example, method, title, and version number, equipment and identification number when more than one, reagents (including manufacturer and lot number), all weighings and calculations, etc. Attachment of documents into the LNB must be made with permanent tape, and the analyst's initials and date should be across the document and onto the book page. This ensures that the document cannot be replaced at a later date without part of the initials and date being omitted.

Forms used for the capture of information must be controlled by a unique number, effective date, and revision number; paginated with the total number of pages, and approved by an SOP in which the use of the form is described. Forms may be revised and approved independently of the SOP provided it does not change the SOP content. Quality control must approve the change and decide if the original approvers need to also approve the form or the SOP requires revision. There are several different methods to control the use of forms and maintain the expected level of control. Whenever possible, the forms should be bound in a book with page numbers as described previously.

DOCUMENT CONTROL

Documents must be controlled to ensure that only official current information is used. SOPs, methods, and specifications are examples of documents that must be approved and only controlled, official copies used. Photocopies are therefore prohibited. Revision histories must be maintained with the original copy for future reference, as this may be

requested during a regulatory inspection several years after being revised. Distribution lists of official copies are also maintained so that copies may be retrieved or confirmation of destruction received from the holders when revised versions are issued. All master/original documents must be maintained in a restricted access area. Consideration must also be given to the potential of fire or water damage of research/development data, and any other irreplaceable data/information. Fireproof cabinets can be expensive for data storage but are a relatively low cost compared to replacing unique data and information. Some documents may be recovered from electronic files backed up on computer networks and archived off-site. Original documents may also be archived in another secured location but must be retrievable within a "reasonable time frame" when requested. Do not wait for a regulatory inspection to test the time for retrieval. This should be part of the regular internal audit program.

Control and issuance of specifications, testing methods, and certificates of analysis must all be defined in SOPs. Only official, controlled copies of methods and specifications can be used. A suitable level of management must approve both documents, which clearly define the effective date. There must be adequate controls in place to ensure that only the new effective document is available and in use on the effective date.

Equipment Logbooks

Equipment logbooks should contain the complete history or at least the occurrence of the event of maintenance, calibration, and repairs. Specific details including methods, associated equipment with their calibration certificates, and actual results, as found and after servicing, may be retained elsewhere but must be accessible. Bound books with numbered pages are expected for equipment and all other types of logbooks, for example, a sample receipt. This maintains not only the completeness but also the integrity of the contents.

A supervisor must review, and document the review, of all types of official record/data book/files for currentness, completeness, and accuracy on a regular and frequent basis. Any discrepancies must be investigated and corrective actions taken with adequate explanation and justification where necessary. This approach maintains the records in a state of control and compliance with procedures and regulatory expectations. A sample of the logbook page is often an SOP attachment to reference the particular steps in the procedure. This can be as simple as listing the required information to be recorded, and the person making the record signs and dates the entry. SOPs have been attached to the inside cover of books but are often unofficial and not current. The SOP covering the logbook can be referenced inside the cover by title and even number, but ensure that this is kept current. Reference to an SOP that was retired some years ago is not a good impression for an auditor.

Charts and Printouts

Charts, for example, temperature and computer printouts, should be signed and dated by the person removing the chart or printing the documents. Any document that is open to a regulatory inspection, including memos, must contain a signature and date to give the

document authenticity. A cross reference to the batch number, project number, or logbook number/page number is also required so that the documents can be traced. Otherwise there may be no other record that a chart exists. It may be difficult to track the correct chart to a project when multiple analyses are being performed simultaneously. Wherever possible the documents should have the cross-reference number entered before the document is printed to avoid the possibility of mixing the results with another analysis.

Use of thermal paper has decreased with the advent of newer printers, but if used this paper will generally fade with time. If there is any doubt concerning the ability of the paper to retain the data it should be photocopied and attach to the printout. The copy must be initialed and dated by the individual checking that the copy and original are exactly the same.

CONCLUSIONS

Electronic capture of data and information, and now electronic signatures, has changed the operations of the analytical laboratory. Equipment has the ability to analyze more samples for more tests in a faster time than was possible only a few years ago. The amount of data collected for interpretation and statistical analysis has increased many times. Conventional calculators are still used but the sheer volume of data requires computers to handle the data before being processed. Traceability, integrity, audit trails, and identification of analysts are required with a computer, as they were with a pen and paper. Regulatory expectations continue to deal with ever-changing electronic advances.

Be honest and hide nothing. Do not intentionally misrepresent information or data. It will definitely come back to haunt you or the company at a later date. Everyone handling regulated documents must be trained in the requirements and that training, with its content, must be documented. If the administrative support position has some involvement in regulated documents, then that person must also be trained in the requirements. The same standard is also required of temporary staff, contractors, and consultants. Not only are there regulatory expectations of the documentation but it also makes good business sense for everyone to follow the same procedure.

The middle of a customer audit or a regulatory inspection is not the best time to try to compile and review supporting documentation to prove an operation took place. Not only does it provide a poor impression of the controls, or lack thereof, that are in place, but keep in mind that everyone reacts differently when under the pressure of the audit. The time to document the data was at the time of the operation, and if something was inadvertently omitted it should have been caught at the time of checking and approval. Internal audit programs must not be solely relied upon to uncover all documentation omissions as they only take a "snap shot" of the whole process. Vigilance during operations, and again at the checking stage, is critical to minimize potential problems later. Quality must be built into the entire process of generating data and summaries/discussion documents that ultimately will be reviewed by a regulatory agency during submission reviews, or possibly when performing a site inspection.

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6

Sample Control and LIM Systems

by Dennis K. Ransom
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OVERVIEW

LIM systems and automated processes create inherent challenges to maintaining the reliability of data. These challenges include traceability, accountability, standardized procedures, adequate resources, and the availability of documentation that supports conformance regulatory controls. This chapter gives an overview of the best practices available to develop, validate, and incorporate the published regulatory guidelines for automated systems. These practices help to develop efficient and compliant electronic recordkeeping systems. Validation, inspection, documentation, and electronic signature control used in LIM systems and automated processes require significant resources, including time and money.

KEY WORDS

- GLP
- GLAP
- LIMS
- Electronic signatures
- Computer systems
- Computer system audits
- LIMS raw data
- GMP
- GAMP
- Software validation
- Revalidation
- Computer system security
- Computer system hardware

INTRODUCTION

The good manufacturing practices (GMPs), the good laboratory practices (GLPs), and the good clinical practices (GCPs) were authored to insure safe production of medical devices and pharmaceuticals. The increased use of computerized data collection in the manufacture of medical devices and pharmaceuticals has resulted in new problems with sample and data integrity. The Environmental Protection Agency (EPA) published the *2185 Good Automated Laboratory Practices* (GALP) in 1995 to aid laboratories that are replacing manual operations with computer technology. On March 20, 1997, the Food and Drug Administration (FDA) published 21 CFR 11, *Electronic Records; Electronic Signatures, Final Rule*. This rule establishes the criteria under which the FDA will view electronic records and electronic signatures as equivalent to paper records and traditional handwritten signatures. In 1998 the FDA wrote the *Guide to Inspections of Computerized Systems in the Food Processing Industry*. In April of 1999 the FDA issued a guidance for industry entitled *Guidance for Industry; Computerized Systems Used in Clinical Trials*. These guidance documents contain many of the best practices for computerized data handling, laboratory information management systems (LIMS), electronic signatures, electronic records, auditing, and validating computer systems. The implementation of these guidelines can help laboratory management maintain the compliance and quality that are fundamental to effective operation.

COMPLIANCE DOCUMENT SUMMARIES

The EPA GALP document covers the definition and implementation of a quality system that would develop a compliant LIMS, electronic data system, or computerized laboratory system. The document discusses laboratory management, personnel, the quality assurance unit, LIMS raw data, software, security, hardware, comprehensive testing, records retention, facilities, standard operating procedures, and definitions. A copy of the document is contained in the appendix at the end of this chapter for reference.

Shortly after the EPA GALP was published, the FDA published the 21 CFR 11, *Electronic Records; Electronic Signatures, Final Rule*. This document describes the scope, implementation, and definitions associated with electronic signatures and records. The document outlines control of electronic records in closed and open computerized systems. Signature and record linking is addressed. Electronic signature components and controls are defined as well as controls for identification codes/passwords. The 21 CFR 11 document enhances the GALP with guidance on electronic signatures and the types of systems they can be implemented on. Valid electronic signatures used in a LIMS system ensure development of a compliant, paperless system.

The 1998 FDA *Guide to Inspections of Computerized Systems in the Food Processing Industry* discusses inspection of computerized systems, particularly in the food processing field. This document is a good source for guidance on automated data recording devices, such as thermocouples, resistance temperature devices (RTDs), pressure transducers, etc. The document gives guidance on computerized system hardware,

maintenance and calibration, system software, validation, and system operation. The document also has an appendix for the "quick guide to computer system evaluation."

The introduction to the FDA document *Guidance for Industry; Computerized Systems Used in Clinical Trials* states, "This document addresses issues pertaining to computerized systems used to create, modify, maintain, archive, retrieve, or transmit clinical data intended for submission to the Food and Drug Administration (FDA)." The document contains guidance for computer systems including standard operating procedures, data entry, electronic signatures, audit trails, and date/time stamps. The document also describes requirements for the collection, inspection, and review of quality data. Physical security and logical security are addressed. Guidance is given on computerized systems documentation, software validation, change control, and software version control. The guide establishes the need for contingency plans, backup, and recovery of electronic records. Methods for inspecting personnel training are discussed.

The previously described documents contain methods and ideas for complying with these regulations for LIMS and computerized laboratory systems. The scope of this chapter is to describe some of the best practices of the GALPs and regulatory agencies' guidance documents in solving and preventing problems, auditing, and validating automated data collection systems. The areas of laboratory management, personnel, the quality assurance unit, training, and standard operating procedures developed as part of the electronic data system or LIMS will not be addressed, since very similar systems should be established with paper systems. Areas that will be addressed will be raw data and raw data storage, software, security, hardware, and comprehensive testing. The validation of a LIMS or computerized system will be discussed, including a validation outline. Also, methods for inspecting and auditing computerized systems will be addressed.

Raw Data and Raw Data Storage

An important aspect of any automated laboratory system is the definition of raw data. The 21 CFR Part 58, *Good Laboratory Practices for Nonclinical Laboratory Studies* states, "Raw data means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. In the event that exact transcripts of raw data have been prepared (for example, tapes which have been transcribed verbatim, dated, and verified as accurate by signature), the exact copy or exact transcript may be substituted for the original source as raw data. Raw data may include photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments."

Further direction on computerized data acquisition affirms the system acceptability when only authorized individuals can make data entries. Furthermore, raw data entries may not be deleted and changes must not obscure the original data entry. The reason for the data change and the signature of the person making the change must be recorded. The database and storage media must be as tamperproof as possible. Procedures must

be in place for insuring the validity of the data and a description of consideration for raw data (hardcopy, printouts, or magnetic or optical media).

The EPA GALP (1995) document defines raw data captured into laboratory information management systems (LIMS) as follows, "LIMS raw data (LRD): original observations recorded by the LIMS that are needed to verify, calculate, or derive data that are or may be reported." Also, LIMS raw data storage media is defined as "The media to which LIMS raw data are first recorded. Media may be paper, microfiche, microfilm, or magnetic or optical storage media. LRD are the first observations recorded that are human-readable by use of software, printout, or other method."

The FDA states in the *Guide to Inspections of Computerized Systems in the Food Processing Industry* (1998) that "electronic records must be maintained in a format that can be presented to the investigator in a readable form. This could be in the form of electronic data that can easily be accessed and read by common computer software, or in the form of accurate hard copy documents produced from electronic records maintained by the firm."

In 21 CFR 11, *Electronic Records; Electronic Signatures, Final Rule*, the FDA defines an electronic record as "any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system."

After the raw data or electronic records have been documented and identified, check that the input of the raw data is traceable to the person who manually input the data or who was responsible for the transmission of the raw data to the LIMS. Time and date must be attached to the record. If the data was transmitted from an instrument, that instrument must have a unique identification code as well as a time and date stamp for the data acquisition.

Data entered manually or electronically must be verified for accuracy. The accuracy of the data for automated collection should be confirmed under validation of the computer or LIMS system. Manual data entry may be verified in a number of ways, such as double entry, blind rekeying of data, or other proven method. Data should be verified periodically, even after successful validation.

The FDA in 21 CFR 11 states, "Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject's electronic records and shall be available for agency review and copying to ensure, as necessary under the circumstances, record authenticity, integrity, and confidentiality." When raw data is changed, the original data or observation needs to be preserved, along with the reason for the change, the person who made the change, and the date of the change. The person authorizing the change, if applicable, should also be recorded. All related government compliance and guidance documents describe similar methods of recording raw data changes. The standard operating procedures (SOPs) describing raw data change procedures should be well-documented and very explicit.

Software

The EPA GALPs (1995) outline specific SOPs that need to be in place for development of software for LIMS production, development, and use. They include software

development methodology, testing and quality assurance, change control, version control, and historical file. The SOPs need to detail the procedures for maintaining historical files. This needs to include all software versions, software operating procedures, and hardware to run the versions. As hardware becomes obsolete, the historical data may be migrated to newer hardware and operating systems to avoid storing and maintaining obsolete hardware systems. Validation of the migration techniques would be required.

All existing and commercially-available systems in use should have a description of the software, the functional requirements, algorithms and formulas, and testing and quality assurance procedures. Also all installation, operation, maintenance, enhancement, and retirement procedures need to be established.

New systems should be documented under a lifecycle system that includes: initiation, requirements analysis, design, programming, testing and quality assurance, installation and operation, maintenance/enhancement, and retirement. Current documentation should be available for users and developers. A historical file of all versions of software must be available. SOPs and documents should be centrally located to prevent their loss or misplacement.

In addition to the EPA GALPs software guidance, the FDA in the *Guidance for Industry; Computerized Systems Used in Clinical Trials* (1999) reiterates many of the ideas discussed in the EPA GALPs as well as identifying some new software development guidance. First, the document states that software "should ensure and document that computerized systems conform to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance. . . . Systems documentation should be readily available. . . . Such documentation should provide an overall description of computerized systems and the relationship of hardware, software, and physical environment."

Purchased off-the-shelf database, word processing, and spreadsheet software that are unmodified should have functional testing, and may not need full design-level validation. This software should not be used for recording raw data or receiving automated data inputs.

Documentation should be established describing written design specifications, including the intended use and methods for achieving the intended use. A protocol should be written based on the design specifications. Documentation should be made of test results and an evaluation of the results demonstrating that the design specifications have been met. Further discussion of the validation of software is described under the section on validation.

Written procedures need to be in place to cover computerized system changes. The procedures need to ensure that software upgrades, equipment, and instrumentation will not change the integrity of the software or electronic record system. The impact of any system change must be evaluated to determine if revalidation is required. The *Guidance for Industry; Computerized Systems Used in Clinical Trials* (1999) states that "revalidation should be performed for changes that exceed operational limits or design specifications." The document also states, "All changes to the system should be documented."

A software version control system must be in place to document the version of software used to generate, collect, maintain, and transmit the raw data. Standard operating procedures should describe contingency plans for continuing data collection by another

method in the event of a computerized system failure. The plans must also include a method for recovery of electronic data in the event of system failure.

Security

The EPA GALP (1999) document states, "LIMS passwords shall contain a minimum of six characters and not be trivial to guess, consist of numerals and alphabetic characters, be changed at least once every ninety days, and not be found in a dictionary or have repetitive characters."

Based on direction from 21 CFR 11, two types of electronic signatures are available, biometric systems and electronic systems. The biometric system is based on recognition of a person based on distinguishing traits. Electronic signatures using biometrics must be designed to be unique to their owners. The electronic system is based on at least two distinct identification components, such as an identification code and password. Typically LIMS applications have a log-in event consisting of a user name, initials, or identifier, as well as a password. The execution of one of the two electronic signature components may constitute a log-in. Another identification code is needed for a valid electronic signing. During a continuous data recording session, all signings need only be verified by one component of the electronic signature. The system needs to ensure that the session is continuous. This may be accomplished by time-outs, password-protected screen savers, or other methods. When signing is not executed continuously, both electronic signature components need to be executed to constitute a valid electronic signature.

Electronic signatures must be used only by the intended person. They must not be loaned out. Procedures and LIMS functions must ensure that the identification codes and passwords are unique and that no two individuals have the same combination of identification. These procedures must insure the security and integrity of the passwords and identification codes. Procedures must also insure control, auditing, recalling, revising, lost, stolen, or missing passwords and identification codes. LIMS needs system safeguards to prevent and detect misuse and unauthorized use of the passwords and identification codes.

According to 21 CFR 11, there must be "(c) protection of records to enable their accurate and ready retrieval throughout the records retention period, and (d) limiting system access to authorized individuals." Methods of achieving this security come through physical and logical security. Security training and responsibility must be instigated and maintained to insure security and availability of the raw data. All LIMS users should be aware of security safeguards.

Safeguards should be built into the system to ensure that access to the LIMS or computerized system servers is restricted to authorized personnel. System security can be enhanced by locked server rooms, limited logical and physical access, locked keyboards, and other security devices. Electrical protection such as surge protectors and uninterrupted power supplies protect the quality of the system. Temperature control should be optimum for safe storage of magnetic media, backup tapes, optical disks, etc. Physical security procedures should also extend to devices used to store software and raw data, including maintenance, accountability, and access to the data storage devices.

Routine backup procedures are needed to ensure the availability of the LIMS data. The backups must be tested regularly to ensure that the data can be restored correctly. Methods should be in place to control computer viruses that can destroy or alter raw data.

Logical security can be addressed on the network. The networked LIMS or computerized systems may be secured in a number of different ways depending on the operating systems and the networking software. All access to the network server is typically controlled via an individual user name and password. File access rights are established by the network manager or the file owner and may only be modified by system management personnel. Only computer system management personnel are assigned rights to modify or control the network operating system. System events such as log-on failures or break-in attempts can be automatically monitored and recorded by the network software. Generally after three failed log-on attempts, a user account can be automatically locked. The account may only be unlocked by the network manager. The network software can also audit system errors and all transactions such as log-ins and log-outs upon request of the auditor. The current full record may also be reviewed online. Walkaway security can be accomplished that suspends the LIMS operation under the security of a user-selected password. Also a password-protected screen saver program, invoked after a set time of keyboard inactivity, can protect computers against unauthorized workstation use.

Disaster recovery and contingency plans are required to ensure that raw data will always be available. Backups are an integral part of the disaster recovery plan. Backups are stored in another location to thwart the loss of all data at one site. The off site storage conditions should be monitored to comply with storage for the raw data media being stored.

Hardware

The computerized or LIMS system hardware must be designed to insure raw data integrity, availability, and confidentiality. Documentation of the system configuration description should be developed and maintained. Hardware consists of computers, networks, storage devices, and peripheral devices including input and output devices. Input devices include thermocouples, resistance temperature devices (RTDs), load cells, touch screens, pH meters, pressure gages, modems, and keyboards. Output devices may include valves, switches, motors, solenoids, cathode ray tubes (CRTs), printers, and alarms. Some peripheral devices have input and output capabilities and are described as I/O devices. Peripheral devices are any computer-associated device that is external to the central processing unit (CPU).

Acceptance criteria, testing, documentation, and final approval of LIMS hardware and communications components should be established in SOPs. The SOPs must include descriptions of hardware required to make raw data human readable. Procedures for signing, dating, and audit-trail generation of raw data created by I/O devices must be addressed. Some electronic recording devices may not have options for operator name and password. The data generated in this method may need to be printed and then signed by the operator. Examples may be sterilizer logs or stand-alone thermocouple devices.

Periodic maintenance of the LIMS hardware should be done on the computer network hardware, including testing and inspection. Document the operations performed and record the results.

VALIDATION

The 21 CFR 11 states, "Validation of systems [is required] to insure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records." Additionally the FDA specified in the *Guidance for Industry; Computerized Systems Used in Clinical Trials* (1999) that the "FDA may inspect documentation, possessed by a regulated company, that demonstrates validation of software. The study sponsor is responsible, if requested, for making such documentation available at the time of inspection at the site where software is used."

Off-the-shelf purchased software should be validated by the company that wrote the software. The documentation of this validation should be available. Even when the company that wrote the software has validation data, functional testing needs to be done (for example, by use of test data sets) to determine limitations, problems, and defects that the software may have when installed in the LIMS or computer system. Software that is developed in-house by the laboratory or manufacturer must be validated if it is produced as described previously. The in-house software must also be validated within the total system.

Documentation is important to demonstrate software and system validation. The documentation should include a written design of what the software and system is intended to do and how it will do it. A written validation or test plan should be developed to include structural and functional analysis. Test results and evaluate the data to demonstrate that the specification of the system or software was met. The validation protocol should also ensure that changes to the software such as upgrades, equipment, component replacement, or new instrumentation will maintain the integrity of the electronic data. The documentation should contain a review of changes to ensure that a revalidation will take place when changes are significant enough to threaten the integrity of the data.

The *Guide to Inspections of Computerized Systems in the Food Processing Industry* (1998) defines a computerized system as "the computer hardware, computer software, peripheral devices, personnel, and computer system documentation (including computer hardware and software manuals, specifications for peripheral devices and standard operating procedures)."

Appropriate tests and challenges should be developed to establish the suitability of a computerized system. The scope and depth of the validation depends on the risk analysis evaluated during the validation protocol design. The validation scope also depends on the complexity of the system. The validation should be sufficient to support a high degree of confidence that the computerized system will consistently perform to the design specification. Many of the separate components of the computerized systems are tested separately before being placed into the LIMS or computerized system. Validation should be done with all components in place. Validation should define unexpected conditions and events. The validation should be done under maximum loads and worst-case scenarios. It is important to determine that under worst-case conditions software routines consistently perform as they are supposed to.

Consideration of computerized system validation should address various areas. Ensure that the accuracy and sensitivities from sensors, thermocouples, RTD, etc., are in the range needed. Make sure that the software captures enough data to comply with regulations. Make sure that the worst-case simulations cover maximum users and data input overload. Develop enough testing to ensure that the system will generate reproducible results. The validated system should include a validation protocol, test results, and test reports, including individuals who conducted the testing, reviewed the data, and approved the validation. If the validation was done by an outside vendor, keep copies of the data on site, including design specifications, protocols, general results, and validation report.

Another area of validation to review is software spreadsheet templates. Spreadsheets are not normally used for the collection of raw data, because of the signature and record linking limitations. Spreadsheets are very useful in calculating, graphing, and manipulating data. The use of a validated spreadsheet saves review time by ensuring that the same calculations are done each time the spreadsheet is used. Only the data entry cells would need to be verified on a valid spreadsheet, saving the time it would take to verify all of the spreadsheet calculation functions.

The computerized system validation protocol may contain a summary with the following checklist or outline:

I. Introduction (defines the scope of the validation)

II. Justification (defines the agency or compliance documents under which the validation is run)

III. Name of the person that developed the protocol and the date

IV. Regulatory References

V. System Description

   A. Software

      1. Media and hardcopy listings of all table structures, methods, procedures, libraries, forms, and graphics

         a. System requirements

         b. User requirements

         c. Training requirements

         d. Development methodology

      2. Network software

      3. Operating system software

      4. Software versions tested

B. Hardware

1. Hardware configuration, operating instructions, wiring diagrams, and cabling requirements

a. Network architecture and cabling descriptions

b. Network hubs, routers, and connectors

c. Network interface cards and performance data

d. Network servers

e. Network printers

f. Prime server's power backup

VI. Testing Description

A. Testing procedures for determining functionality, limits, ranges, etc.

1. Test data

2. Test results

3. Test limit and limits tested

4. Resolve errors

5. Testing conclusions

6. Formal release

VII. Documentation

A. Standard Operating Procedures

B. Validation Documents

C. System-related Documentation

D. Testing Documentation

VIII. Validation Report

A. List all required SOPs for LIMSs

B. List all documentation

C. List all archived and updated software and documentation

D. List all operator documentation

E. Attach all validation protocols

F. List all software versions validated

G. Summary of test conclusions

ELECTRONIC DATA SYSTEM AUDITS

Computer systems are monitored and audited to ensure that they comply with the good automated laboratory practices (GALPs). These audits assure that all LIMS data, hardware, software, network links, etc., are reliable and compliant. Two types of system audits are internal and external audits. Internal audits assure compliance and data validity. External audits are performed to ensure that vendors and suppliers using computerized systems meet the GALP requirements. Regulatory agencies perform these audits.

Absolute data integrity may not be possible, but it is improved by adherence to principles and practices that improve integrity. Audit activities are intended to insure the reliability and compliance of computer systems and LIMS data. Software is difficult to audit via direct observation. However, the output and operation of software can be observed and an inference may be drawn that if the output is as expected, then the software is operating acceptably.

Best Practices for the Detection and Deterrence of Laboratory Fraud (1997) states, "Laboratories should have well-documented procedures for handling electronic data, and conduct periodic audits to insure compliance with the procedures. Elements that should be part of the procedure are:

- A defined convention for naming files that will result in traceable data files for every sample, including quality control samples and calibration data;
- A backup system that can be used to retrieve old data files;
- A policy for making changes to electronic data; and
- A documentation procedure that will flag every data file that has been manually manipulated, show the changes that have been made, explain the rationale for the changes, and identify the individual making the changes and the date and time the changes were made.

"Laboratories should periodically audit their electronic data to verify that the procedures are being followed. There should be a program to perform a random audit of electronic data. In cases where problems are indicated from other quality assurance measures, such as systems audits or performance evaluation samples (PES), electronic data audits should be targeted at the areas of concern. The audit should result in a report that includes description of the tapes inspected, the date of the audit, the person performing the audit, any findings or problems observed, recommended corrective actions, and recommended frequency of future audits [*2185 Good Automated Laboratory Practices*]. Any findings that may affect data quality or data integrity should be reported to the laboratory management. Any findings that are verified to affect data quality or data integrity should be reported to the affected clients."

The following methods can be used to perform internal audits on validated computer systems. Audit and review techniques include: (1) Routine in-service review of LIMS function and raw data, including GALP protocol audits; (2) Monthly review of all applicable logbooks; (3) Automated auditing systems; (4) Review of the network and system configuration; (5) Routine review of all study-related data generated by the computers

before it is released in a final report; and (6) Ensure that raw data is being recorded into the LIMS correctly. Assure that the audit trail is complete and easily reconstructed.

Monthly review of the systems that use computers, computer logbooks, and other computer-specific reviews should be done. Examples of logs audited are described below:

- Backup and restore
- Backup disks and tapes transferred off site
- Computer calibration/maintenance
- Computer equipment receiving
- Computer installation qualification
- Computer nonroutine repair
- Computer peripherals
- Server virus-scan
- LIMS software change request
- Software receiving
- Software change request form
- Source code

Automated auditing systems are usually components of the networking server software. These software programs record transactions and system errors on a continuous basis. Software also monitors user log-in, user log-out, and user file deletions on an ongoing basis. Audit the physical layout of the complete network documentation, servers, attached workstations, and communication links. External audits should be performed on vendors, suppliers, or contract laboratories that may be using computer systems to record raw data. It is important to ensure that data generated by the contract laboratory is GALP compliant.

Determine the products or services being produced with the computerized system. Make sure that the products or services are covered by GMPs and GALPs. Identify the computerized system components. Review the system hardware, including networking and peripheral devices. Determine software used. Review the documentation, including manuals and standard operating procedures. Review personnel for credentials and training. Review the critical software for validation, including function, inputs, outputs, set points, and data manipulation. Determine how the software was developed, in-house, contractor, or off-the-shelf. Review the software security. Determine if the system has accurate records, adequate calibration and accuracy, and that the personnel are trained in operation of the system. Determine how the system can be overridden and who has the authority to do that. Review the computer system validation as described previously. Determine frequency of maintenance, calibration, and revalidation. Review system change procedures including software, hardware, and raw data.

SUMMARY

The use of these best practice guidance documents for computerized data handling and LIMS offers companies an opportunity to develop efficient and compliant electronic recordkeeping. The development of regulatory compliant computerized systems also presents challenges. The continual system improvement through hardware and software upgrades requires great expense. Validation, inspection, and documentation require significant resources, including time and money.

Each computerized system or LIMS is unique. The elements mentioned in this review may or may not apply to every computerized system. The guidance discussed in this review will help to develop a system that will be compliant, valid, and efficient.

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Appendix A

EPA Good Automated Laboratory Practices

United States Environmental Protection Agency | Office of Information Resources Management Research Triangle Park, NC 27711 | 2185 8/10/95

GOOD AUTOMATED LABORATORY PRACTICES

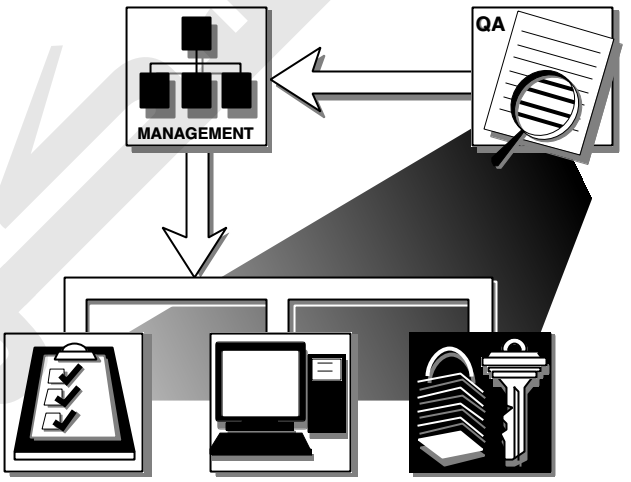
EPA

2185 - Good Automated Laboratory Practices

Principles and Guidance to Regulations For Ensuring Data Integrity In Automated Laboratory Operations

with **Implementation Guidance**

1995 Edition



Good Automated Laboratory Practices

August 10, 1995

Principles and Guidance to
Regulations For Ensuring Data Integrity
In Automated Laboratory Operations

with Implementation Guidance

1995 Edition

Scientific Systems Staff
Office of Information Resources Management
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

IF a man will begin with certainties, he shall end in doubt; but if he will be content to begin with doubts, he shall end in certainties.

—*Francis Bacon*

Preface

Most EPA regulatory and research programs have regulations or requirements by contract clause that govern the conduct of laboratory studies. The GALPs *do not* supersede any existing requirements or regulations of EPA's organizations, nor do they augment them. Some of the GALP provisions guide EPA staff and its agents (contractors or grantees) to existing EPA requirements such as the System Life Cycle Management, Chapter 17 of *Information Resources Management Policy Manual*.

The GALPs are developed from essential principles inherent to sustaining challenges to the reliability of data. These include traceability, accountability, standardized procedures, adequate resources, and, importantly, the availability of documentation that supports conformance with these principles. Each GALP provision embraces at least one of these principles.

The intended objective of the GALPs is to provide EPA organizations with a set of benchmarks to examine in light of their needs and established requirements or regulations. If an organization then determines that changes or additions to their own requirements or regulations are needed, it is the responsibility of that organization to amend their requirements or regulations.

The GALPs have been constructed to address realities of 1995. They may be modified over time to reflect changes in U.S. laws such as the congressionally-mandated Computer Security Act, requirements by the Office of Management and Budget, and others. They may also be modified over time to address advances in automated data management technologies.

Executive Summary

This document describes benchmarks, Good Automated Laboratory Practices (GALPs), for assuring the reliability of laboratory data. The GALPs are principles and guidelines to regulations for laboratories that use or are planning to use a wide range of automated data collection and management systems. The GALPs are EPA's response to mounting evidence of corruption, loss, and inappropriate modification of computerized laboratory data by EPA contractors.

The GALPs are a union of Federal regulations, policies, and guidance documents. Several of the GALP provisions are embodied in EPA's Good Laboratory Practice Standards (GLPs). The GLPs are regulations that govern the management and conduct of most nonclinical laboratory studies submitted to EPA's office of Toxic Substances and its Office of Pesticide Programs.

Several GALPs are contained in EPA's Information Resource Management (IRM) policies. These policies prescribe methodologies and practices for using automated data processing hardware and software. The IRM policies are directed to EPA staff and its agents (contractors and grantees) and generally implement broader Federal mandates such as the congressionally-mandated Computer Security Act of 1987, the Office of Management and Budget Circular A-130, and others. Most of these are also specifically required by EPA Acquisition Regulations.

This document is divided into two sections. The first chapter formally establishes the GALPs, describes the purpose they serve, provides background information about studies that led to their development, and explains their scope and applicability. The second chapter provides laboratories with additional explanations of each provision and other relevant information to assist laboratory staff in implementing each applicable provision.

Acknowledgments

This document culminates a six year program by EPA's Office of Information Resources Management (OIRM). Numerous experts in national and international laboratory standards, laboratory automation experts, senior managers and technical staff in government and private companies provided invaluable support.

Mr. Mickey Cline and Dr. Walter Shackelford, both of OIRM, identified the need for the program, ensured that resources were provided, offered many valuable suggestions that helped to focus the program, and provided encouragement when obstacles seemed insurmountable. Without their support this program likely would not be completed.

Ms. Lynn Laubisch's (Durham, NC) contribution to the publication of this document far exceeded her title, "Micro Graphics Specialist." She is responsible for transforming what could have been a dull, monotonous and probably difficult-to-follow publication into a refreshing, easy to read "text book" that enables complex concepts to be easily accessible to a diverse readership. While a cursory review of the document demonstrates her skill in page layout, font selection, and icon and diagram creation, a careful reading of the text is indicative of her oversight in helping to eliminate convoluted sentences and make the text easily readable.

Ms. Stephanie Taublee, Mr. David Brodish both of Research Triangle Institute (RTI), and Ms. Terrie Baker, formerly of RTI, deserve most of the credit for the areas of quality assurance (QA) the GALPs embrace and explain. Their professional QA experience, dedication, determination and commitment to doing the right thing on time, and their ability to examine highly charged and sensitive issues from several angles were essential.

Mr. Keith McLaurin of Technology Planning and Management Corporation (TPMC), Mr. Don Weyel, formerly of TPMC, and Mr. Bill Hampton, a Consultant to TPMC, instilled a wealth of the discipline of Computer Science to the GALPs. Their knowledge and experience in automated system design and development, computing and

communication technologies, and the evolving specialized area of computer security enabled issues related to current computing environments, system life cycle and a myriad of intricate factors affecting computing security to be thoroughly and accurately explained in the document.

Mr. Dexter Goldman of Goldman and Associates enthusiastically supported this program from its inception. His extensive experience in EPA's *Good Laboratory Practice Standards* is reflected in many areas of the document. His critical review of earlier drafts was essential. He identified and recommended numerous changes not noted by other reviewers that, though subtle, had profound impact.

Dr. Sandy Weinberg of Weinberg, Sax and Spelton Associates deserves much of the credit for getting this program started in the right direction. He afforded the program with an unparalleled wealth of experience in assisting laboratories in complying with national laboratory standards, auditing laboratory operations, and translating national and international laboratory guidelines into laboratory operating standards.

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*Chapter 2 is contained in a separate file, galpchp2

Chapter 1 — GALP Overview

1. PURPOSE

Most of the health and environmental data EPA uses in its regulatory programs are analyzed in and reported by laboratories. Increasingly, these laboratories employ laboratory information management systems (LIMS) to acquire, record, manipulate, store, and archive their data (see 2.c APPLICABLE SYSTEMS). Though many benchmarks are scattered across EPA's regulatory programs, EPA has no consistent set of standards for the use of LIMS that promote integrity of laboratory data.

The purpose of the Good Automated Laboratory Practices (GALPs) is to establish a uniform set of procedures to assure that all LIMS data used by EPA are reliable and credible.

2. SCOPE AND APPLICABILITY

a. Organizations

The GALPs are applicable to all EPA organizations, personnel, or agents (contractors and grantees) of EPA who collect, analyze, process, or maintain laboratory data for EPA. These organizations include the Agency's Regional Laboratories, and laboratories submitting data through contracts or grants with EPA, including the Superfund Contract Laboratory Program (CLP). Other organizations who wish to improve assurance of the integrity of laboratory data where LIMS are used are encouraged to review and implement applicable GALP provisions (see also 6. RESPONSIBILITIES).

b. Relation to Other Regulations and Requirements

Federal regulations, EPA directives, policies, and its contract requirements govern the activities performed by laboratories that submit data to the Agency. Various laboratories are involved in the collection and analysis of environmental data and not all laboratories are subject to the same set of regulations and requirements. EPA's Contract Laboratory Program sets requirements by explicit clauses and clauses incorporated by reference in their governing contracts. Similarly, laboratories that submit studies in support of the registration or re-registration of pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) are subject to the Good Laboratory Practice (GLP) Standards [40 Code of Federal Regulations (CFR) Part 160. Federal Register Vol. 54, No. 158, August 17, 1989]. Laboratories that submit studies required by the test rules and negotiated testing agreements section of the Toxic Substances Control Act (TSCA) are subject to the GLP regulations at 40 CFR Part 792.

The GALPs include many of the GLP requirements for managing the conduct of studies. The GALPs supplement the GLPs with Federal and EPA policies that address automated hardware, software development and operation, electronic transfer, and systems security. These are collectively referred to by the term Information Resources Management (IRM) policies. Thus the GALPs integrate GLP practices and procedures with IRM practices and procedures, to ensure the integrity of data that are entered, stored, and manipulated by the LIMS (see Figure 1.1).

c. Applicable Systems

The GALPs use the acronym LIMS, laboratory information management system, to describe the automated laboratory systems that collect and manage data discussed in this Directive. There is a limitless range of possible configurations of automated data collection and processing equipment, communication components, types of operating system software, database management systems, and application software that can constitute a LIMS. The GALPs are directed to *most* configurations that are involved with entering, recording, manipulating, modifying, and retrieving data.

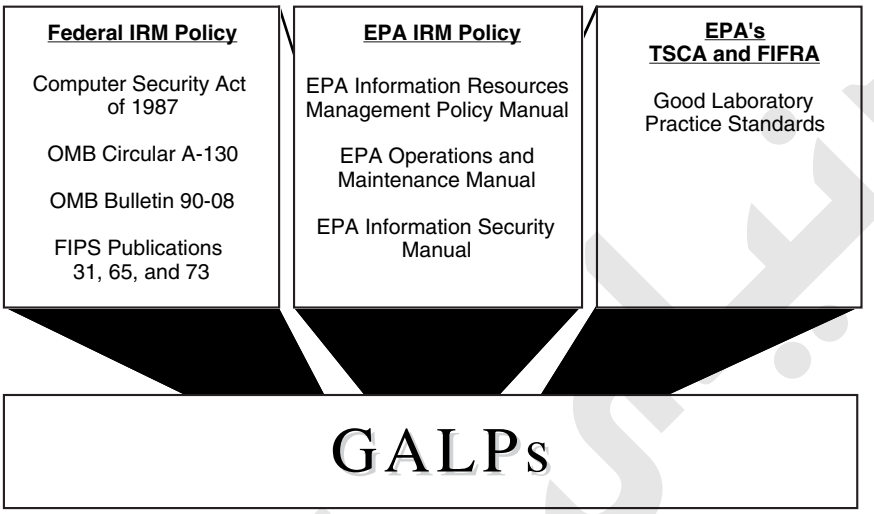

Figure 1.1. Principles and Regulations Used in Developing the GALPs
(See 10. ACRONYMS)

Not all automated laboratory systems are LIMS. Automated laboratory systems that record data but do not allow changes to the data are not LIMS (see Figure 1.2). For example, an instrument that measures weights and produces or maintains a readout of the weight is not a LIMS, if the true reading cannot be altered by a person prior to recording.

The ability to effect changes to original observations or measurements is the factor in determining whether the automated laboratory system is a LIMS (see Figure 1.3). If data entering automated laboratory systems can be manipulated or changed in any way by the action of a person prior to being recorded, then that automated laboratory system is a LIMS.

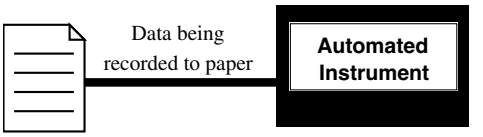

Figure 1.2. Automated Laboratory Systems NOT Subject to the GALPs

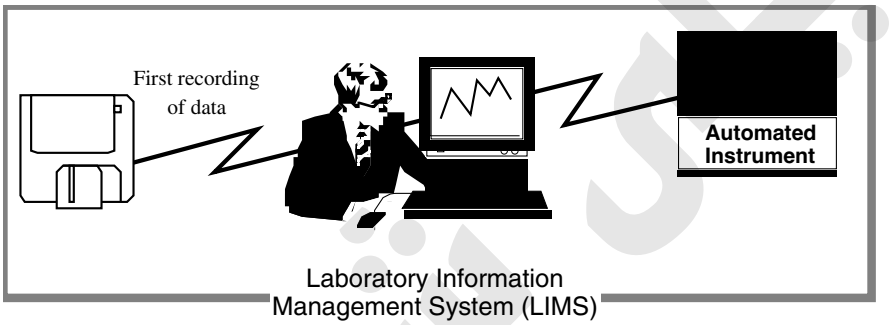

Figure 1.3. Automated Laboratory Systems Subject to the GALPs

3. DOCUMENT ORGANIZATION

This document is organized into two chapters. This first chapter, GALP OVERVIEW, describes basic facts about the GALPs, including the purpose they serve, the scope, applicability and organization of this directive, the policy the GALPs implement, authorities and references supporting the GALPs, responsibilities of organizations, background information, the GALP provisions, definitions of terms, list of acronyms, and sources for Federal information resources management publications referenced in the GALP.

Chapter 2, GALP IMPLEMENTATION ASSISTANCE, provides additional information about each GALP provision. It is intended to assist in the successful application of each GALP provision. See the introduction to Chapter 2 for additional discussion.

4. POLICY

It is EPA policy to implement and comply with all applicable information management laws mandated by Congress, all requirements issued by the Office of Management and Budget (OMB), all Federal Information Resource Management Regulations (FIRMR) issued by the General Services Administration (GSA), and all Information Processing Regulations issued by the National Institute of Science and Technology (NIST).

It is also EPA policy that data collected, analyzed, processed, or maintained to support health and environmental effects studies be of sufficient accuracy and integrity to support effective environmental management.

EPA recognizes that absolute data integrity is not possible and that reliability and defensibility are determined by adherence to principles and practices that contribute to improving integrity. The GALPs balance risk against cost, incorporating existing Federal and EPA policies.

5. AUTHORITIES AND REFERENCES

a. Authorities

(1) Computer Security Act of 1987, Public Law 100-235

(2) EPA Information Resources Management Policy Manual, Chapter 17 and Chapter 18, September 1994

(3) EPA Information Security Manual, December 1989

(4) EPA Operations and Maintenance Manual, April 1990

(5) Federal Information Processing Standards (FIPS) Publication 31: Guidelines for Automatic Data Processing Physical Security and Risk Management, June 1974

(6) Federal Information Processing Standards (FIPS) Publication 65: Guidelines for Automatic Data Processing Risk Analysis, August 1979

(7) Federal Information Processing Standards (FIPS) Publication 73: Guidelines for Security of Computer Applications, June 1980

(8) Federal Insecticide, Fungicide and Rodenticide (FIFRA); Good Laboratory Practice Standards. 40 CFR Part 160. Federal Register Vol. 54, No. 158, August 17, 1989

(9) Office of Management and Budget (OMB) Circular A-130, Management of Federal Information Resources, as Amended, April 29, 1992 *(this Circular may be subject to revision*)

(10) Office of Management and Budget (OMB) Bulletin 90-08, Guidance for Preparation of Security Plans for Federal Computer Systems that Contain Sensitive Information, July 1990

(11) Toxic Substances Control Act (TSCA); Good Laboratory Practice Standards. 40 CFR Part 792. Federal Register Vol. 54, No. 158, August 17, 1989

b. References

(1) Automated Laboratory Standards: Current Automated Laboratory Data Management Practices, EPA/OIRM (Final, June 1990)

(2) Automated Laboratory Standards: Evaluation of Good Laboratory Practices for EPA Programs, EPA/OIRM (Draft, June 1990)

(3) Automated Laboratory Standards: Survey of Current Automated Technology, EPA/OIRM (Final, June 1990)

(4) Automated Laboratory Standards: Evaluation of the Use of Automated Financial System Procedures, EPA/OIRM (Final, June 1990)

(5) Automated Laboratory Standards: Evaluation of the Standards and Procedures Used in Automated Clinical Laboratories, EPA/OIRM (Draft, May 1990)

(6) National Institute of Science and Technology (NIST) Special Publication 500-166, Computer Viruses and Related Threats: A Management Guide (August 1989)

(7) U.S. Department of Commerce National Bureau of Standards (NBS) Special Publication 500-101, Care and Handling of Computer Magnetic Storage Media (June 1983)

6. RESPONSIBILITIES

a. The Office of Information Resources Management (OIRM) shall:

(1) be responsible for developing, establishing, providing, and maintaining the GALPs.

(2) provide guidance and technical assistance, where feasible and appropriate, in implementing and improving the provisions of the GALPs.

b. Each "Primary Organization Head" (defined by EPA Order 1000.24 as the Deputy Administrator, Assistant Administrators, Regional Administrators, the Inspector General, and the General Counsel) is responsible for:

(1) complying with all applicable Federal and EPA rules and regulations affecting the collection, analysis, processing, storage, or maintenance of LIMS data. These are indicated in each GALP provision by the use of underlined lettering, such as *EPA Information Security Manual*.

(2) reviewing the GALPs and taking the necessary measures to implement appropriate provisions provided in the GALPs that will improve the integrity of LIMS data.

7. BACKGROUND

a. EPA relies heavily on laboratory data to accomplish its mission. The accuracy and integrity of these data are essential to EPA's ability to effectively formulate policy, make decisions, and take action on issues involving public health and the environment. Laboratory data are therefore critical Agency assets and must be managed and protected as such.

b. The computer is increasingly replacing and augmenting many manual operations in the laboratory. Much of the laboratory data now submitted to EPA have been created, collected, processed, managed, or in other ways manipulated by LIMS.

c. Laboratory data are exposed to potential loss and misuse from a variety of accidental and deliberate causes. Cases involving the corruption, loss, and inappropriate modification of computerized laboratory data provided to EPA have resulted in debarments, suspensions, fines, and criminal prosecution.

d. EPA's OIRM conducted several studies to assess the automated data management practices employed by laboratories to ensure data integrity. Principal findings and recommendations of these studies included:

(1) The integrity of computer-resident data is at risk in many laboratories providing scientific and technical data to EPA. Inadequate system security, data verification, standardized procedures, designation of responsibility, and documentation are to a large extent responsible for these risks.

(2) EPA has no Agencywide policy for laboratories that collect and manage LIMS data. The laboratories that provide data to EPA are subject to differing regulations, policies, and contract requirements for the conduct of studies and management and operation of the laboratory.

(3) In many cases, the requirements that a laboratory must follow in conducting a study are vague or ambiguous regarding the special concerns and issues related to LIMS. For example, FIFRA and TSCA GLPs refer to "recorded data from automated instruments"; however, standards or guidance for performing LIMS risk assessments and LIMS software development and modification are not directly addressed in the GLPs.

(4) EPA has no definitive guidelines to aid the Agency's inspectors and auditors when they inspect laboratories that use LIMS in the conduct of a study.

(5) The need for Agencywide standards and guidance is recognized and acknowledged by the laboratory community and LIMS vendors.

(6) Data management practices should be standardized for all laboratories supporting EPA programs and the Agency should assume the responsibility for establishing these standards. The guidance and training provided to the Agency's inspectors and auditors should also be augmented accordingly.

e. In response to the findings of these studies, OIRM initiated the development of the GALP. The first draft of the GALP was issued in December 1990. Since that time, over one thousand copies of the draft GALP document have been distributed to EPA regional and program offices, other Federal agencies, industry, associations, and private citizens and groups.

f. OIRM received over 600 individual comments on the first draft of the GALP document. OIRM additionally contracted for the review of the document by

subject-area experts in the fields of laboratory data systems, laboratory management, systems security, telecommunications, systems development, quality assurance, and information resources management. Document comments received from all sources were reviewed and evaluated by OIRM in the development of this final version of the GALP.

8. GOOD AUTOMATED LABORATORY PRACTICES

8.1 LABORATORY MANAGEMENT

When LIMS Raw Data (see **8.4.1**) are collected, analyzed, processed, or maintained, laboratory management shall:

8.1.1 ensure that personnel clearly understand the function(s) they are to perform on the LIMS.

8.1.2 ensure that a Quality Assurance Unit (QAU) monitors LIMS activities as described in **8.3**.

8.1.3 ensure that personnel, resources, and facilities are adequate and available as scheduled.

8.1.4 receive reports of QAU inspections of the LIMS (see **8.3.3**) and audits of LIMS Raw Data (see **8.3.5**) and ensure that corrective actions are promptly taken in response to any deficiencies.

8.1.5 approve the standard operating procedures (SOPs) setting forth the methods that assure LIMS Raw Data integrity, ensure that any deviations from SOPs and applicable GALP provisions are appropriately documented and that corrective actions are taken and documented, and approve subsequent changes to SOPs (see **8.11**).

8.1.6 assure that each applicable GALP provision is followed. With the exception of **8.1**, **8.2**, and **8.3**, laboratory management may delegate GALP implementation and compliance to one or more responsible persons.

8.2 PERSONNEL

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall ensure that all LIMS support staff and users:

8.2.1 have adequate education, training, and experience to perform assigned LIMS functions.

8.2.2 have a current summary of their training, experience, and job description, including their knowledge relevant to LIMS design and operation, maintained at the facility.

8.2.3 are of sufficient number for timely and proper operation of the LIMS.

8.3 QUALITY ASSURANCE UNIT

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall designate a Quality Assurance Unit (QAU) to monitor LIMS functions and procedures. The QAU shall:

8.3.1 be entirely separate from and independent of LIMS personnel, and shall report directly to laboratory management.

8.3.2 have immediate access to the LIMS data, SOPs, and other records pertaining to the operation and maintenance of the LIMS.

8.3.3 inspect the LIMS at intervals adequate to ensure the integrity of the LIMS Raw Data (see **8.3.5**); prepare inspection reports that include a description of the LIMS operation inspected, the dates of the inspection, the person performing the inspection, findings and problems observed, action recommended and taken to resolve existing problems, and any scheduled dates for reinspection; and report to laboratory management any problems that may affect data integrity.

8.3.4 determine that no deviations from approved SOPs were made without proper authorization (see **8.1.5**) and sufficient documentation.

8.3.5 periodically audit the LIMS Raw Data to ensure their integrity.

8.3.6 ensure that the responsibilities and procedures applicable to the QAU, the records maintained by the QAU, and the method of indexing such records are documented and are maintained.

8.4 LIMS RAW DATA

Laboratory management shall ensure that:

8.4.1 LIMS Raw Data (LRD) and LRD storage media on which they reside (see **9. DEFINITIONS** LIMS Raw Data and LIMS Raw Data storage media) are identified and documented. This documentation shall be included in the laboratory's SOPs.

8.4.2 the individual(s) responsible for entering and recording LIMS Raw Data is (are) uniquely identified when the data are recorded, and the time(s) and date(s) are documented.

8.4.3 the instrument transmitting LIMS Raw Data is uniquely identified when the data are recorded, and the time and date are documented.

8.4.4 procedures and practices to verify the accuracy of LIMS Raw Data are documented and included in the laboratory's SOPs, and managed as described in **8.11**.

8.4.5 procedures and practices for making changes to LIMS Raw Data are documented and provide evidence of change, preserve the original recorded documentation (see **8.4.2** and **8.4.3**), are dated, indicate the reason for the change, identify the person who made the change and, if different, the person who authorized the change. These procedures shall be included in the laboratory's SOPs, and managed as described in **8.11**.

8.5 SOFTWARE

When software is used to collect, analyze, process, or maintain LIMS Raw Data, laboratory management shall ensure that:

8.5.1 SOPs are established, approved, and managed as described in **8.11** for:

8.5.1.1 development methodologies that are based on the size and nature of software being developed. EPA and its agents shall comply with *EPA Information Resources Management Policy Manual, Chapter 17*.

8.5.1.2 testing and quality assurance methods to ensure that all LIMS software accurately performs its intended functions, including: acceptance criteria, tests to be used, personnel responsible for conducting the tests, documentation of test results, and test review and approval.

8.5.1.3 change control methods that include instructions for requesting, testing, approving, documenting, and implementing changes. When indicated, change control methods shall also include reporting and evaluating problems, as well as implementing corrective actions.

8.5.1.4 version control methods that document the LIMS software version currently used.

8.5.1.5 maintaining a historical file of software, software operating procedures (manuals), software changes, and software version numbers.

8.5.2 documentation is established and maintained to demonstrate the validity of software used in the LIMS:

8.5.2.1 for existing and commercially-available LIMS, minimum documentation shall include, but not be limited to: a description of the software and functional requirements; listing of all algorithms and formulas; and, as they occur, testing and quality assurance, installation and operation, maintenance/enhancement, and retirement.

8.5.2.2 for new LIMS development or modification of existing LIMS, documentation shall cover all phases of the generic software life cycle. EPA laboratories and those of its agents (contractors and grantees) shall comply with the documentation requirements specified in *EPA Information Resources Management Policy Manual*, *Chapter 17*.

8.5.3 all documentation specified in **8.5.2** is readily available in the facility where the software is used, and the SOPs specified in **8.5.1** are readily available in the laboratory areas where procedures are performed.

8.5.4 a historical file of software and the documentation specified in **8.5.2** are retained according to procedures outlined in **8.9**.

8.6 SECURITY

Laboratory management shall ensure that security practices to assure the integrity of LIMS data are adequate. EPA laboratories and those of its agents (contractors and grantees) shall comply with EPA's Information Security Policy.

8.7 HARDWARE

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall ensure that LIMS hardware and communications components are:

8.7.1 of adequate design and capacity, and a description is documented and maintained.

8.7.2 installed and operated in accordance with manufacturer's recommendations and, at installation, undergo acceptance testing that conforms to acceptance criteria. SOPs shall be established and maintained to define the acceptance criteria, testing, documentation, and approval required for changes to LIMS hardware and communications components.

8.7.3 adequately tested, inspected, and maintained. SOPs for and documentation of these routine operations shall be maintained. Documentation of non-routine maintenance shall also include a description of the problem, the corrective action, acceptance testing criteria, and the acceptance testing performed to ensure that the LIMS hardware and communications components have been adequately repaired.

8.8 COMPREHENSIVE TESTING

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall ensure that comprehensive testing of LIMS performance is conducted, at least once every 24 months or more frequently as a result of software (see **8.5.2**) or hardware (see **8.7.2**) changes or modifications. These tests shall be documented and the documentation shall be retained and available for inspection or audit.

8.9 RECORDS RETENTION

Laboratory management shall ensure that retention of LIMS Raw Data, documentation, and records pertaining to the LIMS comply with EPA contract, statute, or regulation; and SOPs for retention are documented, maintained, and managed as described in **8.11**.

8.10 FACILITIES

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall ensure that:

8.10.1 the environmental conditions of the facility housing the LIMS are regulated to protect against LIMS Raw Data loss.

8.10.2 environmentally adequate storage capability for retention of LIMS Raw Data, LIMS Raw Data storage media, documentation, and records pertaining to the LIMS are provided.

8.11 STANDARD OPERATING PROCEDURES

Laboratory management shall ensure that:

8.11.1 SOPs include, but are not limited to, those specified in **8.4.1, 8.4.4, 8.4.5, 8.5.1.1** through **8.5.1.5, 8.7.2**, **8.7.3**, and **8.9**. Each current SOP shall be readily available where the procedure is performed.

8.11.2 SOPs are periodically reviewed at a frequency adequate to ensure that they accurately describe the current procedures.

8.11.3 SOPs are authorized and changed in accordance with **8.1.5**.

8.11.4 a historical file of SOPs is maintained.

9. DEFINITIONS

The definitions below generally come from existing Federal and EPA information management publications. While broader or narrower definitions, published in other authoritative sources, could have been used, those below were selected because they are more focused on the environment of laboratory data management.

Acceptance testing Formal testing conducted to determine whether or not a system satisfies its acceptance criteria and to enable the customer to determine whether or not to accept the system. *FIPS Publication 101, June 1983*.

Assurance A measure of confidence that the security features and architecture of [a LIMS] accurately mediate and enforce the security policy. Modified from *EPA Risk Analysis Guideline (Draft) March 1992*.

Audit A qualitative and quantitative evaluation of the documentation and procedures associated with the LIMS to verify that resulting LIMS Raw Data are of acceptable quality. Modified from EPA Quality Assurance Management Staff, January 6, 1994.

Change control Management and implementation methodologies associated with increasing or correcting system capabilities, a partial system redesign, or determining software obsolescence. *EPA Operations and Maintenance Manual, April 1990*.

Commercially-available software Software that is available through lease or purchase in the commercial market. Software that is furnished as part of the [LIMS] system

but that is separately priced is included. *EPA Information Resources Management Policy Manual, Chapter 17, September 1994*.

Data A representation of facts, concepts, information, or instructions suitable for communication, interpretation, or processing by humans [or by a LIMS]. *EPA Risk Analysis Guideline (Draft) March 1992*.

Design (software life cycle) The stage that specifies the automated and manual functions and procedures, the computer programs, and data storage techniques that meet the requirements identified and the security and control techniques that assure the integrity of the system. *EPA Information Resources Management Policy Manual, Chapter 17, September 1994*.

Documentation The process of gathering written or electronic information describing, defining, specifying, reporting, or certifying activities, requirements, procedures, or results. Modified from *ASME NQA-1, Quality Assurance Program Requirements for Nuclear Facilities, 1989 edition as cited in ANSI/ASQC E4-1994*.

Facility The premises and operational unit(s) that are necessary for operating a LIMS. Modified from *Organization for Economic Cooperation and Development Series on Principles of Good Laboratory Practice and Compliance Monitoring Number 1: The OECD Principles of Good Laboratory Practice. Environment Monograph No. 45 (1992).*

Hardware Physical equipment such as the computer and its related peripheral devices, tape drives, disk drives, printers, etc. *EPA Information Resources Management Policy Manual, Chapter 17, September 1994*.

Information Any communication or reception of knowledge such as facts, data or opinions, including numerical, graphic, or narrative forms, whether oral or maintained in any medium, including computerized databases (e.g., floppy disk and hard disk), papers, microform (microfiche or microfilm), or magnetic tape. *EPA Risk Analysis Guideline (Draft) March 1992*.

Initiation (software life cycle) A request for the development of a system to meet a need for information or to solve a problem for the individual making the request. *EPA Information Resources Management Policy Manual, Chapter 17, September 1994*.

Inspect To measure, examine, test or gauge one or more characteristics of an entity and compare the results with specified requirements in order to establish whether

conformance is achieved for each characteristic. Modified from *ANSI/ASQC 34-1994 Specifications and Guidelines for Quality Systems for Environmental Data Collection and Environmental Technology Programs, January 3, 1995*.

Installation and operation (software life cycle) Incorporation and continuing use of the new system by the organization. *EPA Information Resources Management Policy Manual, Chapter 17, September 1994*.

Integrity Sound, unimpaired or perfect condition. That computer security characteristic that ensures that computer resources operate correctly and that the data in the databases are correct. This characteristic protects against deliberate or inadvertent unauthorized manipulation of the system and ensures and maintains the security of entities of a computer system under all conditions. Integrity is concerned with protecting information from corruption. *EPA Risk Analysis Guideline (Draft) March 1992*.

Laboratory Information Management System (LIMS) See **2.c APPLICABLE SYSTEMS.**

Laboratory management Those individuals directly responsible and accountable for planning, implementing, and assessing work, and for the overall operation of a facility. Modified from *ANSI/ASQC 34-1994 Specifications and Guidelines for Quality Systems for Environmental Data Collection and Environmental Technology Programs, January 1995*.

LIMS Raw Data (LRD) Original observations recorded by the LIMS that are needed to verify, calculate, or derive data that are or may be reported.

LIMS Raw Data (LRD) storage media The media to which LIMS Raw Data are first recorded.

Maintenance/enhancement (software life cycle) Resolving problems not detected during testing, improving the performance of the product and modifying the system to meet changing requirements. (Full-scale enhancements require full life cycle analysis.). *EPA Information Resources Management Policy Manual, Chapter 17, September 1994*.

Original observations The first occurrence of human-readable information.

Programming (software life cycle) Coding of the program modules that implement the design. *EPA Information Resources Management Policy Manual, Chapter 17, September 1994*.

Quality Assurance Unit Any person or organizational element designated by laboratory management to monitor the LIMS functions and procedures. Modified from *EPA GLPs, August 17, 1989*.

Records All books, papers, maps, photographs, machine-readable materials, or other documentary materials, regardless of physical form or characteristics, made or received by an agency of the United States Government under Federal law or in connection with the transaction of public business and preserved or appropriate for preservation by that agency or its legitimate successor as evidence of the organization, functions, policies, decisions, procedures, operations, or other activities of the government or because of the informational value of the data in them. Library and museum material made or acquired and preserved solely for reference or exhibition purposes, extra copies of documents preserved only for convenience of reference, and stocks of publications and of processed documents are not included. *44 U.S.C 3301*.

Requirements analysis (software life cycle) Determination of what is required to automate the function(s) identified by the organization. *EPA Information Resources Management Policy Manual, Chapter 17, September 1994*.

Retirement (software life cycle) The stage which ends use of the system. *EPA Information Resources Management Policy Manual, Chapter 17, September 1994*.

Security The set of laws, rules, and practices that regulate how an organization manages, protects, and distributes sensitive data. *EPA Risk Analysis Guideline (Draft) March 16, 1992*.

Software Computer programs, procedures, rules and associated documentation pertaining to the operation of a computer system. *EPA Information Resources Management Policy Manual, Chapter 17, September 1994*.

Software life cycle The period of time beginning when a software product is conceived and ending when the product no longer performs the function for which it was designed. The software life cycle is typically broken into phases such as initiation, requirements analysis, design, programming, testing and quality assurance, instal-

lation and operation, maintenance, and retirement. *EPA Information Resources Management Policy Manual, Chapter 17, September 1994*.

Software version control Management of changes or revisions to a specific baseline software module or application. Software version control provides a mechanism to control changes and to return to any previous revision of the application or module.

Standard Operating Procedures (SOPs) Documentation setting forth methods of operation that laboratory management is satisfied are adequate to insure the quality and integrity of LIMS Raw Data. Modified from *EPA GLPs, August 17, 1989*.

Testing The examination of the behavior of a program by executing the program on sample data sets. *EPA Information Resources Management Policy Manual, Chapter 17, September 1994*.

Testing and quality assurance (software life cycle) Ensuring that the system works as intended and that it meets applicable organization standards of performance, reliability, integrity and security. *EPA Information Resources Management Policy Manual, Chapter 17, September 1994*.

Validity A state or quality of software that provides confirmation that the particular requirements for a specific intended use are fulfilled. In design and development, validity concerns the process of examining a product or result to determine conformance to user needs. Modified from *ISO 8402:1994, Quality Management and Quality Assurance* as cited in *ANSI/ASQC E4-1994*.

Verify To review, inspect, test, check, audit, or otherwise establish and document whether or not LIMS Raw Data are accurate. Modified from *FIPS Publication101, June 1983*.

10. LIST OF ACRONYMS

CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
EPA	Environmental Protection Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FIPS	Federal Information Processing Standard
FIRMR	Federal Information Resource Management Regulation
GALP	Good Automated Laboratory Practice
GLP	Good Laboratory Practice
GSA	General Services Administration
IRM	Information Resources Management
LIMS	Laboratory Information Management System
LRD	LIMS Raw Data
NIST	National Institute of Science and Technology
OIRM	Office of Information Resources Management
OMB	Office of Management and Budget
QAU	Quality Assurance Unit
SOP	Standard Operating Procedure
TSCA	Toxic Substances Control Act

11. SOURCES

Copies of the Federal information resources management publications referenced in the GALP can be ordered via mail, telephone, or the Internet.

Computer Security Act of 1987

This is a Federal regulation and should be available in local public libraries.

The Internet World Wide Web address is:

http://www.first.org/secplcy/csa_87.txt

Office of Management and Budget (OMB) publications

Office of Management and Budget
Assistant Director of Administration
OMB Publications
725 17th Street, NW
Washington, D.C. 20503

telephone: (202) 395-7332 (then press 2)

The Internet addresses for OMB publications are:

World Wide Web: http://www2.infoseek.com/Titles?qt=OMB

Gopher: gopher://pula.financenet.gov:70/11/docs/central/omb

EPA publications

U.S. Environmental Protection Agency
OARM/FMSD
Publication Distribution Section
Mailcode 3204
401 M St., SW
Washington, D.C. 20460

telephone: (202) 260-5797

For References 1 through 5 on page 1-6 (Automated Laboratory Standards), contact:

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The Internet addresses for EPA IRM documents are:

World Wide Web:	http://www.epa.gov/docs/IRMPolicy.html
Gopher:	gopher://gopher.epa.gov:70/11/Initiatives/IRM.Policy

National Institute of Standards and Technology (NIST) and National Bureau of Standards (NBS) publications

National Technical Information Service
U.S. Department of Commerce
5285 Port Royal Road
Springfield, VA 22161
(703) 487-4650

The Internet World Wide Web address for NIST is:
http://www.ncsl.nist.gov

The Internet World Wide Web address for FIPS Publications is:
http://www.ncsl.nist.gov/fips/

Contents

Chapter 2 — Implementation Assistance

Implementation Listing

This section is divided into 11 sections which discuss each of the 41 GALP provisions, 8.1 through 8.11 (numbered with reference to Chapter 1). It is intended to provide laboratory management and personnel with additional information to assist in implementing each specific GALP. While atypical situations may require further recommendations and procedures, the explanatory comments, discussion, and special considerations are provided to laboratories to implement the GALP provisions successfully and cost-effectively.

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Chapter 2
GALP Implementation Assistance

The GALP Implementation is based on established data management principles.

1. PRINCIPLES

Control is the essential objective behind most data management principles. Effective management and operation of an automated laboratory cannot be assured unless use and design of the LIMS is consistent with principles intended to assure LIMS control. Although accuracy and reliability of data must be ensured by a control based system of management, the most effective management systems invoke the participation of those employees affected by the control process. Most importantly, the GALPs assume laboratory professionals are personally motivated to follow the principles of their professions, and that they will take every practical step to ensure the accuracy and the reliability of the data and analyses produced by their laboratory.

The GALP guidance is built on six principles.

a. ***Laboratory management must provide a method of assuring the integrity of all LIMS data.***

Communication, transfer, manipulation, and the storage/recall process all offer potential for data corruption. The demonstration of control necessitates the collection of evidence to prove that the system provides reasonable protection against data corruption.

b. ***The formulas and decision algorithms employed by the LIMS must be accurate and appropriate.***

Users cannot assume that the test or decision criteria are correct; those formulas must be inspected and verified.

c. ***A critical control element is the capability to track LIMS Raw Data entry, modification, and recording to the responsible person.***

This capability utilizes a password system or equivalent to identify the time, date, and person or persons entering, modifying, or recording data.

d. ***Consistent and appropriate change controls, capable of tracking the LIMS operations and software, are a vital element in the control process.***

All changes must follow carefully planned procedures, be properly documented, and when appropriate include acceptance testing.

e. ***Procedures must be established and documented for all users to follow. Control of even the most carefully designed and implemented LIMS will be thwarted if the user does not follow these procedures.***

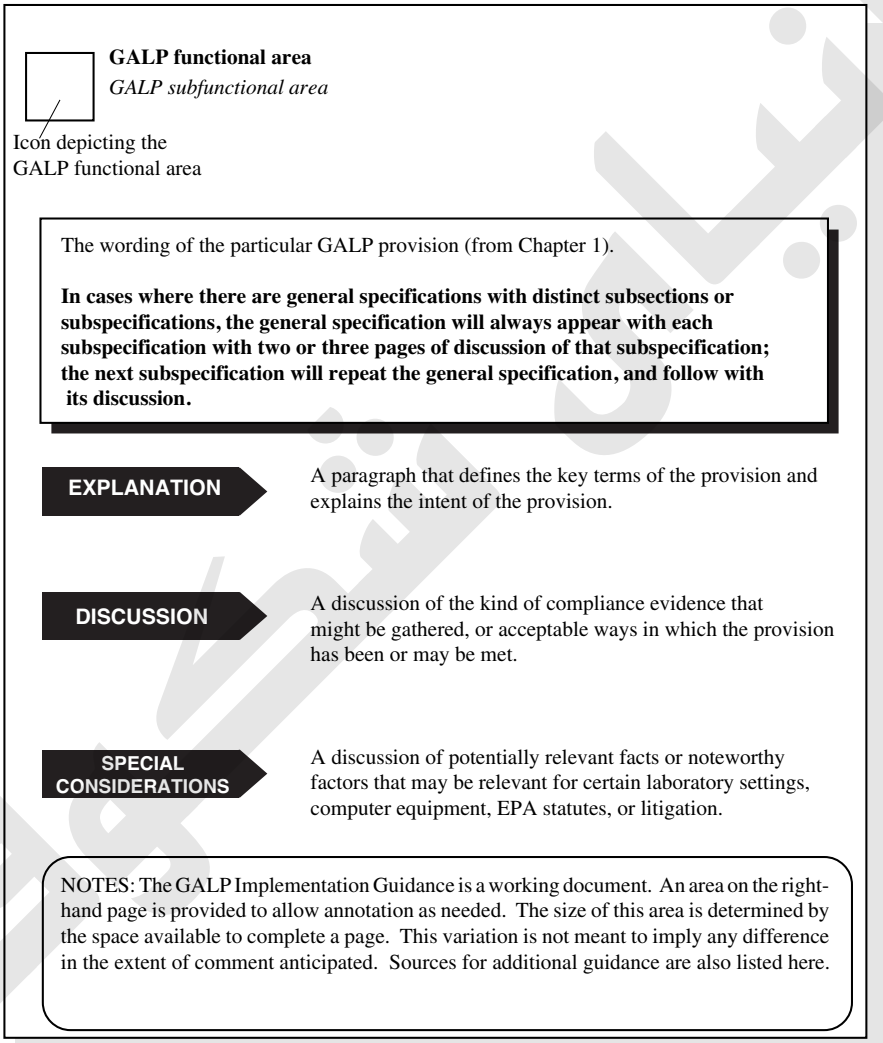
This principle implies the development of clear directions and SOPs, the training of all users, and the availability of appropriate user support documentation.

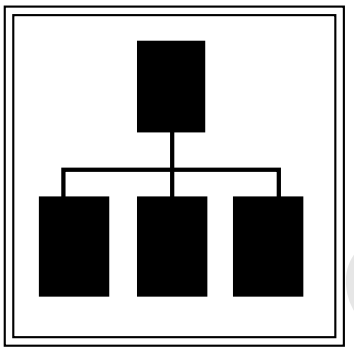
f. ***The risk of LIMS failure requires that procedures be established and documented to minimize and manage their occurrence.***

Where appropriate, redundant systems must be installed and periodic system backups must be performed at a frequency consistent with the consequences of the loss of information resulting from a failure. The principle of control must extend to planning for reasonable unusual events and system stresses.

2. IMPLEMENTATION KEY

This page is a key for using the GALP IMPLEMENTATION ASSISTANCE. The model below, with commentary notes, illustrates the format and information that follows.

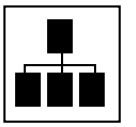




LABORATORY MANAGEMENT

8.1 Laboratory Management

1) Personnel



SPECIAL CONSIDERATIONS

Because of its significance in evaluating the applicability of the GALPs, the identification and documentation of LIMS Raw Data (LRD) should be provided to all employees involved in the operation of the LIMS. It should be sufficiently specific and unambiguous to enable employees to readily identify LRD (see 8.4.1) so that each employee knows when the GALPs must be followed.

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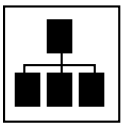


8.1 Laboratory Management

2) Quality Assurance Unit

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall:

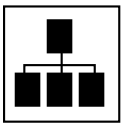
2) ensure that a Quality Assurance Unit (QAU) monitors LIMS activities as described in 8.3.

EXPLANATION

Laboratory management shall designate a group or individual as the QAU. This designation shall be consistent with the provisions set forth in 8.3. The QAU responsibilities are primarily inspection, audit, and review of the LIMS and its data.

DISCUSSION

An organizational plan should be developed to define lines of communication, reporting, inspection, and review of the LIMS and its data. The QAU must be entirely separate from and independent of the personnel engaged in the direction and conduct of a study, and should report to laboratory management. In smaller laboratories, a single individual may have many LIMS managerial responsibilities, but may not be the designated QAU.



8.1 Laboratory Management

3) Personnel, Resources, and Facilities

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall:

3) ensure that personnel, resources, and facilities are adequate and available as scheduled.

EXPLANATION

Laboratory management shall ensure that personnel, resources, and facilities are adequate to handle LIMS functions and operation *in a timely fashion*. Resources include the LIMS equipment, materials, software, and training.

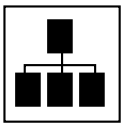
DISCUSSION

Laboratory management should ensure that backup staff for critical functions are available. In laboratories where time-critical functions are frequently encountered, laboratory management should be particularly sensitive to the need for adequate staff, backup, and other necessary resources.

Laboratory management should periodically assess the staffing levels for LIMS supervision, support, and operation, in order to determine if resources are adequate. Laboratory management may review training records to maintain awareness of the current status of training received and needed, observe job performance to determine the performance levels of current staff and possible needs for additional training, and examine project schedules and work backlogs to determine the adequacy of current staff and whether the LIMS is receiving proper staffing support.

8.1 Laboratory Management

3) Personnel, Resources, and Facilities

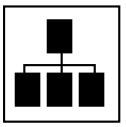


SPECIAL CONSIDERATIONS

Laboratory management is responsible for *ensuring* all resources are adequate to support LIMS functions, but may find it necessary, particularly in larger operations, to delegate responsibility for *assessing* the adequacy of personnel, resources, and facilities to another individual.

When laboratory management delegates LIMS resource assessment, he/she shall ensure that the designated person has the experience, skills, and education to fulfill the responsibilities. Laboratory management is also responsible for ensuring that the designated person is available and has sufficient time and resources to fulfill the specific responsibilities. These responsibilities must be fully documented and consistent with 8.1.6.

Notes…



8.1 Laboratory Management

4) Quality Assurance Report

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall:

4) receive reports of QAU inspections of the LIMS (see 8.3.3) and audits of LIMS Raw Data (see 8.3.5) and ensure that corrective actions are promptly taken in response to any deficiencies.

EXPLANATION

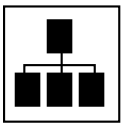
The flow of information concerning all laboratory operations, including LIMS inspections and LRD audits, should expeditiously move to laboratory management. Laboratory management should review QAU inspection reports and audits, and may recommend remedial actions. It is ultimately the responsibility of laboratory management to ensure that any errors or deficiencies, discovered through QAU activities, are acted upon and rectified.

DISCUSSION

Laboratory policy or SOP should clearly state that all QAU inspection and audit reports are presented in a timely manner to laboratory management for review. These reports should have a provision for laboratory management's signature and date. Likewise, an SOP or policy should define the responsibility of management to follow up on all deficiencies found in the QAU report.

SPECIAL CONSIDERATIONS

A relevant legal concept is that the laboratory should be able to demonstrate due diligence in *carrying out* its own rules, not just have them.



8.1 Laboratory Management

5) Approving SOPs and Documenting Deviations

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall:

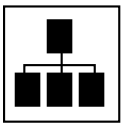
5) approve the standard operating procedures (SOPs) setting forth the methods that assure LIMS Raw Data integrity, ensure that any deviations from SOPs and applicable GALP provisions are appropriately documented and that corrective actions are taken and documented, and approve subsequent changes to SOPs (see 8.11).

EXPLANATION

Laboratory management is ultimately responsible for all activity within the laboratory, including approval of SOPs and any subsequent changes, and implementation of required GALP provisions. An SOP or laboratory policy should state that any departure from laboratory SOPs and applicable GALP provisions will be reported to laboratory management. Laboratory management should then ensure that the deviation is properly documented and that appropriate corrective actions are taken and similarly documented.

DISCUSSION

As part of a comprehensive LIMS policy, there should be documented assurance that laboratory management is made aware of deficiencies or departures from the laboratory SOPs and required GALP provisions. The SOP or policy should state that laboratory management is responsible for ensuring that all deviations are noted and corrective actions taken and documented.



8.1 Laboratory Management

6) Compliance With GALP Provisions

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall:

6) assure that each applicable GALP provision is followed. With the exception of 8.1, 8.2, and 8.3, laboratory management may delegate GALP implementation and compliance to one or more responsible persons.

EXPLANATION

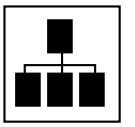
Laboratory management is responsible for complying with each GALP provision that is required by the EPA program for which data are submitted. Laboratory management, particularly in large laboratories, may find it necessary to delegate GALP compliance responsibilities to one or more responsible persons. The GALP provisions in **8.1**, **8.2**, and **8.3** may not be delegated.

When GALP compliance responsibilities are delegated, laboratory management shall ensure that the designated responsible persons have the experience, skills, and education necessary to fulfill their responsibilities. Laboratory management is also responsible for ensuring that designated responsible persons are available and provided sufficient time and resources to fulfill their responsibilities.

Laboratory management shall ensure that delegation of GALP compliance responsibilities are fully documented and current. This documentation shall identify the individual who is assigned responsibility for compliance with each GALP provision and shall clearly specify each individual's job responsibilities and duties. The documentation shall be signed by each responsible person to demonstrate that each person is aware of his/her responsibilities.

8.1 Laboratory Management

6) Compliance With GALP Provisions



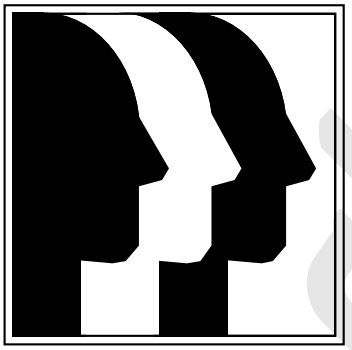
DISCUSSION

The manner by which GALP compliance responsibilities are distributed is at the discretion of laboratory management. At small laboratories, one person may be responsible for compliance with all GALP provisions. At larger laboratories, responsibilities may be distributed among a number of people. Larger laboratories might distribute responsibilities organizationally, functionally, by area of scientific study, or other methods that meet the laboratory's needs.

SPECIAL CONSIDERATIONS

It is strongly recommended that secondary responsible persons be designated. The designation of secondary responsible persons minimizes disruptions in the event of the prolonged absence of the primary responsible person.

Notes…



8.2
PERSONNEL

8.2 Personnel

1) Education

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall ensure that all LIMS support staff and users:

1) have adequate education, training, and experience to perform assigned LIMS functions.

EXPLANATION

All LIMS support staff and users shall have adequate education, training, and experience to perform assigned LIMS functions. This provision encompasses all LIMS functions used to collect, transmit, report, analyze, summarize, store, or otherwise manipulate data. Laboratory management is expected to use appropriate professional hiring and assignment criteria, coupled with appropriate training, to ensure that all users are able to use the LIMS effectively.

DISCUSSION

In certain cases, specialized training or attendance at special courses and certification programs may substitute for formal education requirements. Demonstrated experience may also substitute for formal education requirements. Either basis for substitution should be thoroughly and accurately documented. In certain cases, especially for personnel with advanced education and training, self-certification may be possible. Laboratory management should use professional judgment as to the appropriateness of self-certification.

8.2 Personnel

2) Training

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall ensure that all LIMS support staff and users:

2) have a current summary of their training, experience, and job description, including their knowledge relevant to LIMS design and operation, maintained at the facility.

EXPLANATION

This provision states that documentation of personnel backgrounds, including education, training, and experience, is current and available. Pertinent LIMS design, support, and operations knowledge for each person with access to and responsibility for the LIMS should be included in the documentation. Evidence of training and experience that indicates knowledge sufficient for job requirements is essential.

DISCUSSION

Résumés (including references to education and degrees obtained, professional certificates, previous job titles, and responsibilities), reports of completed training, and current job descriptions may be centrally filed at the facility. Job performance evaluations may be used to demonstrate proper levels of LIMS knowledge and experience. Documentation of prior success in similar responsibilities may be sufficient.

SPECIAL CONSIDERATIONS

When outside vendors are involved, the required education, training, knowledge, and experience may be so indicated on their résumés.

8.2 Personnel

3) Number of Persons

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall ensure that all LIMS support staff and users:

3) are of sufficient number for timely and proper operation of the LIMS.

EXPLANATION

Laboratory management is expected to maintain a staff that is adequate in size to ensure that functions for the LIMS will be performed in an accurate and timely manner, including all system-related tasks, and particularly time-critical functions.

DISCUSSION

By designing and following a work plan for any particular study, laboratory management can anticipate staffing requirements necessary for a particular need. Laboratory management must be aware of any delays in operations due to inadequate staffing and take proper action.

Persistent and excessive overtime, excessive LIMS downtime, or delayed responses to hardware and software changes may indicate insufficient staffing.

Information regarding the adequate competence of personnel is discussed in **8.2.1**.

8.3
QUALITY ASSURANCE UNIT

8.3 Quality Assurance Unit

1) Independent QAU

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall designate a Quality Assurance Unit (QAU) to monitor LIMS functions and procedures. The QAU shall:

1) be entirely separate from and independent of LIMS personnel, and shall report directly to laboratory management.

EXPLANATION

The QAU is responsible for assuring laboratory management of the integrity of the LRD; therefore, any real or apparent conflict of interest with LIMS personnel, including LIMS management, shall be avoided. Because laboratory management is ultimately responsible for compliance with all of the GALPs, the QAU shall necessarily report directly to laboratory management.

DISCUSSION

Documentation of the organization should be available providing clear evidence that the QAU reports directly to laboratory management. Similarly, descriptions of the positions and responsibilities of each QAU staff member should be available for review and provide evidence of their independence from LIMS personnel and management. These descriptions should also provide evidence of the role of QAU staff members in monitoring LIMS activities to assure LRD integrity. Organizational charts and job descriptions may be useful in providing this documentation.

SPECIAL CONSIDERATIONS

In LIMS operations where the number of personnel is small, there could be a real or apparent conflict of interest between the QAU and LIMS personnel and managers. In these situations, an extramural QAU may be required in the absence of alternative solutions to resolving the real or apparent conflict of interest.

8.3 Quality Assurance Unit

2) Documentation Availability

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall designate a Quality Assurance Unit (QAU) to monitor LIMS functions and procedures. The QAU shall:

2) have immediate access to the LIMS data, SOPs, and other records pertaining to the operation and maintenance of the LIMS.

EXPLANATION

A complete and current set of SOPs shall be available and accessible at all times to the QAU. The QAU should also have access to the most current and version-specific set of LIMS operations and maintenance manuals, data, and other operations and maintenance documentation.

DISCUSSION

A complete and current copy of LIMS SOPs and technical documentation should exist as part of standard documentation and be accessible to the QAU. Documentation of the procedures described above may be set forth in SOPs and/or LIMS management policy. The documentation may be in writing or electronically maintained.

SPECIAL CONSIDERATIONS

If SOPs are stored electronically, the QAU shall be responsible for verifying that they are secure, retrievable, and readable; maintaining a hard copy of the electronic versions; and ensuring that the hard copy versions are identical to the electronic versions.

8.3 Quality Assurance Unit

3) Inspections

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall designate a Quality Assurance Unit (QAU) to monitor LIMS functions and procedures. The QAU shall:

3) inspect the LIMS at intervals adequate to ensure the integrity of the LIMS Raw Data (see 8.3.5); prepare inspection reports that include a description of the LIMS operation inspected, the dates of the inspection, the person performing the inspection, findings and problems observed, action recommended and taken to resolve existing problems, and any scheduled dates for reinspection; and report to laboratory management any problems that may affect data integrity.

EXPLANATION

A LIMS that is consistently reliable and accurate is a major goal of QAU activity. To assure reliability and accuracy, the LIMS must be inspected on a regular basis. Inspection shall be performed at a frequency adequate to ensure the integrity of the LRD. The LIMS shall also be inspected immediately after any change to LIMS software or hardware.

Records of each inspection shall be prepared and maintained and shall include the following: the specific LIMS operation inspected, the name of the inspector, and the date of the inspection. Findings from the inspection and any problems observed shall be recorded. Actions recommended and those taken to resolve any problems that were found and scheduled dates for reinspection shall be documented. In all cases where problems affecting the integrity of LRD were observed during inspection, these problems shall be immediately reported to laboratory management. Documentation of reports to laboratory management should be maintained.

DISCUSSION

Although the QAU is responsible for reporting directly to laboratory management and is required to be independent of LIMS personnel, problems affecting the integrity of LRD may also be communicated directly and immediately to the appropriate LIMS personnel; thus a more rapid resolution of these problems can occur.

8.3 Quality Assurance Unit

4) Deviations

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall designate a Quality Assurance Unit (QAU) to monitor LIMS functions and procedures. The QAU shall:

4) determine that no deviations from approved SOPs were made without proper authorization (see 8.1.5) and sufficient documentation.

EXPLANATION

The QAU shall ensure that no deviations from SOPs have been made without prior authorization and complete documentation of the change. Authorization for the planned deviation entails obtaining the approval, signature, and date of laboratory management prior to its occurrence. Documentation of any deviation shall include, but not be limited to: an explanation of the departure from methods established in the SOP, the reason for the departure, and the accompanying date of the departure.

DISCUSSION

In order to maintain complete control over LIMS operations and functions, it is important to ensure that the LIMS is consistently operated in compliance with approved SOPs.

In certain situations, unplanned deviations from the SOPs may occur. These deviations must be documented and include the explanation of the departure from the methods established in the SOPs, the reason for the departure, the signature and date of laboratory management, and its affect on the LIMS data.

8.3 Quality Assurance Unit

5) LIMS Raw Data Audit

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall designate a Quality Assurance Unit (QAU) to monitor LIMS functions and procedures. The QAU shall:

5) periodically audit the LIMS Raw Data to ensure their integrity.

EXPLANATION

Periodic review of LRD that are being reported or will be reported are conducted to ensure the integrity and reliability of the LRD. By examining reported data and correlating it with the LRD for a specific LIMS reporting activity, the QAU will ensure the integrity of LRD.

DISCUSSION

An audit should be undertaken if QAU inspection problems are found that jeopardize LRD integrity. It is recommended that an SOP be established that requires periodic review of final reports and their corresponding LRD. Integrity problems or deviations arising from these audits should be reported to laboratory management as discussed in **8.3.3**.

If LIMS hardware or software are changed or relocated consistent with **8.7.2** and **8.5.2**, a review of reportable data against LRD is recommended.

SPECIAL CONSIDERATIONS

Movement of non-LIMS equipment, particularly those emitting magnetic radiation in close proximity to LIMS equipment, may affect LRD integrity. In these situations, it is strongly recommended to also review reported data against the LRD.

8.3 Quality Assurance Unit

6) Records

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall designate a Quality Assurance Unit (QAU) to monitor LIMS functions and procedures. The QAU shall:

6) ensure that the responsibilities and procedures applicable to the QAU, the records maintained by the QAU, and the method of indexing such records are documented and are maintained.

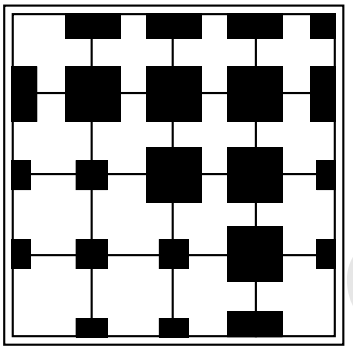
EXPLANATION

The methods and procedures of the QAU shall be fully documented, consistently followed, and maintained by the QAU. The method of indexing such records shall also be documented and maintained.

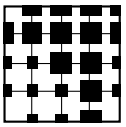
DISCUSSION

It is important that the QAU inspection and audit reports discussed in **8.3.3** and **8.3.5** are identified and maintained to include date, time, and investigator(s). The complete set of documentation, including QAU responsibilities and procedures and their inspection reports should be indexed so as to be readily accessible.

Because the QAU must maintain all records and documentation pertaining to their activities, a policy or SOP may be developed to establish specific procedures for this.



8.4
LIMS RAW DATA (LRD)



8.4 LIMS Raw Data

1) Identification and Documentation

Laboratory management shall ensure that:

1) LIMS Raw Data (LRD) and LRD storage media on which they reside (see 9. DEFINITIONS LIMS Raw Data and LIMS Raw Data storage media) are identified and documented. This documentation shall be included in the laboratory's SOPs.

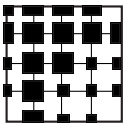
EXPLANATION

The objective of the GALPs is to provide EPA with assurance of the integrity of LIMS Raw Data (LRD). Thus the GALPs prescribe how LRD are to be entered, changed, stored, and secured. Laboratory management or designee (see **8.1.6**) shall assess data that are entered in, processed, maintained, or reported by the LIMS to identify and document those data that are LRD. The documentation shall also include a description of the LRD storage medium. LRD and their respective storage media shall be identified in the laboratory's SOPs. Copies of the SOPs shall be made available to all personnel with access to LRD, and laboratory management should assure that these personnel clearly understand the importance of LRD.

DISCUSSION

LRD are original observations recorded by the LIMS that are needed to verify, calculate, or derive data that are or may be reported. Original observations mean the first occurrence of human-readable information. The media to which the LRD are first recorded is the LRD storage media. The media may be paper, microfiche, microfilm, magnetic or optical storage media.

As an example: *Person A* places an environmental sample into a laboratory instrument that analyzes the sample and transmits signals to a personal computer (PC). The PC software captures the signals, analyzes them, and displays a graphical representation of the analyzed signals on a monitor. *Person B* examines the graphic, concludes it is realistic, and then issues a command to the PC software to record the analyzed data on a disk. The data stored on the disk are the LRD, and the disk is the LRD storage medium. The instrument, communications components, PC, PC software, monitor, recording device, and disk are a LIMS (see Figure 1.3).



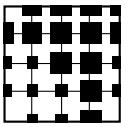
Alternatively, *Person B* could issue a command to first record the analyzed signal to paper before it is recorded to disk. In this case, the paper is the LRD storage medium.

The documentation for the above example may be an SOP or SOPs that describe data entry, analysis, and recording. For example, a single SOP could be developed and maintained that documents data entry, analysis, and recording. It would specify recording of the instrument, *Person A*, time and date, and *Person B*, time and date, on the disk, and that the LRD and LRD storage medium are those recorded by *Person B* on the disk (or paper, depending on which the LRD are first recorded).

SPECIAL CONSIDERATIONS

1. Some EPA programs may require additional data beyond those discussed in the example above. To demonstrate the reliability of instrumentation, an EPA program may also require that the initial high and low values sent from the instrument to the LIMS be included with the LRD discussed in the example.
2. Original observations that have been recorded prior to entry to the LIMS (see Figure 1.2) are not LRD (see 3. below). However, laboratory management may want to extend the definition of LRD to include these observations, thus ensuring that they are GALP-compliant.
3. For 2. above, some EPA programs require that the original observations be maintained and stored on their original recording medium. For example, the GLPs define raw data as any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a study and are necessary for the reconstruction and evaluation of the report of that study.

Notes…



8.4 LIMS Raw Data

2) Entry and Recording Person

Laboratory management shall ensure that:

2) the individual(s) responsible for entering and recording LIMS Raw Data is (are) uniquely identified when the data are recorded, and the time(s) and date(s) are documented.

EXPLANATION

Laboratory management shall ensure that LRD input is traceable to the person who manually input the LRD or who was responsible for transmission to the LIMS, and, if different, the person who was responsible for the recording of the LRD by the LIMS. The time and date for each of these actions shall also be documented.

DISCUSSION

The usual method for accomplishing this identification is to have the LIMS record a unique user identification code as part of the data being entered or recorded. The user ID code can then be referenced back to the associated data entry or data recording person to allow identification of all entered data.

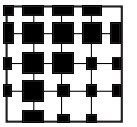
SPECIAL CONSIDERATIONS

The person who operated the instrument may not be same as the person who transmitted the data. Knowing who operated the instrument, however, may be as important as knowing who entered or recorded the data into the LIMS. Thus, the laboratory should also document the instrument operator with the data entry/recording person(s). Laboratory management should ensure that the time and date for each action above is correct and has not been altered in an unapproved manner.

In the case of manual entry, the original data generally are study raw data (see **8.4.1** Special Considerations) and can be audited; the LRD are derived data.

8.4 LIMS Raw Data

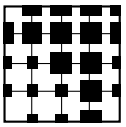
2) Entry and Recording Person



Notes…

For additional guidance, see: *Automated Laboratory Standards: Evaluation of the Use of Automated Financial System Procedures, EPA/OIRM (June 1990);* and *Automated Laboratory Standards: Evaluation of the Standards and Procedures Used in Automated Clinical Laboratories, EPA/OIRM (May 1990).*

See Chapter 1, **11. SOURCES** for addresses and ordering information.



8.4 LIMS Raw Data

3) Instrument Identification

Laboratory management shall ensure that:

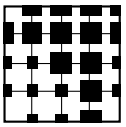
3) the instrument transmitting LIMS Raw Data is uniquely identified when the data are recorded, and the time and date are documented.

EXPLANATION

Laboratory management shall ensure that documentation for instruments that transmit data to the LIMS that are or will become LRD exists, is maintained, and includes the date and time of each transmission. It must be possible to trace to the source instrument the date and time of data transmission to the LIMS.

DISCUSSION

This can be accomplished by including a unique instrument identification code that also documents the date and time during transmission to the LIMS and records this information with the LRD.



8.4 LIMS Raw Data

4) Verification

Laboratory management shall ensure that:

4) procedures and practices to verify the accuracy of LIMS Raw Data are documented and included in the laboratory's SOPs, and managed as described in 8.11.

EXPLANATION

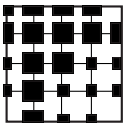
The integrity of data can be compromised during data entry, electronic transfer from automated instruments, and particularly during manual entry. Procedures for verifying the accuracy of the LRD entered manually or electronically into the LIMS shall be documented and included in the laboratory's SOPs and managed as described in **8.11**. The implementation of these procedures shall be enforced by laboratory management.

DISCUSSION

Data verification methods, such as double-keying of manually entered data, blind re-keying of data entered automatically, or other proven methods, can be practiced to provide assurance of LRD integrity.

8.4 LIMS Raw Data

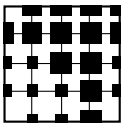
4) Verification



Notes…

For additional guidance, see: *Automated Laboratory Standards: Evaluation of the Use of Automated Financial System Procedures, EPA/OIRM (June 1990)*.

See Chapter 1, **11. Sources** for addresses and ordering information.



8.4 LIMS Raw Data

5) Changes

Laboratory management shall ensure that:

5) procedures and practices for making changes to LIMS Raw Data are documented and provide evidence of change, preserve the original recorded documentation (see 8.4.2 and 8.4.3), are dated, indicate the reason for the change, identify the person who made the change and, if different, the person who authorized the change. These procedures shall be included in the laboratory's SOPs, and managed as described in 8.11.

EXPLANATION

When LRD are changed after initial recording, documentation shall exist that preserves the original recorded required documentation (see **8.4.2** and **8.4.3**), provides clear evidence that a change was made, explains the reason for the change, records the date of change, the person who made the change and, if different, the person who authorized the change. The laboratory's SOPs shall include procedures for making changes to LRD in compliance with these recording requirements, and shall specify who has authority to make changes or to authorize changes, if different. These procedures shall be included in the laboratory's SOPs, and shall be established, approved, and managed as described in **8.11.**

DISCUSSION

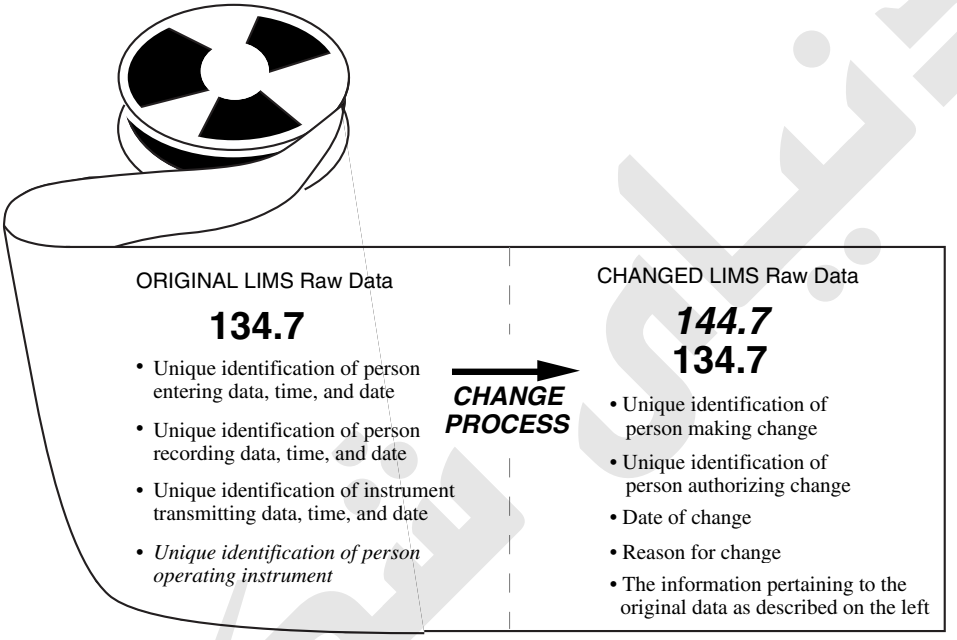
This GALP provision requires maintaining all LRD and changes to LRD so that all modifications are clearly documented. All documented changes shall be stored and retained as specified in **8.9** and **8.10.2**. If LRD are purged from the LIMS, a verified copy of the LRD should be maintained, for at least the required retention period.

SPECIAL CONSIDERATIONS

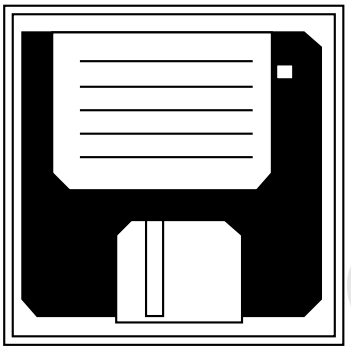
Recording both a person authorizing a change and a different person entering a change may not be feasible in an existing LIMS. To obviate this problem, laboratories may consider establishing a policy by which only one individual has authority to authorize changes and make changes to data on the LIMS. An alternative may be to retain paper copy authorizations or logs.

8.4 LIMS Raw Data

5) Changes



Notes…



8.5
SOFTWARE

8.5 Software

1) Standard Operating Procedures

1) Development Methodology

When software is used to collect, analyze, process, or maintain LIMS Raw Data, laboratory management shall ensure that:

1) SOPs are established, approved, and managed as described in 8.11 for:

1) development methodologies that are based on the size and nature of software being developed. EPA and its agents shall comply with *EPA Information Resources Management Policy Manual, Chapter 17*.

EXPLANATION

An SOP shall be prepared for LIMS software development methodology. In preparing this SOP, all GALP provisions, especially **8.4** and **8.6**, should be considered. *EPA Information Resources Management Policy Manual, Chapter 17,* serves as software development guidance for the Agency. The methodology set forth in this guide shall be used by EPA and its agents (contractors and grantees) when developing software. If an EPA office has supplemented *EPA Information Resources Management Policy Manual* with its own guidance, the laboratory must consider the applicability of this specific guidance to the software to be developed. The SOP documenting the development methodology shall be established, approved, and managed as described in **8.11**.

DISCUSSION

When selecting a LIMS software development methodology, the laboratory's goal is the reliability of LIMS Raw Data. The methodology and techniques selected should contribute to the software's accuracy and reliability in meeting user needs. In most cases, the methodology should include user involvement throughout the development cycle.

Laboratory management should consider several factors in selecting the development methodology. A large system that will be used for several years by many users is a good candidate for the full develop-

8.5 Software

1) Standard Operating Procedures

1) Development Methodology

ment methodology documented in *EPA Information Resources Management Policy Manual*. A stand-alone program, a single-user system, or a system that will be used for only a short period of time would more likely be suited to rapid application development techniques and less formally structured development methods.

Notes…

For additional guidance, see: *EPA Information Resources Management Policy Manual, Chapter 17 (September 1994)*.

See Chapter 1, **11. SOURCES** for addresses and ordering information.

8.5 Software

1) Standard Operating Procedures

2) Testing and Quality Assurance

When software is used to collect, analyze, process, or maintain LIMS Raw Data, laboratory management shall ensure that:

1) SOPs are established, approved, and managed as described in 8.11 for:

2) testing and quality assurance methods to ensure that all LIMS software accurately performs its intended functions, including: acceptance criteria, tests to be used, personnel responsible for conducting the tests, documentation of test results, and test review and approval.

EXPLANATION

SOPs shall be prepared for conducting and documenting testing and quality assurance. Testing and quality assurance involves evaluating new or changed software to determine that it performs correctly and meets user requirements. SOPs shall document when testing and quality assurance are required, as well as how they are to be conducted, the acceptance criteria, personnel responsible for testing, and documentation of test results, test review, and approval. Testing and quality assurance are specified in *EPA Information Resources Management Policy Manual, Chapter 17*. SOPs for testing and quality assurance shall be established, approved, and managed as described in **8.11**.

DISCUSSION

Testing and quality assurance procedures are standard integral parts of the change control process, that also apply to implementation of new software. Users should be involved in testing programs in an environment that will not affect the production system. New software should also be tested in a similar way by potential users. Acceptance criteria should be documented before testing begins to ensure that testing is predicated on meeting those standards, as discussed in **8.5.2.2**. SOPs may include provisions for laboratory management to review the tests and results to ascertain that criteria are appropriate and are met to their satisfaction.

8.5 Software

1) Standard Operating Procedures

2) Testing and Quality Assurance

SPECIAL CONSIDERATIONS

Testing and quality assurance procedures should be performed by individuals responsible for installation and operation of the LIMS and not by the QAU (see **8.5.2.2** Special Considerations).

Notes…

For additional guidance, see: *EPA Information Resources Management Policy Manual, Chapter 17 (September 1994).*

See Chapter 1, **11. SOURCES** for addresses and ordering information.

8.5 Software

1) Standard Operating Procedures

3) Change Control

When software is used to collect, analyze, process, or maintain LIMS Raw Data, laboratory management shall ensure that:

1) SOPs are established, approved, and managed as described in 8.11 for:

3) change control methods that include instructions for requesting, testing, approving, documenting, and implementing changes. When indicated, change control methods shall also include reporting and evaluating problems, as well as implementing corrective actions.

EXPLANATION

SOPs shall be prepared for problem reporting and change control procedures that apply to all layers of software used in the laboratory, including custom-developed and commercially-available software. The procedures should be tailored to each kind of software. SOPs for change control shall be established, approved, and managed as described in **8.11**.

Change control procedures shall specify:

- persons authorized to request software changes
- requirements to be met for approval of change requests
- responsibilities and methods for documenting testing and quality assurance
- approval procedures for changed versions
- procedures for moving changed versions to the production environment.
- forms designed for change request/problem reports
- methods for establishing the priority of change requests
- LIMS archives from which to take copies of programs to be amended (see **8.5.4**)
- procedures for maintaining amended copies that conform with SOPs

8.5 Software

1) Standard Operating Procedures

3) Change Control

DISCUSSION

Change control procedures should also be tailored to handle changes of different priorities. For example, procedures for dealing with emergency problems should expedite corrective action. The laboratory should consider a centralized change control system (manual or automated) that includes all change requests, including emergency problems, corrections to software errors, and enhancement requests. A centralized change control system may allow better tracking and control than separate systems. The change control procedure should designate a person authorized to move changed program versions to the production environment.

Problem report forms with written instructions for completion may be developed, and problem logs may be maintained by a designated person. Analysis and initial reporting may be required within a specific time frame and may be performed by the responsible person until resolution is reached.

Notes…

For additional guidance, see: *EPA Information Resources Management Policy Manual, Chapter 17 (September 1994).*

See Chapter 1, **11. SOURCES** for addresses and ordering information.

8.5 Software

1) Standard Operating Procedures

4) Version Control

When software is used to collect, analyze, process, or maintain LIMS Raw Data, laboratory management shall ensure that:

1) SOPs are established, approved, and managed as described in 8.11 for:

4) version control methods that document the LIMS software version currently used.

EXPLANATION

SOPs shall be prepared to document the process that establishes and maintains the identification of the LIMS software version in use at the time each data set was created. SOPs for version control shall be established, approved, and managed as described in **8.11**.

DISCUSSION

This process can be met by ensuring that the date and time of generation of all data sets are documented, and that the LIMS software version generating the data set is identified in the data file. The laboratory shall ensure that historical files (see **8.5.4**) are established and maintained to indicate the current version and all previous versions of the software releases and individual programs, including dates and times they were put into and removed from the LIMS production environment.

8.5 Software

1) Standard Operating Procedures

5) Historical File

When software is used to collect, analyze, process, or maintain LIMS Raw Data, laboratory management shall ensure that:

1) SOPs are established, approved, and managed as described in 8.11 for:

5) maintaining a historical file of software, software operating procedures (manuals), software changes, and software version numbers.

EXPLANATION

SOPs shall be prepared to document the procedures by which historical files are maintained. These files shall include, but not be limited to, all software versions (see **8.5.1.4**) and software operating procedures for each version. Consistent procedures for management of historical files shall be documented to assure that these files are current, complete, and easily accessible. SOPs for maintaining a historical file of software shall be established, approved, and managed as described in **8.11**.

DISCUSSION

The ability to verify the accuracy of LRD and reportable data necessitates that all software versions, all software changes, and all operating instructions are available, maintained, complete, and current. To assure this, an SOP should specify methods for storage and retention times that comply with **8.9**. The SOP should specify that all historical files be maintained in a designated location that is safe and secure, and that adequately preserves the software for the required retention period.

8.5 Software

2) Documentation

1) Existing and Commercially-Available Systems

When software is used to collect, analyze, process, or maintain LIMS Raw Data, laboratory management shall ensure that:

2) documentation is established and maintained to demonstrate the validity of software used in the LIMS:

1) for existing and commercially-available LIMS, minimum documentation shall include, but not be limited to: a description of the software and functional requirements; listing of all algorithms and formulas; and, as they occur, testing and quality assurance, installation and operation, maintenance/enhancement, and retirement.

EXPLANATION

To demonstrate the validity of software used, LIMS software documentation should include, within practical limits, all phases of the software life cycle (see **8.5.2.2**). For existing and commercially-available LIMS software, the minimum documentation shall include:

A. LIMS software description and functional requirements

B. algorithms and formulas

C. testing and quality assurance procedures

D. installation and operation, maintenance/enhancement, and retirement procedures

DISCUSSION

For commercially-available software and LIMS software in use prior to publication of the GALPs, the documentation of additional life cycle phases is governed by the magnitude of the programming effort involved in creating the software. Large, complex applications that require lengthy and expensive software development efforts necessitate an equivalent level of effort in the creation of detailed documentation that describes the application throughout each software life cycle phase. A small, less detailed program written by one programmer in a short period of time (such as a

8.5 Software
2) Documentation
1) Existing and Commercially-Available Systems

week), requires less documentation that may involve only a paragraph describing each phase of the software life cycle.

For existing or commercially-available LIMS software, documentation may be difficult to obtain. However, LIMS software descriptions and functional requirements can be developed. User requirements that lead to the purchase of a commercially-available LIMS can be used to develop the functional requirements documentation.

Software vendors may provide some LIMS software design documentation, but for proprietary reasons, it may not be complete. File layouts, program descriptions, and functional specifications may be provided, but program specifications and source code may be unavailable. If the minimum documentation described above is not provided, an attempt to obtain it from the vendor should be made; however, it may be necessary to reconstruct it in-house.

A. LIMS Software Description and Functional Requirements

A description shall be documented and maintained for the LIMS software that provides detailed information on the functions the software performs. Depending on the nature or internal structure of the software, the documentation for the functional requirements may include: flowcharts or block diagrams that illustrate step-by-step processing of a software module, data flow diagrams that illustrate the movement of data through the LIMS, or entity-relationship diagrams that illustrate the relationship of the data within the database.

B. Algorithms and Formulas

All algorithms and formulas used in the LIMS, and modules that allow user entry of formulas or algorithms, shall be documented and retained. Documentation of the algorithms and formulas should be

8.5 Software

2) Documentation

1) Existing and Commercially-Available Systems, continued

easily discernible. These listings should identify the locations in which the formulas and algorithms occur in the LIMS software.

Documentation for all such formulas and algorithms can be maintained in a central location. In some cases, formulas and algorithms for purchased software may be obtained from vendor-provided documentation. For software currently in use, it may be possible to extract the formulas and algorithms from source code.

C. Testing and Quality Assurance

Documentation shall be established and maintained to support testing and quality assurance. The documentation should describe procedures that ensure the LIMS works as intended and that it meets organizational standards for performance, reliability, integrity, and availability. Testing documentation should include evidence of integration and validation testing. Test specifications and results (unit tests, system tests, integration tests) should be documented and maintained.

D. Installation and Operation, Maintenance/Enhancement, and Retirement Procedures

Documentation shall be established and maintained to support the initial and continuing operations of the LIMS software. The documentation includes implementation plans and procedures, methods for regulating and controlling software changes (see **8.5.1.3**), routine support requirements, and post-implementation reviews. Retirement plans and procedures identify a means of retrieving LIMS data after the LIMS is replaced or is no longer operational.

8.5 Software

2) Documentation

2) New Systems

When software is used to collect, analyze, process, or maintain LIMS Raw Data, laboratory management shall ensure that:

2) documentation is established and maintained to demonstrate the validity of software used in the LIMS:

2) for new LIMS development or modification of existing LIMS, documentation shall cover all phases of the generic software life cycle. EPA laboratories and those of its agents (contractors and grantees) shall comply with the documentation requirements specified in *EPA Information Resources Management Policy Manual, Chapter 17*.

EXPLANATION

The goal of LIMS software documentation efforts shall be to demonstrate the validity of the software used. The documentation shall accurately describe the software's functions and internal structures as they exist, or will exist, during each of the software life cycle phases. The terms used to describe each software life cycle phase have varied over time and have been published using different "standard" terminology However, the general structure and progression of the software life cycle has remained the same for many years.

For new LIMS software (under development, or to be developed) used in EPA-sponsored studies, laboratories shall establish and maintain life cycle documentation that conforms to the specifications of *EPA Information Resources Management Policy Manual, Chapter 17*. The extent of the documentation shall be consistent with the software application's size, cost, sensitivity of data, policy implications, and diversity of organizations using the LIMS. New LIMS software documentation should generally include the following, which are intended to cover all phases of the software life cycle:

- initiation
- requirements analysis
- design
- programming
- testing and quality assurance
- installation and operation
- maintenance/enhancement
- retirement

8.5 Software

2) Documentation

2) New Systems

DISCUSSION

SOPs may be established and maintained to ensure that each phase of the software life cycle is documented. Laboratory management review of milestones ensures that required documentation is available before giving approval for LIMS software development to proceed.

Documentation standards for initiation and requirements analysis can be established. The initiation documentation can include a request for LIMS development or enhancement, and the needs that are resolved. The requirements analysis documentation identifies the functions that the LIMS will perform.

Design and programming standards ensure that minimum requirements are met and foster consistency and uniformity in the software. File layout formats, screen formats, and report formats can be included in the design standards. Explanatory comments, section and function labels, the programming language, identification of the programmer, dates of original writing and all changes, the use of logical variable names, and other programming documentation requirements are established by the programming standards.

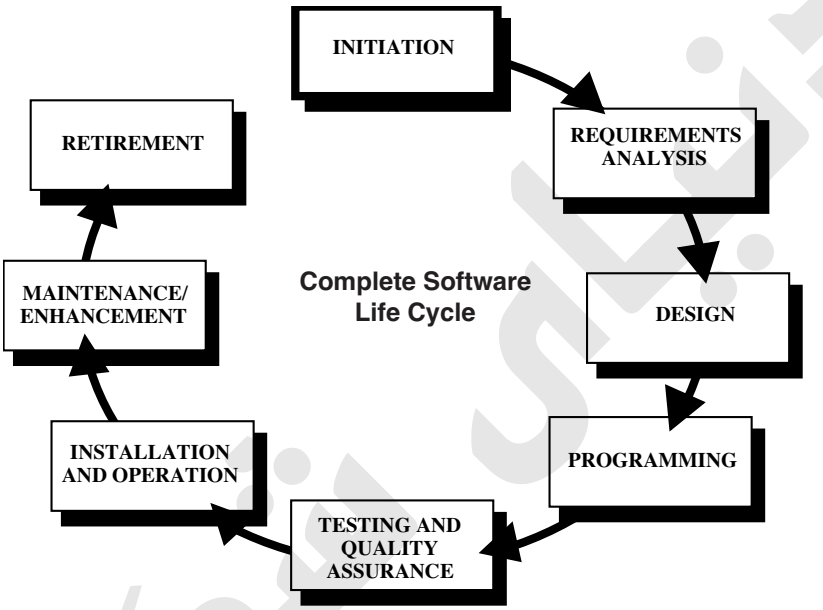
Testing and quality assurance standards ensure that the LIMS performs as it was intended. Testing and quality assurance include both unit and integration testing. It assures that the LIMS meets standards for performance, reliability, integrity, and security.

Installation and operation standards assure a smooth transition from existing laboratory operations to the LIMS. Maintenance/enhancement standards improve the continuing operation of the LIMS. The maintenance/enhancement procedures identify change control procedures for resolving problems not discovered during testing, improving LIMS performance, and modifying the LIMS to meet changing needs or new requirements. The retirement standards identify procedures for ending use of the LIMS due to obsolescence or replacement. The retirement procedures identify a means of retrieving historical LIMS data.

8.5 Software

2) Documentation

2) New Systems, continued



SPECIAL CONSIDERATIONS

Testing and quality assurance must be performed on LIMS software to ensure that it functions as intended and meets applicable standards. Software testing and quality assurance procedures should be performed by individuals responsible for installation and operation of the LIMS and not by the QAU, because the QAU must be entirely separate from and independent of LIMS personnel (see **8.3.1**). However, the QAU may monitor and review quality assurance procedures throughout the software life cycle.

8.5 Software

2) Documentation

2) New Systems, continued

Notes…

For additional guidance, see: *EPA Information Resources Management Policy Manual, Chapter 17 (September 1994).*

See Chapter 1, **11. SOURCES** for addresses and ordering information.

8.5 Software

3) Availability of Documentation

When software is used to collect, analyze, process, or maintain LIMS Raw Data, laboratory management shall ensure that:

3) all documentation specified in 8.5.2 is readily available in the facility where the software is used, and the SOPs specified in 8.5.1 are readily available in the laboratory areas where procedures are performed.

EXPLANATION

All documentation and SOPs, or copies thereof, shall be available in the work areas of LIMS developers, operators, and/or users, as applicable. SOPs shall be available to each department or work group within a laboratory, and importantly, shall be current.

DISCUSSION

Original SOPs and documents should be maintained centrally to prevent their loss or misplacement. Persons responsible for producing SOPs or documentation manuals may maintain a record of SOPs or documentation issued, their numbers, and identification of persons to whom they were issued, thus facilitating ease in issuing updates. User manuals should be readily available to all users. It is particularly important that SOPs and documentation pertinent to development methodologies, testing and quality assurance, change control, version control, and historical files be immediately available where the work is performed.

8.5 Software

4) Historical File

When software is used to collect, analyze, process, or maintain LIMS Raw Data, laboratory management shall ensure that:

4) a historical file of software and the documentation specified in 8.5.2 are retained according to procedures outlined in 8.9.

EXPLANATION

Previously used software, LIMS manuals, user maintenance manuals, and other documents specified in **8.5.2** shall be retained in compliance with **8.9.** If the retention time is not specified, the period should be sufficient to allow the laboratory to support any challenges to the integrity of the LRD.

Files of all versions of software programs shall be created and maintained so that the history of each program is evident. Differences between the versions and the time of their use shall be evident.

DISCUSSION

The laboratory should ensure that historical files indicate all previous versions of software releases and individual programs, including the dates they were placed into and removed from production. Software program listings can include internal references to a project number. For each data set, the historical file should identify the version of software used in creating each set of LRD.

8.5 Software
4) Historical File

Notes…

For additional guidance, see: *EPA Operations and Maintenance Manual (April 1990)*.

See Chapter 1, **11. SOURCES** for addresses and ordering information.

8.6
SECURITY

8.6 Security

Laboratory management shall ensure that security practices to assure the integrity of LIMS data are adequate. EPA laboratories and those of its agents (contractors and grantees) shall comply with EPA's Information Security Policy.

EXPLANATION

Requirements for protecting LIMS data from destruction, disclosure, alteration, delay or undesired manipulation can vary greatly according to laboratory needs and requirements. Laboratory management is responsible for ensuring that threats to the LIMS and its data have been assessed, compensating safeguards implemented, and, where required, other established security requirements implemented.

EPA's Information Security Policy (described in *EPA Information Resource Management Policy Manual*, *Chapter 8*) formally establishes a comprehensive, Agencywide information security program. This policy implements OMB Circular A-130 and describes individual and organizational responsibilities for EPA staff and its agents. A procedural manual, *EPA Information Security Manual*, explains how to comply with this policy and with the congressionally-mandated Computer Security Act of 1987. The following Discussion summarizes the detailed information contained in these documents.

DISCUSSION

Security of LIMS is often an afterthought that LIMS staff and users frequently minimize as an unnecessary imposition, or view as preventing free information exchange, rather than as safeguards for the destructive effects of malicious hackers, LIMS failures or natural disasters. Congress emphasized the importance of security by enacting the Computer Security Act of 1987. Experienced LIMS staff and users are becoming acutely aware of the need for safe-

8.6 Security

guards to protect against undesired and frequently unforeseen events. These events, whether accidental or deliberate, can result in:

- modification or destruction of data,
- unavailability of data or services, or
- the unwanted disclosure of data.

These three general damaging results have shaped the three traditional objectives (see **I. Security Objectives** below) of computer security:

- integrity,
- availability, and
- confidentiality.

They commonly form the basis for all security decisions or initiatives.

Undesired events, commonly referred to as threats (see **III. Threats**), should be identified for all the assets constituting the LIMS. These assets (see **II. Assets**) can include people, hardware, software, physical environment, and others. Reaching a decision about what, if anything, should be done for each identified threat/asset involves two distinct phases:

- risk analysis (see **IV. Risk Analysis**), identifying and estimating the damage of each threat/asset risk; and,
- risk management (see **V. Risk Management**), identifying, selecting, and implementing safeguards to protect against the threat, reduce its impact, or facilitate recovery from its occurrence.

There are some minimum safeguards (see **VI. Minimum Safeguards**) that common sense dictates be implemented to ensure physical protection of LIMS hardware, software, data, and storage media. The cost involved with implementing these safeguards may be very small, if not zero, and thus do not require a formal security risk analysis to justify their implementation.

8.6 Security, *continued*

I. Security Objectives

The **integrity objective** provides owners and users of laboratory data with assurance that their data are reliable and accurate. Achieving this objective necessitates implementation of safeguards for threats to the integrity of data and the applications that process the data. Examples of safeguards for software that provide assurance of integrity include implementing data verification procedures for manual data entry as specified in **8.4.4**, implementing data change requirements described in **8.4.5**, and password-protecting access to LIMS software (see **VI. Minimum Safeguards**).

The **availability objective** provides protection against the loss of information or services. Serious problems can result from loss of LIMS data because they can be costly to replace. Similarly, if the LIMS cannot be used or cannot provide timely services, the production or reporting of LIMS data can be lost or impaired. Examples of safeguards to provide assurance of the availability of LIMS data include implementing a regular schedule for backups, placing storage media in a secured place, and use of an Uninterruptible Power Supply device to provide virtually complete surge protection, a filter for line noise, and backup power in the event of an outage (see **VI. Minimum Safeguards**).

The **confidentiality objective** addresses those situations where disclosure of data would be undesirable or, in some situations unlawful, such as Confidential Business Information (CBI) (see Notes at end of Discussion for references). Confidentiality ensures the protection of private information from being disclosed to anyone who is not authorized to access it. Examples of safeguards to provide assurance of confidentiality include physical access controls, encryption when transmitting data, and disposal practices for reports when they are no longer needed (see **VI. Minimum Safeguards**).

8.6 Security, *continued*

II. Assets

An asset has value and may be tangible or intangible. An organization should identify all assets that must be protected. Some assets have minimal value and do not require protection. A partial list of potential assets includes the following:

Tangibles	Intangibles
Facilities	Personnel
Hardware	Reputation
Software (system and application)	Motivation
Supplies	Morale
Documentation	Goodwill
Data	Opportunity

Traditionally, tangible assets were viewed as only hardware and were the major concern of security. Placing a value on these assets may be relatively easy because in most cases they are purchased items.

However, tangible assets also include software, data, and documentation. It can be difficult to place a value on data and documentation because these assets are usually derived from expenditures of a variety of laboratory resources. LIMS data are obtained from sources such as observations, analytical instruments, and laboratory equipment. If data are the result of an analytical experiment or sample analysis, value can be derived from examining the resources used during the process that produced them.

Another consideration in determining the value of LIMS data is the capability of reproducing the data itself. Data that cannot be reproduced may have a significantly higher value than data that are easily reproduced. In a similar manner, the value of the documentation for the LIMS and its applications must be determined.

The value of intangible assets is somewhat subjective. However, intangible assets must be identified and considered when performing a security risk analysis.

8.6 Security, *continued*

III. Threats

Once LIMS assets are determined, it is necessary to identify **threats**, **potential threats**, and **future threats** to the assets. By identifying these threats, possible vulnerabilities to integrity, confidentiality, and availability can be identified and addressed. Threats may exist in many forms; they can be the result of natural disasters, intentional or accidental action, or malicious or inadvertent destruction.

Natural disasters and environmental hazards are significant threats primarily to LIMS tangible assets. Potential natural disaster can include floods, tornadoes, or hurricanes. Environmental hazards include fires, water damage (from bursting water pipes), and power failures. These disasters can damage or completely destroy the facility, operating environment, documentation, hardware, software, and LIMS data. Disruption can occur to communication, operations, or applications.

Other significant threats can result from unrestricted access to the LIMS assets. Safeguards are most often needed that limit access to the facility, equipment, hardware, software, documentation, and data. Threats must be assessed for every potential avenue of access. LIMS data are especially vulnerable because they are subject to accidental modification or destruction as well as malicious acts of theft or data sabotage. Accidental data corruption can result from faulty procedures or from failures of system software security. Training of personnel and development and compliance with comprehensive SOPs can eliminate much accidental data corruption or loss.

The threat of computer fraud, frequently motivated by greed and malice, should be considered. The greater the LIMS data value the greater the potential for intentional threats. LIMS data should be reviewed to determine if there is value or liability from an intruder in penetrating the LIMS, disclosing its data, or disrupting operations. Similarly, the LIMS data should also be evaluated to determine the impact of decision making and reporting based on incorrect or corrupted data. In addition to physical controls, the development of and compliance with comprehensive SOPs provides safeguards against theft or sabotage.

8.6 Security, *continued*

IV. Risk Analysis

Risk analysis is a process for estimating potential losses that may result from LIMS vulnerabilities and quantifying the damage that may result if adverse events occur. The ultimate goal of risk analysis is to select safeguards that reduce risks to an acceptable level. Risk analysis is a means of determining the resources needed—in budgetary terms of programming, equipment and people— to minimize the loss of LIMS data integrity, availability, or confidentiality. The extent of the risk analysis depends on the complexity of the LIMS system, its uses, the characteristics of its users, and the value of the LIMS data.

EPA Information Security Manual describes methods for performing risk analyses for different types of LIMS assets.

Step 1	Identification of assets and determination of threats;
Step 2	Identification of existing safeguards;
Step 3	Determining the overall risk to the system based on threats identified and effectiveness of existing safeguards;
Step 4	Evaluation and selection of safeguards; and
Step 5	Preparing a summary of findings and recommendations.

This risk analysis can then be used as the basis for establishing a cost-effective risk management program.

8.6 Security, *continued*

V. Risk Management

Risk management ensures that adequate steps are taken to prevent or mediate situations that can interfere with accomplishing the laboratory's mission. Risk management includes establishing security safeguards and plans for contingencies (disaster recovery plans). A necessary part of risk management is to assure implementation of the safeguards and contingency plans. An important first step is to provide proper training of personnel (security awareness training) to ensure that all employees understand their security roles.

Risk management involves establishing safeguards to improve protection of information and information processing resources and to adequately protect the LIMS data from loss, misuse, unauthorized access or modification, unavailability, or undetected activities. Safeguards may include restricted user interfaces to LIMS system and application software and LIMS data, user verification, isolation of critical LIMS application software, and reviewing and testing the LIMS design. Including safeguards from the start of LIMS development or LIMS procurement effort is the most cost-effective way to optimize integrity, availability, and confidentiality of LIMS data. Risk analysis information, described above, should be used in the design phase of LIMS development to effect the greatest reduction in the annual loss expectancy at the least total cost. This information can also guide laboratory management in developing procedures to meet the LIMS security objectives of integrity, availability, and confidentiality. To maintain LIMS security, audits of security practices assist laboratory management in monitoring security needs and in maintaining reliable compliance with established safeguards.

Another aspect of risk management involves the development of contingency plans (or disaster recovery plans) for LIMS operations in the event of a failure or emergency from a number of potential sources such as natural disasters or equipment malfunction. Laboratory management should develop workable procedures that ensure the continuance of essential functions in the event that LIMS functions are interrupted. The primary objective of contingency planning is to protect against unacceptable data loss. It is also important to provide protection for source documents, input and output data, and application software. It may also

8.6 Security, *continued*

V. Risk Management

be necessary to anticipate the need for alternate hardware and equipment. Contingency plans should include procedures for remote storage of backup data and recovery of data from backup data files. Contingency planning should be coordinated with other hardware safeguards, backup procedures, and recovery plans.

Security awareness training is an important first step in implementing any risk management plan. All employees involved in the management, use, design, development, maintenance, or operation of the LIMS should be aware of their security responsibilities. Laboratory management should select and implement appropriate security awareness techniques such as training, lectures and seminars, posters, and orientation booklets. Incentives for adherence by staff to security procedures may include assigning employee responsibility for security, publicity of security breaches, and rewards for employees who prevent breaches.

Specific requirements for security and disaster recovery plans are found in *EPA Information Security Manual* and *EPA Operations and Maintenance Manual*.

8.6 Security, *continued*

VI. Minimum Safeguards by Asset: Stand-alone, Networked, and Data Center Computing

Meeting the objectives of data integrity, availability, and confidentiality necessitates that certain minimum safeguards be implemented for the LIMS. Minimum safeguards are those common sense measures which may be implemented without performing a risk analysis. These safeguards ensure the physical and environmental protection of LIMS equipment and media, and the effective management of the LIMS.

The cost involved in implementing these safeguards should be minimal. If the LIMS contains sensitive information, OMB Bulletin No. 90-08, *Guidance for Preparation of Security Plans for Federal Computer Systems that Contain Sensitive Information*, (July 9, 1990) applies. (Data are considered sensitive if they meet the criteria established in Federal statutes (see Notes at end of Discussion) and/or are defined as sensitive through risk analysis. Sensitive data also is defined by legal agreement protecting information such as site location or source information.)

This section describes minimum safeguards by LIMS asset, arranged into three categories:

A. Stand-alone Computing
B. Networked Computing
C. Data Center Computing

"Stand-alone computing" is defined as those LIMS that have no physical or logical connection to any other computer system. A logical connection is an active network connection; it is a connection to another computer. A physical connection is a communication connection (wire or optic cable) to another computer or network. Generally, stand-alone computers are those personal computers or workstations that have no connection whatsoever (physical) to a network or to another computer. However, a computer could be considered a stand-alone system if it is physically connected to a network or another computer, but does not

8.6 Security, *continued*

VI. Minimum Safeguards by Asset:
Stand-alone, Networked, and Data Center Computing

have the ability to transmit to or receive data from the network or system. Examples include:

- a computer with no physical connection to another computer
- a computer with a physical connection, but the installed networking software is disabled or is inactive

"Networked computing" is defined as those LIMS that have an active logical connection to a network or to another computer system. In practice, most networked computers are personal computers, workstations, or minicomputers that have active connections to a local area network (LAN) or wide area network (WAN). Many of these systems are increasingly participating in client/server relationships that share the workload over several computers. The majority of these computer systems are usually physically located on or near an employee's work space.

"Data center computing" is defined as those LIMS that are physically located within the confines of a special facility dedicated to computing. Data center computers are almost always large minicomputers and mainframes with specialized peripherals such as external disk arrays, tape drives, and telecommunications interfaces. Certain security issues, mostly those involving special physical and environmental safeguards, apply to data center computers.

Some LIMS computing environments do not fall neatly into one of these categories. For example, most data center computers have active connections to a network. With the rapidly evolving sophistication of networking software, it is conceivable that a stand-alone computer can have small networking modules activated that permit trivial, but highly secure, networking operations to take place. When the system's computing configuration or environment appears to overlap a category, the more stringent safeguard should be applied.

8.6 Security, *continued*

VI. Minimum Safeguards by Asset: Stand-alone, Networked, and Data Center Computing

A. Stand-alone Computing

1. Meeting the Objectives of Data Integrity, Availability, and Confidentiality

Stand-alone LIMS are sometimes considered the least susceptible to the viruses and hacking that have become a threat to networked systems. However, the data integrity and availability of stand-alone systems can be easily compromised if the physical and environmental safeguards specified below are not followed. Data integrity and availability are improved by adherence safeguards for the storage and use of magnetic media and backups. Assurance of integrity can also be improved by carefully avoiding situations that may subject the stand-alone system to viruses borne by removable media such as diskettes. Software copyrights and licensing are a factor that may affect data availability. Data confidentiality can be compromised if stand-alone systems are easily accessible to unauthorized personnel. Data confidentiality of stand-alone systems is best improved by defining, training for, and adhering to, individual safeguard responsibilities.

2. Security Responsibility and Training

At least one person, or functional group, should be assigned the overall responsibility for maintaining stand-alone LIMS security. The responsible person or group should have the authority and opportunity to contribute to policy decisions regarding the security topics discussed within this section (physical and environmental, magnetic media safeguards, backups, etc.). All LIMS users should be provided with security awareness training.

3. Physical and Environmental Safeguards

Position stand-alone LIMS equipment in rooms with locking doors whenever possible, and lock the doors when the room is not in use. Otherwise,

8.6 Security, *continued*

VI. Minimum Safeguards by Asset:
Stand-alone, Networked, and Data Center Computing

locate equipment away from easily accessible areas and install a locking device (pad or hardened cables) to the extent possible. Use a standard keyed system cabinet lock. Place equipment and peripherals on stable and secure platforms away from objects that could fall on them.

Store all portable LIMS in a locked cabinet when not in use. Ensure that at least one individual within the organization is responsible for tracking the location of portables on a regular basis, and institute logging procedures that include the release and return dates for authorized users.

Install surge protection devices to protect against electrical power surges. Do not install the electronic equipment, especially personal computers, in direct sunlight or in a location with extremes of hot and cold temperatures (less than 50 degrees Fahrenheit or greater than 100 degrees Fahrenheit). Do not leave a portable in a parked car, which would also subject it to temperature extremes.

Do not eat, drink, or smoke in the immediate vicinity of LIMS equipment and media. Install, as far as practical, away from overhead water pipes or sprinkler heads. Install and use humidifiers when the ambient air is extremely dry.

4. Magnetic Media Safeguards

Keep all magnetic media in a secure area away from electrical devices and, especially, magnets. Magnets can be found in magnetic paper clip holders, building passes and credit cards with magnetized strips, PC hard drive units, speakers, and telephones. Do not flex diskettes, touch their surfaces, or write on them directly with a pencil or hard-tipped pen. Store them in disk file containers as soon as they are removed from equipment. Store cartridge tapes and removable disk cartridges in their original containers. Backup all files on a fixed disk at regular intervals.

8.6 Security, *continued*

VI. Minimum Safeguards by Asset: Stand-alone, Networked, and Data Center Computing

5. Backups

Routine backup procedures should be established to ensure availability of the LIMS data. Stand-alone personal computers are often the least likely to be backed up. While a precise set of criteria for determining how often to make these backups cannot be provided, frequency of modifications to data files, cumulative development time, and the relative importance of the data are key factors to consider. Many organizations perform backups at least once a week.

The appropriate backup media can vary and may include diskettes, cartridge tapes, removable disk cartridges, or remote hosts such as minicomputers.

In all cases, the resultant backup media should be tested at a frequency adequate to ensure that backup procedures are working correctly. More than one person within an organization should have the knowledge required to perform backups to avoid backup schedule interruptions due to personal leave or termination.

6. Software Copyrights and Licenses

Commercial software is frequently subject to copyright laws and accompanied by a licensing agreement that specifies copying regulations. A copyright generally means that any duplicating, selling, or other distribution of the software for other than backup use by the lawful user(s) is unlawful. Many of these copyrighted software packages may affect data availability. Some software applications cease to function upon expiration of the license; previous data access provided by the software may be lost. Licenses are usually available for single systems or for entire sites. LIMS management should be vigilant to eliminate unlicensed software and maintain current licenses for stand-alone personal computers. Supervisory personnel should educate LIMS users on the importance of adhering to copyright law.

8.6 Security, *continued*

VI. Minimum Safeguards by Asset: Stand-alone, Networked, and Data Center Computing

Registering all copies of commercial software with the vendor can result in significant cost savings in free user assistance, reduced price software upgrades, or free replacement if the software is lost, stolen, or damaged.

7. Viruses

A computer virus is an extra program hidden within an apparently normal program or software package. The normal program or software is referred to as the virus "host" or "Trojan Horse." Some viruses are relatively harmless and only flash a message on the monitor before destroying themselves. Others are truly malicious and modify or destroy programs and data. One means to avoid viruses on stand-alone LIMS is to purchase only commercially-produced software (although commercial software is not immune to viruses, either), and to run a virus scanning program on every diskette before reading the diskette or copying files from it. To combat viruses, a number of specialized programs or software "vaccines" have been developed. Some are available at low cost, or through the operating system vendor. New software should also be tested for viruses on stand-alone computers. A relevant publication, NIST Special Publication 500-166, *Computer Viruses and Related Threats: A Management Guide* (August 1989), should be consulted.

B. Networked Computing

1. Meeting the Objectives of Data Integrity, Availability, and Confidentiality

Networked computing is highly vulnerable to security threats, because of its use by large numbers of individuals throughout an organization or, in the case of the Internet, the world. Due to their predominance on WANs such as the Internet, workstations, minicomputers, and even mainframes historically were the prime targets of viruses and hackers. The lack of security and

8.6 Security, *continued*

VI. Minimum Safeguards by Asset: Stand-alone, Networked, and Data Center Computing

auditing software available for personal computer operating systems makes these systems singularly ill-equipped to deal with sophisticated threats that can exist on local or wide-area networks.

Networked LIMS computing is subject to the same physical and environmental threats as stand-alone or data center LIMS computing. Data integrity, availability, and confidentiality of networked systems may be compromised if the physical and environmental safeguards specified below are not followed. Data integrity, availability, and confidentiality can be improved by adherence to safeguards regarding the treatment of magnetic media, backups, and by implementing safeguards to protect against viruses borne by a local or wide-area network.

Networked computing should implement the minimum operating system and application safeguards described below. Networked personal computers, workstations, file servers, print servers, database servers, and minicomputers that operate outside the confines of a data center should adhere to the minimum safeguards described in **A. Stand-alone Computing**. Networked data center computers should adhere to the operating system and application safeguards (below) in addition to the safeguards described in **C. Data Center Computing.**

2. Operating System and Application Security Safeguards

Minimum application security safeguards are implemented largely according to the sensitivity of data stored within a LIMS system. The presence of sensitive data on a LIMS necessitates more stringent measures than those described below. For LIMS that process sensitive data on a multi-user system, laboratory management should research the cited references (see Notes at end of Discussion) for details regarding application security safeguards for sensitive data. Safeguards can be applied to the operating

8.6 Security, *continued*

VI. Minimum Safeguards by Asset:
Stand-alone, Networked, and Data Center Computing

system, commercial and internally developed software programs running on the multi-user system, and data stored on the system.

Minimum operating system safeguards on a networked LIMS include:

- implementation of individual username and password management programs
- file access safeguards maintained by the data or file owner
- assignment of operating system privileges only to systems management personnel
- monitoring of system events such as logon failures or break-in attempts
- emergency, backup, disaster recovery, and contingency plans
- application-specific safeguards

Usernames should be assigned and maintained by the individual or group responsible for maintaining the LIMS. Usernames should be provided only to individuals, whenever possible. If group IDs are necessary, they should be assigned limited privileges and revoked as soon as feasible.

Password maintenance is ultimately the responsibility of the individual LIMS user, but basic syntax rules are necessary, especially where the LIMS is susceptible to password cracking schemes used by hackers through dial-up modems, LANs, or WANs. Passwords should be:

1) a minimum of six characters in length,
2) consist of numerals and alphabetic characters,
3) changed at least once every 90 days, and
4) should avoid common names, words found in a dictionary, or repetitive character sequences.

File access safeguards should be implemented to restrict the use of LIMS data to only users with authorized access. Group or public file access should

8.6 Security, *continued*

VI. Minimum Safeguards by Asset: Stand-alone, Networked, and Data Center Computing

be discouraged. Assigning write or delete privileges to increasing numbers of LIMS users effectively cancels several safeguards because of the increased opportunity to modify the LIMS data.

Operating system privileges should be assigned very sparingly, and only to those individuals working directly with the operating systems. Assigning system privileges to the general user population causes a wide array of security problems.

Whenever possible, a system for monitoring events such as logon failures or break-in attempts should be implemented. After three failed logon attempts, the account should be automatically disabled. Event logs should be reviewed on a frequent, and regular, basis. Most minicomputer and mainframe operating systems provide system event logging at no extra cost.

System and data backups (see **C.4 Data Center Backups**) are the keystone of emergency, backup, disaster recovery, and contingency plans. A well thought-out and tested plan is a significant safeguard against unforeseen natural or man-made disasters. The plan includes notification procedures, recovery operations, LIMS interim processing, and restoration planning.

Application-specific safeguards include the use of application-specific usernames and passwords. The commercial database market includes numerous database products that provide additional internal security safeguards, including application-specific usernames and passwords. Most of these also have complex security protection schemes that grant and revoke database privileges, read/write access, and group protections. In many ways, these application protections are as sophisticated as their operating system counterparts, and should be used to augment operating system safeguards.

8.6 Security, *continued*

VI. Minimum Safeguards by Asset: Stand-alone, Networked, and Data Center Computing

C. Data Center Computing

1. Meeting the Objectives of Data Integrity, Availability, and Confidentiality

Because data centers usually involve large, centralized LIMS, such as mainframe computers, that also participate in local and wide area networks, the security measures that apply to networked LIMS should apply to data center computers. Security training of all data center computer users is essential for maintaining data integrity, availability, and confidentiality. Security awareness is important because enormous amounts of potentially sensitive information are concentrated in one area and, frequently, among a small number of large computer systems. Data availability can be compromised by failure to adhere to physical and environmental safeguards. Data integrity and availability are improved by backup and change control practices.

2. Security Responsibility and Training

At least one person, or functional group, should be assigned the overall responsibility for maintaining LIMS security. A responsible person (see **8.1.6**) or group should have the authority and opportunity to contribute to policy decisions regarding the security topics discussed within this section (physical and environmental, safeguards, backups, etc.). All LIMS data center users should be provided with security awareness training. Because most data centers include a complex local area network, and involve interactive logons, users should be provided with training in password maintenance and file protections.

8.6 Security, *continued*

VI. Minimum Safeguards by Asset: Stand-alone, Networked, and Data Center Computing

3. Physical and Environmental Safeguards

LIMS data center management should strive to locate the data center away from the ground floor, frequently traveled or easily accessible areas, and potential sources of explosions (e.g., boiler rooms, hot water heaters). When choosing a site, take advantage of existing physical security. Limit the number of doors and entrances to those needed for safe and efficient operations. Install and use locks on all windows and doors.

When possible, locate master power switches near emergency exits. The switch should cut off all power to the LIMS and, if possible, should also turn off the air conditioning system if it is not designed to filter out smoke.

Use fire extinguishers designed to avoid damage to computer equipment, and mount them in visible, accessible areas. Install smoke and heat detectors. Avoid installing the computer room underneath water pipes or steam pipes. If this is not possible, use water sensors to detect water seepage. If practical, store waterproof plastic in a visible, accessible location so that it can be draped over equipment in an emergency.

Prohibit eating, drinking, and smoking in the computer room. To reduce dust, avoid coat racks, throw rugs, venetian blinds, and other furnishings that collect dust and static electricity. Vacuum carpeted areas frequently. Control static electrical charges by using anti-static carpeting or sprays. To reduce fire hazards, never store flammable materials in the computer room. Keep on-site paper supplies to a minimum.

4. Backups

A precise set of criteria for determining how often to make backups cannot be provided. Frequency of modifications to data files, cumulative development time, and mission criticality of on-line data are key factors to consider.

8.6 Security, *continued*

VI. Minimum Safeguards by Asset:
Stand-alone, Networked, and Data Center Computing

Backups are a key element in disaster recovery plans, and should occur on a regular and published schedule. The resultant backup media and recovery procedures should be tested frequently to ensure that backup procedures are working correctly. The appropriate backup media can vary and can include diskettes, cartridge tapes, removable disk cartridges, or remote hosts such as minicomputers. LAN server backups should occur on a regular and published schedule. More than one person within an organization should have the knowledge required to perform backups to avoid backup schedule interruptions due to personal leave or termination.

5. Change Control

Threats to integrity, availability, and confidentiality are introduced through unauthorized change to hardware or software. To help achieve effective change control, laboratory management shall maintain accurate records of hardware and software inventories, configurations, and locations (see **8.5.4** and **8.7.2**); and shall comply with the terms of software licensing agreements. Prescribe a standardized, formalized method of introducing changes to both software and hardware (see **8.5.1.3** and **8.7.2**). To ensure data availability, prepare a contingency plan, or other procedure to revert to a previous version of the software, in the event that the change does not work as intended.

SPECIAL CONSIDERATIONS

EPA Information Security Manual is currently being revised and is in internal review.

8.6 Security, *continued*

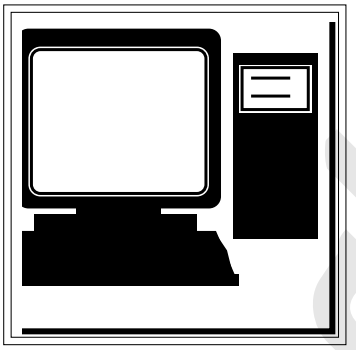
Notes…

Federal statues that set the criteria for sensitive data include *Computer Security Act of 1987, OMB Circular A-130, OMB Bulletin No. 90-08, "Guidance for Preparation of Security Plans for Federal Computer Systems that Contain Sensitive Information" (July 9, 1990)*, *EPA Information Security Manual (December 1989)*, and *EPA Operations and Maintenance Manual (April 1990)*.

For additional information on computer viruses, see: *NIST Special Publication 500-166, Computer Viruses and Related Threats: A Management Guide (August 1989)*.

For more information on security, see NIST computer security standards and guidance, "Computer Security Clearinghouse," at this Internet World Wide Web address: http://csrc.ncsl.nist.gov/

See Chapter 1, **11. SOURCES** for addresses and ordering information.



8.7
HARDWARE

8.7 Hardware

1) Design

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall ensure that LIMS hardware and communications components are:

1) of adequate design and capacity, and a description is documented and maintained.

EXPLANATION

LIMS hardware and communications components shall be configured to meet user performance requirements. The LIMS shall be designed to ensure LRD integrity, availability, and confidentiality (see **8.6**). Storage capacity and response times must meet user needs. A system configuration description shall be documented and maintained, and include descriptions of all hardware and communication components. Documentation describing the LIMS hardware, including installation specifications, functions, and usage, should be current and available to laboratory personnel responsible for use and maintenance.

DISCUSSION

Proper performance of the LIMS hardware and communications components is often dependent on the capacity of the system and the appropriate configuration of the components. Periodic review of LIMS design may be valuable in assessing the need for modifications to improve productivity, reduce risk of malfunction, and improve LRD integrity, availability, and confidentiality (see **8.6** Discussion).

Maintaining a current description of the LIMS hardware and communications components assists maintenance personnel in tracking problems with the equipment and in repair and replacement, and assists LIMS personnel in assessing current functionality and future needs.

8.7 Hardware

2) Installation and Operation

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall ensure that LIMS hardware and communications components are:

2) installed and operated in accordance with manufacturer's recommendations and, at installation, undergo acceptance testing that conforms to acceptance criteria. SOPs shall be established and maintained to define the acceptance criteria, testing, documentation, and approval required for changes to LIMS hardware and communications components.

EXPLANATION

Installation shall be according to manufacturer's specifications, unless otherwise documented, and shall be tested in conformance with documented acceptance test criteria before the hardware and/or communications components are determined to be acceptable for use in the LIMS. The installation site should be planned to facilitate use and maintenance of the hardware and communications components.

The laboratory shall develop SOPs for acceptance criteria, testing, documentation, and final approval of LIMS hardware and communications components installation and changes. The SOPs shall be readily available to all personnel with responsibility for modification or changes to LIMS hardware and communications components.

The SOPs shall require that changes are described and documented. The documentation shall include testing and quality assurance criteria and test results, the authorization approval needed prior to implementation of changes or modifications, and dates of each activity.

DISCUSSION

Evaluating user performance requirements is the first step in LIMS hardware modification or enhancement. New user requirements should be periodically reviewed by laboratory management.

8.7 Hardware

2) Installation and Operation

Vendor documentation can be obtained for guidance with installation and initial acceptance testing. Diagnostics provided with equipment and normally indicated in the documentation can demonstrate performance in accordance with specifications. However, additional testing beyond vendor components specifications may be necessary to adequately demonstrate proper functioning of changes to LIMS hardware and communications components prior to their actual usage on the LIMS.

Laboratory management should not risk using inadequately tested equipment to receive, store, or manipulate LRD. Laboratory management should review all testing results and documentation before approving hardware and communications components and returning them to production.

Notes…

8.7 Hardware

3) Maintenance

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall ensure that LIMS hardware and communications components are:

3) adequately tested, inspected, and maintained. SOPs for and documentation of these routine operations shall be maintained. Documentation of non-routine maintenance shall also include a description of the problem, the corrective action, acceptance testing criteria, and the acceptance testing performed to ensure that the LIMS hardware and communications components have been adequately repaired.

EXPLANATION

Periodic maintenance of LIMS hardware and communications components shall be performed and include testing and inspecting. The purpose of these routine maintenance operations is to ensure the integrity of LRD. The frequency of these routine maintenance operations shall be described in the SOPs and shall comply with manufacturer's specifications. SOPs shall be developed to describe the operations and the documentation required.

Documentation of the regularly scheduled LIMS hardware and communications components maintenance operations shall be maintained and include: descriptions of operations performed, the names of persons who conducted them, dates operations were performed, and the results.

All repair of malfunctioning or inoperable LIMS hardware and communications components shall be documented and include: a description of the problem, correction action taken, acceptance testing criteria, and the testing performed to ensure proper performance prior to returning the LIMS hardware and communications components to production.

DISCUSSION

Only personnel with training and experience in testing, inspecting, and maintenance should be authorized to perform these functions. A program of testing, inspecting, and routine maintenance opera-

8.7 Hardware
3) Maintenance

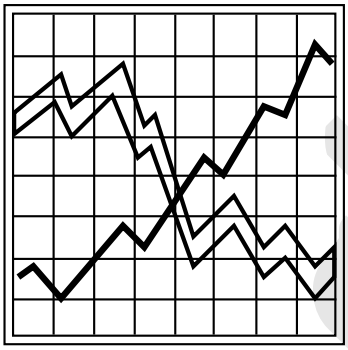
tions should be instituted and designed to assure continued proper operation of the LIMS. The maintenance program and procedures should be determined by the vulnerability of the LIMS.

All maintenance specified in the SOPs, whether performed by in-house personnel or outside contractors, should be included in the documentation. The operations maintenance documentation should be kept with the hardware and communications components for ready access.

SPECIAL CONSIDERATIONS

A "repair log" may be used to document non-routine maintenance performed on the LIMS. It should be easily accessible to the LIMS personnel responsible for updating the log and to the personnel using the LIMS hardware and communications components. This documentation should be retained for as long as needed to support evidence of LRD integrity, or longer if required by other regulations (see **8.9**), and should be reviewed on a regular basis by LIMS management. When repairs are performed by the manufacturer's service representative or other outside personnel, a written report is usually provided. This report can be helpful to document the problem and should be retained. Centralized responsibility for contacting outside service support and maintaining the documentation of service calls may prove beneficial to organization and record keeping. For in-house service, forms may be established to document the required information for the repair log.

Notes…



8.8 COMPREHENSIVE TESTING

8.8 Comprehensive Testing

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall ensure that comprehensive testing of LIMS performance is conducted, at least once every 24 months or more frequently as a result of software (see 8.5.2) or hardware (see 8.7.2) changes or modifications. These tests shall be documented and the documentation shall be retained and available for inspection or audit.

EXPLANATION

In order to ensure ongoing LIMS reliability, performance, and accuracy, comprehensive testing of the LIMS shall be conducted at least once every 24 months.

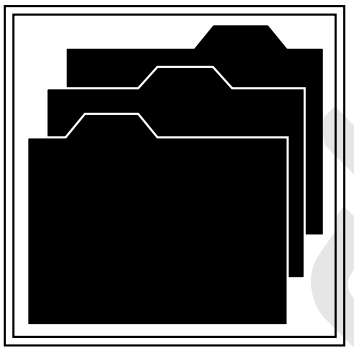
This testing should also include a complete document review (SOPs; change, security, and training documentation; error logs; problem reports; disaster plans, etc.). Laboratories that change LIMS software or hardware within the 24-month interval shall conduct acceptance testing as required by **8.5.2** and **8.7.2**.

DISCUSSION

A comprehensive testing team can be assembled that may include LIMS users, support personnel, and laboratory management, so that the interests and skills of these individuals can be addressed in the testing process. A test data set can be developed that significantly exercises all important functions of the system. This test data set can then be retained and re-used for future system tests. It may have to be enhanced if new functionality is added to the system. System test protocols and test objectives can be developed and re-used. A checklist can be developed to ensure that all important areas of testing and document review are addressed.

SPECIAL CONSIDERATIONS

Consultation with QAU personnel during comprehensive testing may be advantageous. However, QAU's independence from LIMS staff must be maintained (see **8.3.1**).



8.9
RECORDS RETENTION

8.9 Records Retention

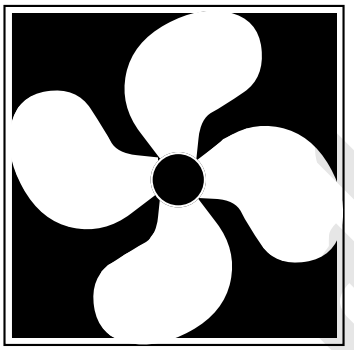
Laboratory management shall ensure that retention of LIMS Raw Data, documentation, and records pertaining to the LIMS comply with EPA contract, statute, or regulation; and SOPs for retention are documented, maintained, and managed as described in 8.11.

EXPLANATION

Laboratory management shall ensure that LRD and all LIMS-related data or documentation are retained by the laboratory for the period specified in the EPA contract, regulation, or statute, and that SOPs for retention are documented, maintained, and managed as described in **8.11**.

DISCUSSION

Contract clauses or EPA statutes pertinent to record retention periods can be copied and forwarded to a person designated to manage records retention, who can monitor compliance and disposal or destruction, as appropriate, when retention periods have expired. This individual can be responsible for determining retention periods for any records lacking such information, can ensure that the storage media used is adequate to meet retention requirements, and can institute procedures to copy data stored on magnetic media whose retention capabilities do not meet requirements (see also **8.10.2**).



8.10
FACILITIES

8.10 Facilities

1) Environment

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall ensure that:

1) the environmental conditions of the facility housing the LIMS are regulated to protect against LIMS Raw Data loss.

EXPLANATION

The LIMS shall be housed in an environment that allows it to operate correctly. Control systems should be applied to all environmental factors that might affect LRD loss or integrity. At a minimum, LIMS hardware should be installed in accordance with the environmental standards specified by the manufacturer. Control systems (see **8.6 Minimum Safeguards** Discussion) should ensure:

- proper temperature and humidity
- freedom from dust and debris
- adequate power supply and grounding
- protection from power surges and spikes
- fire detection and suppression
- water detection and suppression
- protection from natural disasters

DISCUSSION

The provisions to regulate environmental conditions are discussed in greater detail in **8.6 Minimum Safeguards by Asset**. The provisions are summarized here to emphasize their importance.

Climate control systems

LIMS hardware should be installed according to manufacturer's climate specifications. Heating, ventilation, and air conditioning dedicated to the computer room or other location where hardware is installed should be considered. Monitoring or control devices for temperature and humidity are usually installed. Backup climate control systems may be worthwhile if time is critical.

8.10 Facilities

1) Environment

Power provision

Power supplies should comply with the computer hardware manufacturer specifications. It may be appropriate to install backup power supply systems where electrical outage would cause critical loss or where electrical outage frequently occurs.

Fire and water control systems

Detection and suppression devices for fire and water should be considered. A sprinkler system may be suitable for some facilities, but a CO_2 system may be suitable for others.

Protection against natural disasters

The facility should be designed and protected according to geographic conditions. Where earthquakes are likely, housing should be examined for potential destruction of the LIMS and its data. Where tornadoes are likely, consideration should be given to locating computer equipment on lower levels of the facility. Where flooding is likely, consideration should be given to locating computer equipment on upper levels of the facility.

Operating procedures

Routing procedures for checking and maintaining detection and suppression devices will ensure that devices are in working order. Additional procedures may be established that describe how to operate the LIMS during emergency situations (for example, powering down).

Notes…

8.10 Facilities

2) LIMS Raw Data Storage

When LIMS Raw Data are collected, analyzed, processed, or maintained, laboratory management shall ensure that:

2) environmentally adequate storage capability for retention of LIMS Raw Data, LIMS Raw Data storage media, documentation, and records pertaining to the LIMS are provided.

EXPLANATION

Environmentally satisfactory and adequate storage space shall be available for LRD, LRD storage media, and documentation and records (which may be retained in hard copy format or on magnetic or optical media).

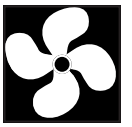
DISCUSSION

Operations personnel should maintain an adequate supply of required tapes, magnetic disks, and/or optical disks and ensure that storage space is sufficient to meet current and anticipated needs. Storage facilities for retention of LRD in hard copy or electronic format must be available and environmentally satisfactory for the LRD storage media. At a minimum, the storage facility should have a heating, ventilation, and air conditioning system to control temperature and humidity that will meet the storage condition specifications of the specific media.

Offsite storage is recommended for backups. Backups can be cycled through the offsite location. For example, the most recent backup may be kept on the premises while the previous backup is kept offsite. This procedure retains the most recent version onsite for convenience while securing another version offsite for use in the event of disaster. Offsite storage facilities must have the same environmental control and security systems required of onsite storage facilities. In addition, fire and water control systems and protection against natural disasters should be considered as discussed in **8.10.1**.

8.10 Facilities

2) LIMS Raw Data Storage



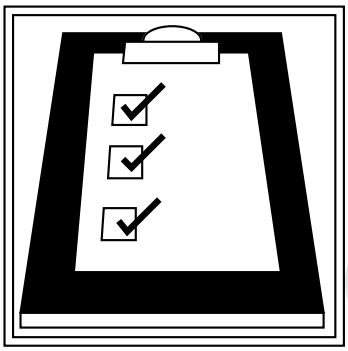
SPECIAL CONSIDERATIONS

National Bureau of Standards Special Publication 500-101, *Care and Handling of Computer Magnetic Storage Media* provides guidelines for appropriate protective measures and factors for evaluating exposure for the storage of electronic information. This publication provides guidelines for performing automated data processing risk analysis, which includes the condition of the storage facility.

Notes…

For additional guidance, see: U.S. Department of Commerce National Bureau of Standards (NBS) Special Publication 500-101, *Care and Handling of Computer Magnetic Storage Media,* June 1983.

See Chapter 1, **11. Sources** for addresses and ordering information.



8.11 STANDARD OPERATING PROCEDURES

8.11 Standard Operating Procedures

1) Availability

Laboratory management shall ensure that:

1) SOPs include, but are not limited to, those specified in 8.4.1, 8.4.4, 8.4.5, 8.5.1.1 through 8.5.1.5, 8.7.2, 8.7.3, and 8.9. Each current SOP shall be readily available where the procedure is performed.

EXPLANATION

SOPS shall be established and maintained for, but not limited to:

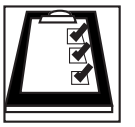
- LIMS Raw Data and LIMS Raw Data storage media identification and documentation (**8.4.1**)
- LRD verification (**8.4.4**)
- LRD changes (**8.4.5**)
- Software development methodologies (**8.5.1.1**)
- Software testing and quality assurance (**8.5.1.2**)
- Software change control (**8.5.1.3**)
- Software version control (**8.5.1.4**)
- Software historical file (**8.5.1.5**)
- Hardware changes (**8.7.2**)
- Hardware testing, inspection, and maintenance (**8.7.3**)
- Records retention (**8.9**)

Each current SOP or copy shall be placed in a location that allows LIMS staff who are responsible for performing the procedure easy and immediate access to it.

This proximity of the SOP to the LIMS personnel provides assurance that the approved procedures are accessible. When changes to an SOP are approved, the new version of the SOP shall be provided to the LIMS staff responsible for following the procedure. The

8.11 Standard Operating Procedures

1) Availability



previous version shall be removed from the work area and retired according to **8.11.4**. If multiple staff perform the same procedure in different locations, copies of SOPs shall be available in each location. When LIMS staff changes occur, the replacement staff shall be provided with the SOPs.

DISCUSSION

If multiple copies of SOPs exist, then maintaining the originals in a secure location is recommended (see also **8.11.4**). Laboratory management should ensure that all copies of SOPs are kept current and that copies of retired versions of SOPs are removed from circulation.

Notes…

8.11 Standard Operating Procedures

2) Periodic Review

Laboratory management shall ensure that:

2) SOPs are periodically reviewed at a frequency adequate to ensure that they accurately describe the current procedures.

EXPLANATION

It is laboratory management's responsibility to establish and ensure that current SOPs accurately document current LIMS activities. Laboratory management shall ensure that SOPs are reviewed at a frequency adequate to assure the integrity of LIMS Raw Data.

DISCUSSION

The adequacy of SOPs is laboratory management's responsibility; therefore, direct and frequent communication with LIMS staff is implied. The QAU can assist laboratory management in assuring that the SOPs are current by reporting any differences between an SOP and the corresponding LIMS activity. Inspections, and SOP review can be used by the QAU for this purpose (see **8.3.3** and **8.3.4**).

SPECIAL CONSIDERATIONS

Changes in critical LIMS support staff or major LIMS hardware and software changes are important milestones for the QAU or laboratory management to review the accuracy of SOPs with respect to LIMS activities.

8.11 Standard Operating Procedures

3) Authorization and Change

Laboratory management shall ensure that:

3) SOPs are authorized and changed in accordance with 8.1.5.

EXPLANATION

SOPs set forth and document the methods that assure laboratory management of the integrity of LIMS Raw Data. Thus, laboratory management shall authorize each SOP and any subsequent changes to the SOP. The previous version or copy of the SOP shall be retained according to **8.11.4**.

DISCUSSION

Authorization of SOPs and all changes to SOPs by laboratory management ensures that procedures are consistent with all laboratory policies and requirements. It allows management to exercise control of the activities of the laboratory operations. This also communicates to the LIMS staff the importance of compliance with the approved SOPs. See **8.1.5** for further discussion.

8.11 Standard Operating Procedures

4) Historical File

Laboratory management shall ensure that:

4) a historical file of SOPs is maintained.

EXPLANATION

All versions of SOPs, including retired SOPs, shall be maintained in historical files. The effective dates of each SOP shall be indicated. Retired SOPs shall be retained in accordance with **8.9**.

DISCUSSION

A centralized historical file or files of SOPs may be an advantage because of the assurance that the file is properly maintained and effectively managed. However, larger LIMS operations may appropriately maintain separate historical files of SOPs critical to LIMS Raw Data integrity. Depending on the LIMS operations, multiple historical files may be preferable over a single file for all SOPs.

SPECIAL CONSIDERATIONS

Historical files of SOPs may be stored on magnetic media. However, storage conditions must be consistent with **8.10.2** so that the SOPs remain available over time.

SOURCES

Copies of the Federal information resources management publications referenced in the GALP can be ordered via mail, telephone, or the Internet.

Computer Security Act of 1987

This is a Federal regulation and should be available in local public libraries.

The Internet World Wide Web address is:

http://www.first.org/secplcy/csa_87.txt

Office of Management and Budget (OMB) publications

Office of Management and Budget
Assistant Director of Administration
OMB Publications
725 17th Street, NW
Washington, D.C. 20503

telephone: (202) 395-7332 (then press 2)

The Internet addresses for OMB publications are:

World Wide Web: http://www2.infoseek.com/Titles?qt=OMB

Gopher: gopher://pula.financenet.gov:70/11/docs/central/omb

SOURCES

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Copies of the Federal information resources management publications referenced in the GALP can be ordered via mail, telephone, or the Internet.

EPA publications

U.S. Environmental Protection Agency
OARM/FMSD
Publication Distribution Section
Mailcode 3204
401 M St., SW
Washington, D.C. 20460

telephone: (202) 260-5797

For OIRM Automated Laboratory Standards publications, contact:

Rick Johnson	Voice:	(919) 541-1132
EPA (MD-34)	Fax:	(919) 541-1383
RTP, NC 27711	Internet:	johnson.rick@epamail.epa.gov

The Internet addresses for EPA IRM documents are:

World Wide Web:	http://www.epa.gov/docs/IRMPolicy.html
Gopher:	gopher://gopher.epa.gov:70/11/Initiatives/IRM.Policy

National Institute of Standards and Technology (NIST) and National Bureau of Standards (NBS) publications

National Technical Information Service
U.S. Department of Commerce
5285 Port Royal Road
Springfield, VA 22161
(703) 487-4650

The Internet World Wide Web address for NIST is:
http://www.ncsl.nist.gov

The Internet World Wide Web address for FIPS Publications is:
http://www.ncsl.nist.gov/fips/

7

Laboratory Equipment Qualification

by Joseph A. Manalo, John C. Brown, and Kenneth W. Sigvardson
DuPont Pharmaceuticals Company

With contributions by Boyd Montigney, Fred E. Burris, and Christopher M. Riley

OVERVIEW

A model for qualifying laboratory equipment that addresses general considerations with proposed solutions is given. This model is applicable for all types of laboratory equipment. The solutions do not address data integrity and computer validation issues but are in harmony with current computer-system validation practices. All of the established elements of laboratory equipment qualification, which include design qualification (DQ), installation qualification (IQ), operation qualification (OQ), and performance qualification (PQ), are discussed, although the emphasis is on IQ and OQ. Also, calibrations were separated from OQ in order to provide a model that is more harmonized with process equipment qualification. The relationship between regulatory requirements, equipment specifications, and test acceptance criteria is also demonstrated. This gives a clear understanding of how equipment qualification can be directly used to meet FDA requirements and expectations.

KEY WORDS

- Design qualification (DQ)
- Installation qualification (IQ)
- Operational qualification (OQ)
- Performance qualification (PQ)
- Calibration

INTRODUCTION

Regulations regarding the qualification of laboratory equipment generally have been vague. For example, language such as "appropriate design and adequate capacity,"[1] "adequately tested, calibrated and/or standardized,"[1] and "routinely calibrated, inspected, or checked according to a written program designed to assure proper performance"[2] is used in good laboratory practice (GLP) regulations. Medical device regulations state, "Each manufacturer shall ensure that all inspection, measuring, and test equipment, including mechanical, automated, or electronic inspection and test equipment, is suitable for its intended purposes and is capable of producing valid results."[3] Documentation of appropriate design and adequate capacity has formed the nucleus of installation qualification (IQ). Documentation that equipment is adequately tested, calibrated, and/or standardized has become calibration and operational qualification (OQ). Regulatory guidance for implementing the qualification tests required within IQ, OQ and calibration has also been subject to broad interpretation.

The concept of validation originated in the manufacturing area in order to demonstrate that manufacturing processes were maintained in a state of control. The goal was to demonstrate that consistent product could be produced. In 1987, regulatory guidance was given directly by the FDA.[4] This document has guidance on qualifying manufacturing equipment. After that time, expectations have been expanded to include qualifying the equipment used to make decisions regarding the "safety, identity, strength, quality, or purity of the drug substance."[5] More recent publications by the Parenteral Drug Association (PDA) have focused on computerized equipment in order to guide industry in managing this complex aspect of validation.[6,7] These have dealt heavily with computerized data integrity issues and lightly with the equipment qualification issues. Some general guidance on qualifying laboratory equipment has recently been published,[8,9] but are influenced strongly by equipment manufacturers' service and equipment capabilities. Other publications have dealt primarily with qualification of chromatographic systems[10,11] but did not adequately address other types of laboratory equipment.

This chapter discusses an approach for handling any laboratory device that is used to generate valid data. Today, many laboratory devices are controlled by computers. These devices necessarily require computer validation when data acquisition is involved. The mechanical components of a computerized laboratory equipment system can usually be qualified during the validation of the computerized analytical data generation processes. However, the equipment qualification and data integrity verification activities can usually be separated. Verification of computerized control of equipment operation is part of the equipment qualification process, but data acquisition and processing should be part of the computer system validation process. Validation of computerized laboratory data acquisition and information management systems will be mentioned but the details are beyond the scope of this chapter. The focus will be on the capability of making valid analytical measurements.

PHASES OF EQUIPMENT QUALIFICATION

The term validation was defined as "establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes."[4] This definition applies to processes and products. In laboratories, the product of the analyses is data. Therefore, the entire data generation process must be validated.

Typically, projects are broken into three phases: design, build, and implement. Laboratory equipment qualification projects have followed this model but have deemphasized the build phase because that is under the control of the equipment manufacturer. Laboratory equipment qualification has been divided into design qualification (DQ), installation qualification (IQ), operation qualification (OQ), and performance qualification (PQ).[9,10] The DQ phase represents the design or evaluation of design and the IQ, OQ, and (sometimes) PQ phases represent implementation. Classically, OQ included calibrations. For process equipment, calibrations are part of IQ. As a way to simplify the understanding of equipment qualification, calibration can be separated from IQ and OQ because of the timing of the testing and the instrument components being tested. By differentiating between calibration and OQ for laboratory equipment, a qualification model similar to manufacturing process equipment qualification can be obtained. Formal definitions of terms relating to equipment qualification are given in Table 7.1.

Table 7.1 Equipment qualification definitions.

Term	Definition	Comments
Instrument	• A device (chemical, electrical, hydraulic, magnetic, mechanical, optical, pneumatic) utilized to test, observe, measure, monitor, alter, generate, record, calibrate, manage, or control physical properties, movements, or other characteristics. (MIL-STD-1309C PAR 3.1.326) • A device that takes a physical measurement and displays a value or has no control or analytical function, e.g. stopwatches, timers, and thermometers. (Phillip A. Cloud, Validating a Laboratory Incubator, *BioPharm*, November, 1997, pp. 30–42.)	
Equipment	• The collective analytical measurement instruments, in conjunction with firmware, assembled to perform a mechanical process. • In a computerized system, the equipment is controlled by the computer system. The computer collects measurement data from the equipment. • A device or collection of components that perform a process to produce a result. (Phillip A. Cloud, Validating a Laboratory Incubator, *BioPharm*, November, 1997, pp. 30–42.)	
Process Validation	• Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes. (*Guidelines on General Principles of Process Validation*, US FDA, Rockville, MD, May 1987.)	

(continued)

Term	Definition	Comments
Equipment Qualification	• The action of proving that any equipment works correctly and actually leads to the expected results. (*The rules governing medicinal products in the European Community*, Volume IV, Office for Official Publications for the European Communities, Luxembourg, 1992.)	Includes IQ and OQ. Some include DQ and/or PQ.
Design Qualification	• Defines the functional and operational specifications of the instrument and details the conscious decisions of the selection of the supplier. (P. Bedson, The development and application of guidance on equipment qualification of analytical instruments, *Accred. Qual Assur.* 1 (6): 265–274, 1996.)	Includes functional requirements and specifications as well as the design specifications.
Installation Qualification	• Establishes that the instrument is delivered as designed and specified, that it is properly installed in the selected environment, and that this environment is suitable for the operation and use of the instrument. (P. Bedson, The development and application of guidance on equipment qualification of analytical instruments, *Accred. Qual Assur.* 1 (6): 265–274, 1996.) • Documented verification that all key aspects of hardware installation adhere to appropriate codes and the computer system specification. (*Validation of Computer-Related Systems, PDA Technical Report No. 18,* PDA Journal of Science and Technology, Volume 49, Number S1, 1995.) • Establishing confidence that process equipment and ancillary systems are capable of consistently operating within established limits and tolerances. (*Guidelines on General Principles of Process Validation*, US FDA, Rockville, MD, May 1987.)	
Operation Qualification	• The process of demonstrating that equipment will function according to its operational specifications in the selected environment. (P. Bedson, The development and application of guidance on equipment qualification of analytical instruments, *Accred. Qual Assur.* 1 (6): 265–274, 1996.) • Documented verification that the system or subsystem operates as specified in the computerized system specifications throughout representative or anticipated operating ranges. (*Validation of Computer-Related Systems, PDA Technical Report No. 18*, PDA Journal of Science and Technology, Volume 49, Number S1, 1995.)	
Performance Qualification	• The process of demonstrating that an instrument consistently performs according to a specification appropriate for its routine use. (P. Bedson, The development and application of guidance on equipment qualification of analytical instruments, *Accred. Qual Assur.* 1 (6): 265–274, 1996.) • Documented verification that the integrated computerized system performs as intended in its normal operating environment; i.e., the computer-related system performs as intended. (*Validation of Computer-Related Systems, PDA Technical Report No. 18*, PDA Journal of Science and Technology, Volume 49, Number S1, 1995.)	
Process Performance Qualification	• Establishing confidence that the process is effective and reproducible. (*Guidelines on General Principles of Process Validation*, US FDA, Rockville, MD, May 1987.)	

(continued)

Term	Definition	Comments
Product Performance Qualification	• Establishing confidence through appropriate testing that the finished product produced by a specified process meets all release requirements for functionality and safety. (*Guidelines on General Principles of Process Validation*, US FDA, Rockville, MD, May 1987.)	
Change Control	• A formal monitoring system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status to determine the need for corrective action that would assure that the system retains its validated state. (*Validation of Computer-Related Systems, PDA Technical Report No. 18*, PDA Journal of Science and Technology, Volume 49, Number S1, 1995.) • A formalized program by which qualified representatives review proposed and actual changes to products, processes, equipment, or software to determine their potential impact on the validation status. (J. Agalloco, Master Planning of Validation, *PDA Training and Research Institute*, April 1998.) Started after IQ.	Started after IQ.
Revalidation	• Repetition of the validation effort or a selected portion of it. (J. Agalloco, Master Planning of Validation, *PDA Training and Research Institute*, April 1998.)	
Requalification	• Repetition of the qualification effort or a selected portion of it. (J. Agalloco, Master Planning of Validation, *PDA Training and Research Institute*, April 1998.)	Requalification is a revalidation activity.
Calibration	• The set of operations that establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by material measure and the corresponding values of the measurand. (NCSL RP-1)	Used by regulatory agencies to refer to the process of checking or adjusting instruments.
Verification	• Confirmation by examination and provision of evidence that specified requirements have been met. (ISO/IEC Guide 25: *General requirements for the competence of calibration and testing laboratories*, 3rd ed., 1990.)	
Standardization	• The assignment of a compositional value to one standard on the basis of another standard. (NIST PUB 260-100 Handbook for SRM Users)	

It is important to differentiate between laboratory instruments and laboratory equipment. An instrument, whether in a laboratory or process application, is a device that measures or controls a process variable. Examples of instruments are balances, pH meters, timers, thermometers, spectrophotometers, etc. The testing of instruments that demonstrates that the measurements are within accuracy and precision limits is called *calibration*. In contrast, *equipment* is a device that performs physical or mechanical transformations. Equipment may consist of one or more instruments that control or monitor process variables and maintain conditions necessary to produce the desired output.[12] Examples of laboratory equipment include refrigerators, incubators, dissolution baths, automated sample preparation robotics, chromatographs, autoclaves, etc. The

term equipment has also been called equipment system or instrument system. Equipment produces outputs that can be either directly or indirectly tested for consistency and quality. If the product of the process can be directly qualified, then PQ should be done (for example, the sterilization process in an autoclave or the separation process in a chromatograph). If the product cannot be tested directly, then the conditions that control the process should be tested via OQ. This supports the device regulation stating, "Where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance and approved according to established procedures."[13] Guidelines for categorizing laboratory devices are given in Table 7.2. The scope of qualification testing required is shown in Table 7.3.

Table 7.2 Guidelines for categorizing laboratory devices.

The device performs a computerized process (i.e. electronically transforms an input into an output).		Classify it as a "system." Computerized systems require validation, especially if data are captured, manipulated, and/or stored. Document all of the critical hardware and software components.
	The software is embedded.	Document the firmware version.
	The software is configurable.	Develop and test backup and recovery procedures. Retain software backups for emergencies.
	The program requires security but lacks electronic log-in functions.	Physically limit access to the system.
	Data are acquired electronically.	Test that the system has the random access memory, processing speed, and storage capability to maintain the expected data flow.
	The program or acquired data resides on a network.	Test that the network can handle the expected worst case outputs.
The device performs a mechanical process (i.e., mechanically transforms an input into an output).		Classify it as "equipment." Equipment may be composed of several interconnected instruments that control or monitor the process.
	The output of the process can be tested.	Test the output during performance qualification (PQ).
	The input of the process varies, therefore the output cannot be tested for consistency and quality.	Test all possible operating conditions during OQ.
	The critical functions of each component can be tested, such as automated timers, alarms, and interlocks.	Test all critical functions during operation qualification (OQ).
	The equipment requires a special laboratory environment or special utilities or requires a piping & instrumentation diagram (P&ID) to reproduce its design and construction.	Capture the P&ID and environmental requirements in the installation qualification (IQ).
	The equipment is critical to the operation and requires spare parts that are prone to failure and are difficult to obtain.	Document these parts in the PM SOP. Maintain these parts in a spare parts inventory.
	The equipment consists of instrumentation which monitor or control critical process variables.	Document those instruments and put them on a calibration schedule.

(continued)

The device measures or controls a measurement.		Classify it as an "instrument." Further instrument classifications are described below. It would be useful to print these classifications on the equipment tags to clarify the lack of calibration labels on some instruments.
	The instrument's measurement or output is not critical to the control of a process or does not directly affect the results of an analysis.	Classify it as "Calibration Not Required."
	The instrument's measurement or output is critical to the control of a process or directly affects the results of an analysis.	Classify the instrument as "Calibration Required." These instruments require calibration, verification, and/or standardization procedures.
	An instrument component is calibrated as part of a loop with another critical instrument component.	Classify that component as "Calibration in Loop with…" instead of "Calibration Required." Document the other component to which it is loop calibrated.
	The instrument's measurement is used only to monitor a parameter that controls a process which has an output that is checked more frequently than the calibration interval.	Classify it as "Calibration on Installation."
If the device contains mechanical parts that are prone to degradation, and if failures can be prevented by inspecting, cleaning, lubricating, or replacing parts on a regular basis, then implement a preventive maintenance (PM) plan. Document replacement parts in a spare parts list in a PM procedure.		

Table 7.3 Scope of qualification.

Device	IQ	PM	Cal.	OQ	PQ
Ancillary equipment accessories	X	X			
Instrument	X	X	X		
Equipment	X	X		X	
Process or analytical method					X

Some laboratory instruments and equipment are part of computerized control and/or data acquisition systems. When electronic data acquisition is used, additional regulations must be followed.[14] Critical functions for automated equipment, whether controlled by embedded or configurable software, can be tested during OQ. These functions include alarms, interlocks, or timed operations. This should be done if the failure of these functions could cause product inconsistencies to go unnoticed. Data acquisition, processing, and retention functions must also be tested during OQ. Guidance for handling computerized systems is available from the PDA.[7]

Equipment qualification is necessary to ensure that valid data can be generated. It consists of IQ, instrument calibration, and OQ. For some applications, calibrations are done during IQ and for others during OQ. For illustrative purposes, calibrations will be discussed separately from IQ and OQ. However, all of the activities combined can be referred to as equipment qualification. Because formal definitions for IQ and OQ have caused much confusion among many analytical chemists, they should not be considered critical to equipment qualification. What is important is that the necessary activities are appropriately performed and documented.

When the need to qualify laboratory equipment arose, scientists sought the aid of equipment manufacturers. Equipment manufacturers delivered solutions that they could supply, such as qualification services and extensive documentation packages. The services supplied were suited to manufacturer specifications or general requirements of the analytical technique. The disadvantage of those qualification packages was that they did not document or test to method accuracy and precision requirements or user ranges. There was no traceability between analytical method requirements, equipment/instrument specifications, and test acceptance criteria. Many laboratories have since devised their own testing procedures using their own acceptance criteria to satisfy regulatory requirements. Vendor specifications and general requirements of the analytical technique have thus evolved into design qualification (DQ).

DESIGN QUALIFICATION

Design qualification is a proactive evaluation of equipment before purchasing. It is useful for purchasing previously untested equipment or software. There are no regulatory requirements for performing this activity with equipment, but in certain circumstances it makes good business sense. DQ is useful for evaluating custom software development processes because the source codes or expertise to review source codes may not be available. DQ allows the user to evaluate the vendor's compliance practices to gain a high degree of assurance that software codes were written according to sound methodology.

Depending on equipment cost and the impact on laboratory resources, quality evaluations can be made on the equipment and the vendor who supplies the equipment. DQ should be done if the cost failure of the equipment to perform its intended function outweighs the cost to perform the activity. These DQ costs include employee salaries, documentation generation and maintenance costs, and the cost to develop and maintain a program. Failure costs include costs to purchase, install, operate, and dispose of unsuitable equipment.

During the DQ stage, equipment specifications should be compared to analytical technique and laboratory efficiency requirements. If specific operating ranges are known, then they must be addressed. Specifying user requirements is often the most difficult part of qualifying equipment. Limited guidance for specifying user requirements can be found in the United States pharmacopoeia, which is beginning to specify accuracy limits for analytical measurements. Examples are dissolution bath apparatus,[15] spectrophotometer wavelengths,[16] and UV detector wavelengths.[17]

Equipment design is not the specialty of analytical chemists. Therefore, analytical chemists may not have much input regarding design requirements. Some functional specifications that scientists can use to make evaluations include functions that improve productivity, conserve resources, or automate calibration. For example, most new analytical balances are built with internal weights to which the balances automatically standardize. Another example is an HPLC pump that shuts off if a leak is detected. It may also be desirable if the automatic functions can be turned off so that long experiments can be uninterrupted if noncritical disruptions occur.

When evaluating instruments and process control ranges are known, controlling instruments must be at least four times as accurate as the process range. This is what is

defined as a 4:1 accuracy ratio. Setting the calibration tolerance tighter than the process range allows calibration values to drift without letting the process go out of control. Therefore, if the instrument under test (IUT) is found to be out of tolerance during calibration, then there is a small chance that the error affected the quality of the product. If the process does not have at least a 4:1 accuracy ratio, then there is a greater chance that the process could go out of control if the IUT goes out of tolerance.

Another consideration when purchasing new equipment is the services provided by the vendor. These include operator training, repairs, preventive maintenance visits, and calibrations. The presence of a local service representative is an important consideration. This would reduce response time and travel expenses, both of which would affect the cost to operate and maintain the equipment. If the cost of calibrating and maintaining equipment is relatively high, then vendor-supplied calibration and maintenance procedures would allow calibrations to be performed in-house.

A final consideration when evaluating equipment and suppliers is the probability that the product support will be terminated. If the equipment manufacturer is unstable or relatively young, then the equipment may not have support throughout its lifecycle. A mature company that is a leader with technology and has a well-developed product line is most desirable.

INSTALLATION QUALIFICATION

Once new equipment is received, the process of installation qualification can begin. IQ provides documentation that equipment is of "appropriate design and adequate capacity"[1] and is "suitably located for operation, inspection, cleaning and maintenance."[1]

Some sources recommend that contents of packages be compared to purchase orders to reconcile the order.[7] There is no regulatory requirement for this activity. However, it makes good business sense, especially if the vendor does not install the equipment.

Upon installation, adequate facility and utility specifications must be satisfied. The installation and configuration specifications as well as the satisfaction of those requirements should be documented in the IQ form or checklist. Typically, the equipment has manuals and drawings that contain instructions for installation and start up. References to these must be captured in the IQ. If the manuals specify spare parts and maintenance instructions, these can be captured in the preventive maintenance (PM) standard operating procedure (SOP). If the manuals give calibration instructions, then these can be documented in the calibration SOP. The document numbers for the calibration and PM SOPs should be documented in the IQ. Other useful data to obtain are the equipment or instrument model, serial number, location, and custodian. The custodian is the primary user or the person responsible for the operating condition of the equipment or instrument. If the equipment manufacturer supplies any factory acceptance testing (FAT) or site acceptance testing (SAT) documentation, these should also be kept with the IQ. Other IQ activities include issuing maintenance logbooks, tagging the equipment, and putting critical instruments into the calibration and maintenance program. IQ is therefore an implementation event that documents all of the information necessary for performing calibrations and OQ.

CALIBRATION

After all of the IQ documentation is complete, all of the critical instruments must be calibrated. Critical instruments are measuring devices that report measurement data or support processes that directly influence the quality of the data. Calibration ensures that measurements and measurement controls are within accuracy and precision limits. Calibration satisfies the regulation stating that instruments are "adequately tested, calibrated and/or standardized."[1] Periodic calibrations are necessary on instruments that are part of laboratory equipment, because the measurement controls that they provide are used to regulate analytical measurement or sample preparation processes, and because those processes may drift with time and use. If the measurements are not accurate or precise, the analytical process will be out of control. This could result in unidentifiable failures later in the data generation process.

Before calibrations can begin, calibration SOPs must be available that define the responsibilities, intervals, tolerances, calibration points, methods, standards, and test materials.[1] Calibration procedures should be written during the IQ stage of implementation. Guidance on writing calibration procedures is available in Table 7.4. Calibrators executing these procedures must have documented evidence of training. All standards used must have documented evidence of traceability to the National Institute of Standards and Technology or to a reproducible physical constant.

Table 7.4 Calibration SOP considerations.

Necessary calibration/verification tests:		
	The instrument is used for quantitative purposes.	Accuracy, precision, linearity, and/or sensitivity tests may be necessary.
	The instrument is used for qualitative purposes.	Selectivity and/or specificity are crucial. Selectivity and specificity are usually required when two-dimensional data must be collected. These include chromatography, spectrophotometry, spectroscopy, etc. Regulating the dependent variable usually controls selectivity and specificity.
	The process/analysis variable is directly measured.	A linearity test is not necessary. Linearity is demonstrated when multiple calibration points are within tolerance.
	A physical property of the analyte is measured and correlated to responses of known standards and varying amounts of known standards are not measured in each analysis.	A linearity test must be performed. Linearity can be expressed as using a minimum correlation coefficient, a maximum residual, etc.
	A process controller is required to regulate a process variable consistently.	A reproducibility test is necessary. Reproducibility can be expressed as standard deviation, relative standard deviation, range, maximum deviation from set point, etc.
	Sensitivity is critical.	A low limit test such as signal-to-noise should be performed.
Responsibility:		
	Daily calibrations are necessary.	Specify the user.
	Operational knowledge of software or firmware is necessary to perform the calibration.	Specify the custodian.

(continued)

	Metrology has the capability to calibrate the instrument (appropriate standards and personnel).	Specify the Metrology department.
	The expertise or standards necessary to perform the calibration are outside capability of the company.	Specify the vendor.
Interval: base on:		
	1. Experience with the specific model or type of instrument gained by trend analysis. 2. Impact of calibration failures on reported data. 3. Regulatory guidance. 4. Manufacturers recommendations. 5. Industry practice.	If no guidance exists, then start with monthly for three months. If adjustments are necessary after three calibrations, then change to quarterly. Change accordingly to semi-annually, then annually.
Tolerance: base on:		
	1. User range (4:1 accuracy ratio). 2. Experience with the specific model or type of instrument. 3. Regulatory guidance (USP, etc.). 4. Manufacturers recommendations. 5. Industry practice.	If no other guidance exists, then start with the worst case calibration result; then tighten or loosen as experience is gained.
Calibration Points:		
	The instrument under test (IUT) can only be calibrated in the operating environment (e.g., process controllers, recorders, etc.).	Calibrate at the operating point only. For controllers, determine minimum, maximum, range, and/or average where applicable.
	The IUT can only be calibrated with standards that are the source of the signal (e.g., weights, gage blocks, pH meters, etc.).	Calibrate at the discreet set points (source method) between 10 and 90% of its span.
	The IUT is the source of the signal (e.g., weights, gage blocks, glass filters, etc.).	Certify it at the operating point. Certification tolerances should account for drift.
	The IUT is an analog gage calibrated with standards that measure the signal.	Calibrate it at the major scale divisions between 10 and 90% of its span.
	The instrument is intended to be used over a range that is less than or equal to 60% of its span.	Perform a 3-point calibration that includes approximately 0, 50, and 100% of the user range.
	The instrument's intended operating range is over 60% of its span.	Perform a 5-point calibration at approximately 10, 30, 50, 70, and 90% of span.
	The measuring sensor is mechanical with relatively large dead band and/or hysteresis errors.	Perform an upscale, a downscale, and a second upscale calibration.
Instructions: calibration methods:		
	General: 1. Record the condition of the IUT as found. 2. Verify that any power-up diagnostics show no error messages. 3. Allow the STD, the IUT, and the measurement environment to equilibriate before taking measurements. 4. Record measurements as described in steps 5–8 below. 5. Document errors and tolerances at each calibration point. 6. Adjust if out of tolerance or acceptance limits. 7. Remove the old calibration sticker and place a newly completed calibration sticker on the instrument. 8. Complete and submit the calibration report.	Types of calibration methods: 1. Reference method—the STD and IUT are in the same measurement environment. Readings are directly compared. 2. Transfer method—STD and IUT cannot be in the same measurement environment simultaneously. STD values must be measured before and after IUT values to demonstrate measurement environment stability. 3. Source method—the STD provides the process variable input.

Operation ranges for each instrument in the calibration program should be documented in the IQ. Calibration tolerances should be determined based on the operating range and control requirements. Ideally, the calibration tolerance of the instrument under test (IUT) should be at least four times tighter than the process requirement as described earlier. Also, the calibration points should bracket the intended operating range to demonstrate that the instrument was suitable for its intended use.

Many have stressed that instruments should be calibrated to manufacturer specifications. This may have some validity if the analysis or process accuracy and precision requirements are not known. Analytical methods development should determine all critical variables and the ranges required to maintain control during robustness testing in method validation. The requirement of calibrating to manufacturer specifications does not guarantee that your process will be under control. Since regulators hold the analyst responsible for the quality of the data, the calibration tolerances should be determined by the requirements of the analytical method or the analytical technique, not simply by rote adherence to the manufacturer's specification.

Calibrations are part of implementation and occur between IQ and OQ. In process equipment qualification, calibrations are part of IQ. In other laboratory equipment qualification descriptions, calibrations were considered part of OQ. In those descriptions, critical control operational verifications are not typically addressed. Calibrations must, however, be performed before OQ because measurement accuracy is necessary to establish process control.

OPERATION QUALIFICATION

Other equipment controls include automated functions such as safety interlocks, alarms, and timed events. If failure of these functions can affect data and occur without being caught during data review, then they should be tested during OQ. Alarm testing is necessary when there are instruments that monitor analysis or process conditions. If a process variable under control deviates from its acceptable range, then an alarm or pager alert may alert users to the malfunction. Interlocks are used to shut down an analysis or process if a destructive process control deviation occurs. Fortunately, for data generation applications, most data are subject to complete review and strict processing parameters will not allow analytical process controls to deviate unnoticed. Therefore, alarms, interlocks, and timed events of laboratory equipment are generally not considered critical.

There are some laboratory applications that require OQ on equipment. These include automated sample preparation devices such as robotic tablet processing workstations and dissolution workstations. Testing of automatic robotic operations is necessary because there is no complete check of the output of every preparation. For automated sample preparation equipment, OQ involves testing all of the integrated system's operations over all of the expected operating ranges. For dissolution equipment, OQ involves dissolving and analyzing USP calibrator tablets of prednisone and salicylic acid following equipment IQ and critical instrument calibrations.

If users can configure the operations manually, then all intended configurations must be tested. During OQ, equipment should be tested to meet manufacturer specifications

with regard to programming. Since automatic functions are controlled by software, whether embedded or configurable, they only need to be tested upon implementation and after revisions are made. Software changes should be monitored using a change control program. Software-controlled functions should be tested in an actual or simulated working environment to determine if they would adversely affect other aspects of the equipment operation. For example, an interlock activated by opening a column oven door may shut down an HPLC analysis. If the vendor documents alarm and interlock tests during a start up or site acceptance test, then this documentation can be incorporated into the OQ.

Other laboratory applications requiring OQ are critical exposure, heating, refrigeration, or incubation processes. During these processes, samples are prepared by exposure to an environmental condition for a length of time. The exposure conditions must be tested during OQ. All expected operating conditions must be tested and the loading of the container must bracket the expected loading configurations. These applications, or specific loading configurations, should also be maintained under a change control program.

OQ occurs during implementation as part of equipment qualification. OQ tests the controls that regulate a process. If the critical parameters of the process are continuously monitored or the product is verified regularly, then there is no need to repeat OQ unless changes are made to the equipment or process. These changes are monitored by change control. If a continuous process is not monitored, then OQ must be repeated regularly. Once the parameters that regulate a process have demonstrated control, then the product of the process can be tested during PQ.

PERFORMANCE QUALIFICATION

After equipment has undergone IQ, OQ, and instrument calibrations, it can be considered to be qualified or capable for use in method development and sample analysis using a validated method. PQ for laboratory equipment can be viewed as an extension of method validation much as PQ of manufacturing equipment is part of process validation. PQ requires that equipment has previously undergone IQ, calibration, and OQ so that failures would not be the result of the equipment deficiencies.

In the laboratory, PQ qualifies the entire data generating process in the actual operating environment. It involves the equipment, operator, sample preparations, test materials, and test methods. For chromatographic methods, acceptance criteria for PQ should be specified in the system suitability requirements of the analytical method. System suitability includes verifying separation, chromatographic efficiency and reproducibility to demonstrate system specificity and precision. Other tests may include analyzing control samples for reproducibility of the analytical results. Additionally, method validation data can be considered an element of PQ. In general, PQ tests the product for consistency whereas OQ tests the process conditions for consistency.

Performance qualification originated from the term process qualification. Process qualification was used to define the validation batches that are produced to demonstrate that manufacturing processes were well-defined and under control. In order to validate an entire process, the process has to be broken up into stages controlled by separate pieces of equipment. Performance qualification is used to represent the performance

testing of a piece of equipment within a process by testing the output of the process. In pharmaceutical manufacturing process validation, a minimum of three batches are prepared and tested. If the process is proven to be under control, subsequent batches can be produced without extensive characterization and quarantine time.

Some laboratory equipment performs processes that require PQ. These include robotic sample preparation and robotic dissolution equipment. Correlating the automated preparations to manual preparations after the equipment has undergone IQ, OQ, and calibrations provides the PQ for robotic sample preparation methods.

In laboratory chromatographic analyses, PQ is the qualification of the specific separation and quantitation process of a given method. Since all of the factors that control separations (for example, the mobile phase composition and column efficiency) cannot be tightly controlled, the separation parameters of every analysis must be monitored. The acceptance criteria for separation and measurement processes are the system suitability criteria defined during method validation. System suitability tests the resolution of peaks and the precision of the system within an analysis. Another means of monitoring method consistency is the use of control samples. Control samples measure the precision of the method between analyses. Control samples are stable, well-characterized samples that are analyzed in several analyses. Their results are recorded in a control chart to observe if there is drift or imprecision between analyses. In this way, PQ is more of an extension of method validation than equipment qualification.

QUALIFICATION MAINTENANCE

After the qualification stage is complete and the equipment operable, several programs must be in place to maintain equipment in a state of qualification. These include preventive maintenance, calibration, and change control programs (where applicable). Preventive maintenance is an activity that must be performed at regular intervals. PM checklists should have been developed during IQ or at the latest, before the first PM activity begins. These should list the parts to be inspected, cleaned, lubricated, or replaced. It is advisable to list specific part numbers of any replacement parts, for ease in maintaining parts inventories.

Calibrations must also be performed at regular intervals. Many times, calibrations are scheduled at the same time as the PMs. If the PM will affect the measurement accuracy of an instrument and the instrument is not checked by another mechanism (such as during PQ), then the accuracy of the measurements should be checked before modifications are made. This is known as collecting "as found" calibration data before adjustments are made. In many cases, changing mechanical parts does not affect the accuracy of sensors or controllers so that there is no need to collect "as found" data. If adjustments are made that affect the accuracy or precision of measurements, then "as left" calibration data must also be collected after the adjustment.

For some qualified equipment consisting of multiple components, a change control program should be in place. Change controls involve documenting the nature and reason for the change, evaluating the impact of changes to the equipment or the process, notifying affected parties, and documenting any testing that must be done to ensure that the qualified state of the equipment has not changed. Changes include replacing parts (such as in a PM),

exchanging defective instruments, relocating equipment, making repairs, and making modifications to qualified equipment. Change control programs are necessary when the equipment is interrelated with other systems that have an impact on the equipment performance and that performance may not be directly verified. Many times there are different custodians of the associated equipment who must be notified of changes.

When these changes occur, limited requalification may be necessary. For some equipment, only modifications to the equipment list are necessary. This is just a revision of the IQ. For other equipment, calibrations may be necessary if accuracy or precision could be affected. It is advisable to proactively document which instruments require calibrations if specific parts are replaced or if the equipment is moved. If software or firmware revisions are made, then IQ and possibly OQ may need to be repeated. If the nature of the equipment is well understood, then provisions for changes can be written into the calibration and maintenance SOPs. This would obviate the need for those retrospective change control evaluations. Change control decisions must be based on good science and be well-documented.

SUMMARY

As far as data quality and integrity are concerned, PQ is the most important aspect of equipment qualification. If there are controls for meeting PQ requirements that are not tested during PQ, then these should be done during OQ or calibration.

IQ is the gathering of all of the information necessary to plan and execute the calibrations and OQ's to predetermined acceptance criteria. These acceptance criteria should be based on the intended use of the equipment, within its design capabilities. The test criteria must satisfy regulatory requirements as shown in Table 7.5.

IQ and OQ are events that occur during implementation of new equipment. They may need to be repeated if modifications are made to the equipment. Calibrations occur

Table 7.5 Relationship between qualification tests and requirements.

Equipment Test	Equipment Specification	Analysis Requirement	Comment
Installation qualification (document initially and after changes)	Equipment or instrument configuration and set-up specifications		Demonstrates that equipment is of "appropriate design" and "adequate capacity"
Calibration (test periodically due to drift)		Instrument controls required by the technique or analytical method	Demonstrates that instruments are "adequately calibrated"
Operation qualification (test initially and after changes)	Equipment functional specifications		Demonstrates that equipment is "adequately tested"
Performance qualification (test initially or regularly if all critical variables cannot be strictly controlled)		Method validation requirements	Demonstrates that process produces the desired product

during implementation between IQ and OQ and also as ongoing events. In laboratories, calibrations facilitate method transfer by ensuring that measuring instruments are traceable to the same standard. In process equipment qualification, calibrations are performed as part of IQ. In laboratory equipment qualification, calibrations are typically considered OQ, while control events are ignored. In harmonizing laboratory equipment qualification with process equipment qualification and emphasizing the difference in the timing of events, calibrations should be considered separately from IQ and OQ.

Design qualification for equipment is not a regulatory requirement, but has practical uses. It can help avoid purchasing equipment that will not meet method validation requirements or operate under normal laboratory operating conditions.

CONCLUSION

Many authors have developed plans for qualifying a unit of laboratory equipment. Most have used HPLC as an example. In order to translate the plan so that other types of equipment can be managed, a general philosophy must be devised. It is desirable to have a general plan for dealing with equipment and to apply those principles to all new equipment rather than reinventing the process each time. General guidance for dealing with an unknown unit of laboratory equipment is given in Table 7.6. Rather than dealing with each unit of equipment separately, it would be better to have a qualification plan for the entire laboratory and keep the process in a state of readiness and activity.

Table 7.6 Traceability matrix for generic equipment qualification plan.

Regulation/ Parameter	Process or User Requirement	Equipment Specification	Acceptance Test Criteria	Pass (Y/N)
No regulatory requirement, good business practice	*Vendor/Equipment Evaluation Requirements*		*Design Qualification*	
Vendor Availability	History and survivability of company	Vendor evaluation	The vendor has been in business for some time and is expected to stay in business to support the equipment throughout its expected lifetime.	
Vendor Competitiveness	Vendor is one of the leading equipment manufacturers in the field	Vendor evaluation	The vendor is a leader in research in the particular product line.	
Vendor Services	Local service person Repair PM and calibration Operator training	Vendor evaluation	Vendor is local and offers repair, PM, and calibration services. Operator training is available on-site or at vendor facility.	
Vendor Experience Equipment	Vendor experience with equipment type	Vendor evaluation	Vendor has past experience with equipment. (New technology has been evaluated by knowledgeable users.)	

(continued)

Regulation/ Parameter	Process or User Requirement	Equipment Specification	Acceptance Test Criteria	Pass (Y/N)
Vendor Regulatory Experience	Vendor knowledge of customer's regulatory needs	Vendor evaluation	Vendor has sought to make improvements for customers working in a regulated environment. Vendor has and adheres to a documented internal quality system. Company is certified by a voluntary regulatory agency.	
Equipment/ Instrument Suitability	Process/analysis control requirements: alarms, interlocks, automated events, etc.	Equipment's specifications for equipment controls and instrument accuracy and precision	Instrument specifications are at least four times more accurate and precise than the process/ analysis requirement. Equipment has alarms that notify users if continuous process conditions have deviated from intended ranges. Equipment has safety features that prevent operator injury or product damage.	
Appropriate design and adequate capacity		*Design Specifications*	*Installation Qualfication*	
Vendor Documentation	Manuals Drawings Spare parts list PM procedure Calibration procedure Factory acceptance testing Site acceptance testing Vendor audit	Vendor documentation specified	Vendor documentation collected and adequately stored. PM and calibration procedure written and approved. Spare parts list captured in PM procedure. Additional manuals purchased for maintenance department.	
Internal Documentation: Instrument List	Instrument ID Equipment ID Instrument description Location Custodian Associated software or firmware Operating range Measuring range and resolution Calibration points and tolerances Calibration interval Calibration SOP Maintenance interval Maintenance SOP	Accuracy and precision specifications supplied. Recommended calibration interval and procedure supplied.	All internal documentation requirements satisfied.	
Operating Conditions	Operates under normal laboratory conditions	Special facility or utility requirements specified	Special facility or utility requirements met. All connections inspected.	

(continued)

Regulation/ Parameter	Process or User Requirement	Equipment Specification	Acceptance Test Criteria	Pass (Y/N)
Configuration	Vendor provides installation instructions	Vendor installation instructions	Installed according to drawings.	
Ancillary equipment	List all other equipment connected that could be affected by changes	Required ancillary equipment, especially utilities	All ancillary equipment listed.	
Start up	Starts up with no error messages		Starts up with no error messages.	
Adequately calibrated and/or standardized	*Measurement Requirements*	*Accuracy and Precision Specifications*	*Calibration*	
Method accuracy and precision requirements	Accuracy ratio of 4:1 between measurement controls of analytical technique and method	Equipment accuracy and precision specifications	Measurement and control accuracy and precision tolerances met.	
Adequately tested		*Functional Specifications*	*Operation Qualification*	
Safety interlocks	Controls prevent injury to the operator	Manufacturer specified safety interlocks (software or firmware)	All safety interlocks functioned as configured. All measurement and test equipment was calibrated and documentation provided.	
Alarms	Alarms notify operators when the process controls have deviated out of the operating range	Manufacturer specified alarms (software or firmware)	All alarms functioned as configured. All measurement and test equipment was calibrated and documentation provided.	
Timed operations	Operations automate manual processes Analytical technique requirements	Manufacturer specified automation and controls (software or firmware)	All timed and mechanical operations functioned as configured. All measurement and test equipment was calibrated and documentation provided.	
Analysis or Process	*Method Validation and System Suitability Specifications*		*Performance Qualification*	
Analytical Processes, actual conditions	Accuracy Precision Linearity and range Sensitivity Specificity Ruggedness Robustness	N/A	System suitability and method control requirements met.	

Other suggestions for maintaining an entire qualification program are as follows:

1. If DQ must be performed, then:
   a. do it once for all of the same models of equipment;
   b. set it up as a purchase comparison for different equipment; and
   c. do not make it a formal process unless necessary.

2. Streamline IQ documentation to:
   a. standardize SOP formats;
   b. cut out unnecessary signatures on SOPs;
   c. use forms and checklists;
   d. document only the information necessary to maintain control of the equipment; and
   e. put the information in an electronic database to facilitate searches.
3. Do not repeat OQ tests on the same versions of software or firmware for multiple instruments of the same kind.
4. Alternatively, do IQ on:
   a. all copies;
   b. maintain an "equivalent" computing environment of all similar systems; and
   c. reference the original OQ testing of the first one done.
5. Take a master protocol or master SOP approach rather than individual protocols and SOPs in order to streamline implementation and ensure consistency.

These will help to reduce implementation time, maximize operation time during warranty periods, and cut repair and maintenance costs.

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8

Equipment Calibration and Maintenance

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Lycoming Analytical Laboratories

OVERVIEW

The goal of this chapter is to provide the reader with an awareness of equipment calibration and maintenance requirements for analytical laboratories in regulated industries such as pharmaceuticals and foods. A practical approach is presented that balances regulatory requirements with laboratory productivity and efficiency. Areas covered include physical equipment such as analytical balances, pH meters, spectrophotometers, chromatography systems, data systems, atomic absorption, dissolution, and miscellaneous equipment such as ovens and refrigerators. Chemical equipment is also covered and includes such items as analytical standards, reagents, volumetric solutions, and laboratory water.

KEY WORDS

- A structured program of regular, ongoing calibration and maintenance is both smart and essential
- Equipment reliability
- Documentation
- Traceable standards
- Validation
- Verification
- Physical and chemical calibration
- Bracketing
- Routine inspection
- Scheduling

INTRODUCTION

A sound program of regular equipment calibration and maintenance is of paramount importance, and in fact is the foundation upon which all analytical data are built or developed. Consider a situation where a result is out-of-specification, questionable, or so far off target that it is clearly unreasonable. Where does one look to find out what happened? Investigation of suspect data is largely dependent upon knowing the condition and operational status of all laboratory equipment used in developing the data in question. Without knowing about the equipment, another unknown is introduced that can make interpretation of bad data either difficult or meaningless. A structured program of regular, ongoing calibration and maintenance of laboratory equipment is both smart and essential. For the purpose of calibration and maintenance, this chapter defines equipment as both physical and chemical.

PHYSICAL EQUIPMENT

Analytical Balances

The analytical balance is the foundation of most quantitative chemical analyses. Most laboratories have their balances serviced by an outside service engineer once or twice a year. The service call consists of cleaning, calibration, and documentation that the balance was serviced. The documentation is a sticker that the service engineer places inside the balance chamber.

Suppose that an analytical balance is serviced on January 1 and June 1 of each year. Suddenly, one day in April, a number of questionable results are generated. The balance is suspect, and an emergency service call is arranged. The service engineer finds the balance to be out of calibration and corrects the problem. The samples with questionable results are repeated and everything seems to be fine, or is it? What about samples that were run yesterday, last week, or even on January 2? Are those results reliable? The answer is that you don't know for sure. Since the last calibration was January 1, and the balance was found to be out of calibration in April, all weighings made between January 1 and the time of the emergency service call in April are potentially suspect. Why? Because no one knows when the balance went out of calibration. Was it sudden or gradual? Again, no one knows for sure.

When dealing with laboratory equipment whose reliability is critical to the performance of the laboratory, that equipment must be checked as frequently as is needed to assure sound analytical results. In the case of a balance, calibration checks should be done daily, since if a weighing is in error, so is everything that follows.

For older-generation balances, it is recommended that each such analytical balance in the laboratory be serviced by a professional outside service engineer at least semiannually. High volume labs might consider quarterly service. Newer balances with built-in calibration routines may not need outside service intervention unless the balance is in need of actual repair. For all analytical balances, the laboratory should check accuracy every day

with standard balance weights. The weights used should be, at minimum, ANSI/ASTM Class 1 weights. These weights should be certified and supplied with a certificate of calibration. At the beginning of each workday, the balance should be checked with the standard, certified weights, using a series of weights that bracket the expected range of weighings for which the balance will be used. The calibration weighings should be recorded in a hardbound notebook that is reserved for balance calibration and maintenance.

If a balance is found to be out of calibration on any particular day, only weighings made in the past 24 hours are suspect. The balance can be taken out of service and be recalibrated, either in-house, or by a professional service engineer. The process of removing the balance from service, the service call, and reinstitution of balance use should be documented in the balance notebook. In addition to the chronology of events, a reason for actions taken needs to be recorded in the balance notebook. Certified weights can be purchased from almost any scientific supply house, or directly from the weight manufacturer's metrology department. It is recommended that two sets be purchased six months apart, because certified weights must themselves be recertified once a year, and while one set is out, balances still need to be checked on a daily basis. This daily check takes about 10 minutes and is well worth the time.

pH Meters

Another piece of laboratory equipment that is used rather frequently is the pH meter. Modern pH meters are supplied with manufacturer's instructions for calibration and use. These instructions should be followed as written.

pH meters should be calibrated with known buffer solutions. These buffer solutions can be purchased ready-made or can be prepared using buffer recipes found in publications such as the *United States Pharmacopoeia* (USP) or the *Merck Index*. A calibration notebook should be kept near the pH meter. pH meters are used to make measurements over a wide pH range. For calibration purposes, one needs to know whether the expected pH of a sample is less than 7.0 or greater than 7.0. If the pH is greater than 7.0, the meter is calibrated with pH 7.0 buffer and another buffer of higher pH, usually pH 10.0. For measurements below 7.0, buffers of pH 7.0 and 4.0 are generally selected. The reason for this dual calibration is that pH meter amplifiers are perfectly linear, but electrodes are not. The meter is set to pH 7.0 with the pH 7.0 buffer using the *calibrate* knob and with the *slope* control set to 100 percent. The *slope* control is used to set the pH meter to 4.0 or 10.0, depending on the calibration. This procedure matches the nonlinearity of an electrode to the linear pH meter amplifier. The meter should be recalibrated before each and every use and the results of that calibration recorded in the pH meter calibration book. Entries made in the calibration book should include date and time, buffer lot number, and expiration date, plus the percent slope required to adjust the meter.

If the meter cannot be sloped, for example, the value of the buffer cannot be dialed in with the *slope* control, it indicates a problem with either the meter, the buffer, or the electrode. At this point, the meter is taken out of service and corrective action, such as using fresh buffer or reconditioning or replacing the electrode, must be taken. The

corrective action sequence and reasons why should be documented in the pH meter notebook. Calibration of the pH meter before each use is recommended. However, the number of calibrations can be minimized by working in parallel and running groups of measurements at a time.

Spectrophotometers

UV/VIS and IR spectrophotometers are both used to varying degrees for chemical analysis, and can be used for both quantitative and qualitative work.

UV/VIS

UV/VIS instruments can be wavelength calibrated with NIST traceable holmium oxide filters, which are commercially available from instrument manufacturers. Professional service should occur on an annual basis. Inhouse checks with holmium oxide can be done at some suitable interval, perhaps quarterly. The service and calibration record should be recorded in a log book dedicated to UV/VIS spectrophotometers. If the instrument is taken out of service, corrective actions and reasons must also be documented.

For quantitative UV/VIS analyses, standards, the values of which bracket the expected value of the sample, should be run with each analysis. The results of these standards are used to confirm linearity, extinction coefficiency, and sensitivity. For qualitative work, the absorbance minima and maxima at certain wavelengths are compared for a sample versus a standard as a means of confirming identity. Any values for the standards that deviate from what is expected must be investigated, corrected, explained, and documented. The expected values are those defined in each lab's SOP, which should include acceptable ranges for standard parameters. Following these procedures will insure that problems such as weighing, sample transfer errors, or instrument problems are quickly identified.

IR Spectrophotometers

In the case of IR spectrophotometers, when used for quantitative work, the same rules apply as those for UV/VIS units. Infrared spectrophotometers are wavelength calibrated using a thin film of polystyrene. Since the polystyrene wavelength check takes only minutes, it should be done often, perhaps weekly or daily.

Chromatography Systems

Chromatographic systems, specifically gas chromatography (GC) and high performance liquid chromatography (HPLC) systems, are among the most widely used instruments in today's analytical laboratory. These systems are very powerful analytical tools because of their speed and specificity. But they are also complex systems consisting of many parts. Unlike a balance or pH meter, a chromatographic system is actually a combination of several instruments connected together to form an analytical system.

A gas chromatograph is made up of an injector, column oven, column, detector, and in many cases an autosampler. The HPLC system is made up of discrete autosamplers,

pumps, columns, column heaters (optional), and detectors, which are connected together to form complete HPLC systems. How then is the task of calibration and maintenance for these multicomponent systems done?

Rather than deal with each component as a discrete instrument, it makes more sense to treat the entire system as a single entity and to use calibration or checking techniques that define proper operation of that single system. This is accomplished in one of two ways.

The first method is to maintain a checklist of instrument conditions that must be checked at the beginning of each day. For gas chromatography this will include checking gas cylinders, changing injector septa, setting instrument parameters to settings specified in the method monograph, and balancing the detector amplifier output to zero once a steady baseline has been achieved. These items should be documented each day to show that they were done. For HPLC systems, this will include making sure that there is sufficient mobile phase, setting the instrument parameters to settings specified in the method monograph, such as flow rate and detector wavelength, and balancing the detector amplifier to zero once a steady baseline has been achieved. Once the physical checklist is done, it is time to measure system performance criteria.

HPLC Systems

The best performance test is system suitability as defined in the USP. System suitability is established by measuring the relative standard deviation among the results of five or more standard injections, done at the beginning of the chromatographic run. The relative standard deviation in most cases should be 2.0 percent or less. In addition, performance parameters, such as tailing factor, resolution factor, capacity factor (K), and response factors, need to be determined. If all four parameters (relative standard deviation, tailing factor, resolution factor, and response factors) are within limits specified in the applicable SOP, then the entire system is deemed acceptable and suitable for sample analysis. If any deviations are observed, a fully documented investigation, with corrective action, must be performed before resuming sample analysis, assuring that the entire system is operating as expected.

Gas Chromatographs

A standard mixture should be injected prior to the beginning of an analytical run. There needs to be a standard mixture for each different sample mixture. If the retention times, relative retention times, and response factors for the components of the mixture fall within acceptable limits, as defined by the applicable SOP, then the system is ready for analytical work. If there is a deviation from accepted values, a new standard mix should be prepared, and if the deviations still exist, then diagnostic troubleshooting on the system is in order. Daily checkout, downtime, solutions to problems, and explanations of deviations all need to be documented.

System suitability can be applied to gas chromatographs as well, but it isn't as critical, because GC columns are far more durable and consistent than HPLC columns. In general, if retention times, relative retention times, and response factors are within acceptable limits, the system will function as expected. System suitability testing for

GCs is somewhat like chicken soup—it might not help, but it can't hurt—and in the pharmaceutical industry, for example, it is often a regulatory requirement. The important thing is that retention times, detector response, reproducibility, and peak shapes are consistent and conform to a specified standard. This defines injector reproducibility, column performance, and detector response for an integrated analytical system.

In addition to the physical and performance checks described above, which are done prior to analysis of sample, it is necessary to monitor that performance throughout the entire analytical run. This is accomplished by injecting standards periodically, every five or six samples for instance, and at the end of the run, checking these performance criteria each time that a standard is injected. If standards fail to meet established criteria, such as minimum cumulative peak response percentage RSD, the system must be diagnosed and corrected, and all samples injected after the last *good standard* must be reinjected. Only samples that are bracketed by *good standards* should be accepted as valid.

Integrators and Data Systems

There is ever-increasing pressure to validate electronic integrators as a means of proving that they are reliable. It is recommended that integrators be validated on a one-time basis and that the validation be documented in a formal validation report.

There are two parts to integrator/data system validation: accuracy of the electronics in performing integrations of peak signals, and the accuracy of analytical calculations performed by software, based on those integrations. Integrator validation is best accomplished by use of a calibrated input source, such as an electronic peak/signal generator. Such a unit, which is calibrated and NIST (National Institute of Standards and Technology) traceable, is available from several sources.

The validation scheme should start by demonstrating that the output of each integrator is accurate. This is accomplished by inputting a calibrated signal into an integrator and showing that the area unit output corresponds to the microvolts per area unit specified by the manufacturer of the integrator. Once the electronics have been validated in this manner, a standard and sample chromatogram should be used to calculate an assay result manually, then comparing the result with that generated by the integrator/data system. By combining the electronics verification with a manual assay calculation, validation of both the integrator and the data system is achieved.

It is recommended that several sets of data be employed and that all calculation types normally used on a particular data system, such as internal standard, external standard, and area percent be subjected to a manual versus integrator calculation result comparison. It is good practice to check calculations on 12 or more random sample analyses for each calculation modality (external standard, internal standard, area normalization, area percent, etc.). The calculation verification part of the calibration should be repeated whenever a system software change is made (upgrade or revision).

Flame Atomic Absorption Spectrometers

Another commonly used laboratory technique is flame atomic absorption (AA), which is primarily used for quantitative analysis of inorganic cations. Typical examples are

determination of milliequivalents of potassium in potassium chloride tablets, determination of sodium, calcium, potassium, and magnesium in dialysate concentrates and determination of trace levels of arsenic, selenium, lead, and mercury in pharmaceutical active ingredient raw materials.

Atomic absorption units are essentially UV/VIS spectrophotometers whose sample "cell" is a flame (usually either 5 or 10 cm in length), and whose source is a hollow cathode lamp that emits atomic lines specific to one or more elements.

Flame AA units can be treated in a manner similar to UV/VIS units in terms of calibration, but the checkout procedure is somewhat different. Before use, gas supplies must be checked. Acetylene tanks must never be allowed to drop below 75 PSI in order to avoid contamination of the instrument gas box with acetone, which is a solvent for commercial acetylene. Also, nebulizers, tubing, and burner heads need to be checked to be sure that they are in good condition. The instrument is then set up as per manufacturer's operating instructions and analytical parameters are set as called for in the analytical monograph.

The value of each sample is determined by comparison to a standard curve, prepared from fresh standards, whose upper and lower values bracket the expected value of samples that are to be run. One standard should be interspersed approximately every five samples and at the end of the run. This procedure verifies linearity and stability of the standard curve (slope) during the analytical run. As with other calibrations, all setup and verification with standards needs to be documented.

Graphite furnaces, hydride generators, and inductively coupled plasma (ICP) units are somewhat different. They differ from flame units in sensitivity and/or ability to control interferences. However, the concepts of establishing linearity throughout the analytical working range and slope stability still apply.

Dissolution Apparatuses

One of the principal and most important pieces of equipment in today's pharmaceutical laboratory is dissolution equipment. There are currently two dissolution apparatuses listed in USP 23 under "Dissolution" <711> and seven apparatuses listed under "Drug Release" <724>, covering a wide variety of pharmaceutical dosage forms such as tablets, capsules, topicals, and time-release products. There are two principal parts to a dissolution apparatus calibration: physical and chemical.

The physical part involves checking spindle rotation, bath temperature, leveling of the unit, and spindle wobble. Rotation of each spindle should be individually checked using a tachometer or stopwatch, either of which must be calibrated to NIST-traceable sources. Several rotational speeds should be checked to bracket those used in routine work, such as 50, 75, 100 and 250 RPM. Bath temperature should be checked, using NIST-traceable calibrated thermometers, at several different temperatures that bracket those normally used, such as 30, 37 and 40 degrees centigrade. Levels can be easily checked using a carpenter's level. Shaft wobble is best checked using a machinist's run out gauge.

Chemical calibration is performed using USP prednisone and salicylic acid calibrator tablets versus USP prednisone and salicylic acid reference standards, respectively.

For these, follow the instructions supplied by the USP with individual lots of tablets. Percent release must fall within the ranges specified for each spindle of the dissolution apparatus. Note: USP calibrator tablets don't always pass, therefore, follow operational directions meticulously. If a calibrator tablet fails, check all physical parameters, make sure that vessels, paddles and/or baskets are scrupulously clean, and repeat the test until all spindles pass. If the problem still persists, try using calibrator tablets of the same lot but from a different bottle. The entire calibration process, both physical and chemical, must be thoroughly documented.

The reader is strongly encouraged to read the USP carefully in reference to drug release techniques and to be especially attentive to maintenance, usage, and calibration of each dissolution apparatus in the laboratory. Dissolution is an FDA "hot button," and should not be treated lightly.

Miscellaneous Equipment

Ovens, refrigerators, incubators, muffle furnaces, and water baths, or any other controlled temperature device or area should have a log book in which calibration data and/or daily temperature readings are entered. In some cases, such as controlled-temperature storage areas used for stability sample storage, it is important to have a 24-hour recording chart that measures temperature (and often humidity) continuously.

Thermometers used to measure *any* temperature must be calibrated periodically against NIST-traceable thermometers in order to assure their reliability and accuracy. Calibrations must be documented. Certified, NIST-traceable thermometers can be obtained from any scientific supply house. As with certified weights, thermometers need to be periodically recertified. Note: Use of an outside calibration service for ovens, furnaces, refrigerators, environmental chambers, water baths, and thermometers can often be cost effective and should be seriously considered in lieu of in-house calibration.

Top-loading balances, used for rough weighings, should have outside servicing at the same frequency as analytical balances. However, since these are mostly used for general rather than accurate weighings, it is usually not necessary to do daily checks with certified weights. Instead, depending upon usage, monthly or weekly checks with larger weights can be performed, using NIST (formerly National Bureau of Standards [NBS]) Class P weights, which can be obtained individually and are available in denominations of up to 30 kg.

Automatic titrators that utilize a piston-type buret need to have their piston(s) calibrated periodically to insure that delivery of titrant is linear and meets Class-A accuracy or better. This can be accomplished by dispensing water at a known temperature in small increments (0.5 ml or 1.0 ml) across the entire volume of the piston buret. Using the density of water at the temperature measured, actual volume delivered can be calculated for each volume increment dispensed. Plot of actual volume versus observed volume should yield a high linear correlation coefficient (0.9999 minimum). In addition, the accuracy of each volume delivered should meet or exceed Class-A tolerances.

There are other pieces of apparatus that might be used in an analytical laboratory in addition to the more common ones just described. These include polarimeters and

sample preparation devices, such as extractors and head-space units. Whatever the case, some traceable standard or performance parameters must be utilized to assure accuracy and reliability.

CHEMICAL EQUIPMENT

Analytical Standards

A critically important foundation for all analytical work is the integrity of the standards used. For spectroscopy and chromatography, a primary standard of known, certified purity must be used as the reference against which all samples are measured. Such standards can usually be purchased from commercial sources, such as the United States Pharmacopoeial Convention or scientific supply houses that specialize in high purity chemicals, suitable for use as primary standards. When such standards are purchased, they must be logged in by recording the date received, lot number, purity, and expiration date (if any). This information should be kept in a standards logbook.

The standards, when not in use, must be stored under conditions specified by the supplier or by the analytical monograph. This could be room temperature, desiccated, refrigerated, or even frozen. The USP, for example, specifies storage conditions for each standard that it sells. It also specifies any treatment needed prior to use such as, "*Dry at 105°C for 2 hours*." Access to standards, if possible, should be restricted to supervisors, who will issue standards to analysts as needed. When the analyst is finished, the standard must be returned to storage. The issuing and return of standards to storage should also be documented.

Primary standards are expensive and can cause a financial strain on many laboratories. In order to control costs, these laboratories will often use small weighings standards (10 or 20 milligrams) that can compromise accuracy. For frequently run analyses, it is better to use a house standard. A house standard can be prepared by checking the purity of an in-house lot of sample against the primary standard. The purity check should be repeated several times, until acceptable reproducibility is obtained on at least three separate assays, in which separate weighings of primary standard and prospective house standard for each assay have been used. A typical scenario might be as follows:

> *Accurately weigh three separate portions of a USP reference standard and dissolve them each in water to obtain separate standard solutions; each should have a concentration of about 0.5 mg/ml. Similarly prepare three separate solutions of house standard. Using the first standard solutions as the calibration standard, assay the second and third standard solutions plus the three house standard solutions against it. For chromatographic procedures (usually the case), be sure to comply with all system suitability requirements. The results of the house standard certification are acceptable if the second and third standard solutions assay within ±1 percent of the stated purity versus the calibration standard, and if the relative standard deviation between the three house standard assay results is no greater than 1.0 percent.*

One way to determine acceptable reproducibility is to set a maximum percent relative standard deviation limit on the results of the three house standard assays (1 percent or less is recommended). Once the purity of the house material has been determined with certainty, it can be used as an analytical standard. As with the primary standard, all work must be documented, particularly the raw data relating to the certification of the house material as an analytical standard. Special care must be taken to record expiration and recertification dates so that the house standard will not be used beyond its expiration (six months is recommended). For titration work, commercially available titrimetric primary standards are both pure and cost effective.

Reagents

All chemicals purchased by the laboratory should be logged in and the date of receipt, lot number, and expiration date recorded. It is extremely important that a routine inspection of reagent logs be done (monthly, for example) to make sure that out-of-date reagents are removed from the laboratory and discarded. This also applies to test solutions, purchased buffer solutions, and other prepared solutions. Each should be labeled with a date of preparation (or date of receipt) and an expiration date. In addition, for reagents prepared in the laboratory (such as test solutions), a notebook reference to the preparation should be part of the documentation.

Volumetric Solutions

The preparation and standardization of volumetric solutions also needs to be thoroughly documented. The items that need to be recorded are the lot number and expiration date of the materials used to prepare the solution, the lot number and expiration date of the primary standard used to perform the standardization, and the raw data for the standardization, including weights, titers, calculations, and results. Standardizations should be performed in triplicate with a precision (not percentage RSD) of 0.5 percent or better, where precision is defined as the average deviation from the mean divided by the mean times 100. For example:

1. Three normality results are 0.1025N, 0.1019N, and 0.1020N.
2. The mean is 0.1021N.
3. Individual deviations from the mean are:

   0.1025 – 0.1021 = 0.0004

   0.1021 – 0.1019 = 0.0002

   0.1021 – 0.1020 = 0.0001
4. Average deviation from mean = 0.0002.
5. Precision = $\left\{ \frac{0.0002}{0.1021} \right\} \times 100 = 0.229\%$

The final volumetric solution needs to be properly stored and affixed with a label that states the name of the solution, the exact normality, date of standardization, expiration date, and notebook reference to raw data on preparation and standardization.

As with any other reagent, expiration date checking should be done regularly. In the case of volumetric solutions, if a significant amount of solution remains after the expiration date, the solution can usually be restandardized. Thus, the expiration date of volumetric solutions is often referred to as the restandardization date. Note: Even store-bought standardized solutions should be standardized in-house.

Laboratory DI Water

Deionized water used for analytical work must be chemically pure. In general, particularly for use in HPLC work, water meeting the criteria for purified water, USP should be used (Type I water). Most laboratory water systems use in-line conductivity meters to measure the resistance of the purified water put out by the system. The reading should be recorded daily. In addition, a regular check of conductivity (monthly) using a calibrated conductivity meter should be done to verify readings obtained from the in-line conductivity meter. Also record any deviation or corrective action taken to remedy any problems such as changing membranes, cartridges and filters, or sanitizing the system.

In addition to conductivity, the total organic carbon (TOC) needs to be checked periodically. Fortunately, USP 24 has seen the light and provided a loophole for getting around the absurd USP-style TOC test that has plagued the pharmaceutical industry for the last few years. The new USP 24 allows for use of "alternative technologies," which in plain English means "try something else that actually works." This author suggests chemical oxygen demand (COD) or even the original oxidizable substances test as reasonable alternatives.

In terms of operating cost, low volume water for analytical use (two or less cartridge changes per year) can usually be handled by a stand-alone DI system that consists of a 4-cartridge train consisting of pretreatment, high-purity ion exchange, ultra-high purity ion exchange, and organics removal. For high-volume water usage, particularly for labs doing frequent dissolution testing, an RO/DI system is preferable. The reverse osmosis (RO) unit will provide high volumes of pure water, which is then fed through the DI unit for conversion to Type I Grade. When an RO unit is used, DI cartridges will last an exceptionally long time, thereby reducing cost over time. A typical RO unit will give return on investment in less than two years versus cost of replacement of DI cartridges.

FINAL NOTE

For each piece or type of equipment needing calibration and/or maintenance, there should be standard operating procedures (SOPs) in place that include a detailed description of equipment to be calibrated, frequency of calibration/maintenance, the

person responsible for implementation, details or components of the actual calibration/maintenance, documentation requirements, and actions to be taken in the event of a calibration failure.

Maintaining current SOPs, having documented training on those SOPs, following those SOPs as written, plus strict adherence to scheduled calibration and maintenance, is the key to a successful laboratory instrument maintenance and calibration program.

9

Laboratory Water and Water Purification Systems

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OVERVIEW

This chapter provides an overview of water quality for laboratory use, a description of the types of systems installed for purifying water for laboratory use, and a discussion of some key critical control points in laboratory water systems. Maintenance, sampling and testing, and ongoing awareness of the limitations of a "benchtop," turnkey-type water purification system are important parts of assuring the quality attributes of water.

KEY WORDS

- Water purification
- Resistivity
- Sampling plan
- Trend analysis
- Bacterial retentive filter
- Standard operating procedure (SOP)
- Calibration

Every laboratory has multiple uses of water, some critical to testing outcomes and others not so critical. Water used for testing as a control, a reagent, a diluent, or for ultra-cleaning of glassware, is usually purified to a standard relevant to its intended use. A variety of water standard specifications have been written. Some are shown in Tables 9.1, 9.2, 9.3, 9.4., and 9.5.

Table 9.1 EPA National Primary Drinking Water Standards.

Contaminant	MCLG[1] (mg/L)[4]	MCL[2] or TT[3] (mg/L)[4]
Inorganic Chemicals		
Antimony	0.006	0.006
Arsenic	none[5]	0.05
Asbestos (fibers>10 micrometers)	7 million fibers per Liter (MFL)	7 MFL
Barium	2	2
Beryllium	0.004	0.004
Cadmium	0.005	0.005
Chromium (total)	0.1	0.1
Copper	1.3	Action Level = 1.3; TT[6]
Cyanide (as free cyanide)	0.2	0.2
Fluoride	4.0	4.0
Lead	zero	Action Level = 0.015; TT[6]
Mercury (Inorganic)	0.002	0.002
Nitrate (measured as Nitrogen)	10	10
Nitrite (measured as Nitrogen)	1	1
Selenium	0.05	0.05
Thallium	0.0005	0.002
Organic Chemicals		
Acrylamide	zero	TT[7]
Alachlor	zero	0.002
Altrazine	0.003	0.003
Benzene	zero	0.005
Benzo(a)pyrene	zero	0.0002
Carbofuran	0.04	0.04
Carbon tetrachloride	zero	0.005
Chlordane	zero	0.002
Chlorobenzene	0.1	0.1
2,4-D	0.07	0.07
Dalapon	0.2	0.2
1,2-Dibromo-3-chloropropane (DBCP)	zero	0.0002
o-Dichlorobenzene	0.6	0.6
p-Dichlorobenzene	0.075	0.075
1,2-Dichloroethane	zero	0.005
1-1-Dichloroethylene	0.007	0.007
cis-1, 2-Dichloroethylene	0.07	0.07
trans-1,2-Dichloroethylene	0.1	0.1
Dichloromethane	zero	0.005
1-2-Dichloropropane	zero	0.005
Di(2-ethylhexyl)adipate	0.4	0.4
Di(2-ethylhexyl)phthalate	zero	0.006
Dinoseb	0.007	0.007
Dioxin (2,3,7,8-TCDD)	zero	0.00000003
Diquat	0.02	0.02
Endothall	0.1	0.1
Endrin	0.002	0.002
Epichlorohydrin	zero	TT[7]
Ethylbenzene	0.7	0.7
Ethylene dibromide	zero	0.00005
Glyphosate	0.7	0.7
Heptachlor	zero	0.0004
Heptachlor epoxide	zero	0.0002
Hexachlorobenzene	zero	0.001
Hexachloro-cyclopentadiene	0.05	0.05
Lindane	0.0002	0.0002
Methoxychlor	0.04	0.04
Oxamyl (Vydate)	0.2	0.2
Polychlorinated biphenyls (PCBs)	zero	0.0005
Pentachlorophenol	zero	0.001
Picloram	0.5	0.5
Simazine	0.004	0.004
Styrene	0.1	0.1

(continued)

Contaminant	MCLG[1] (mg/L)[4]	MCL[2] or TT[3] (mg/L)[4]
Tetrachloroethylene	zero	0.005
Toluene	1	1
Total Trihalomethanes (TTHMs)	none[5]	0.10
Toxaphene	zero	0.003
2,4,5-TP (Silvex)	0.05	0.05
1,2,4-Trichlorobenzene	0.07	0.07
1,1,1-Trichloroethane	0.20	0.2
1,1,2-Trichloroethane	0.003	0.005
Trichloroethylene	zero	0.005
Vinyl chloride	zero	0.002
Xylenes (total)	10	10
Radionuclides		
Beta particles and photon emitters	none[5]	4 millirems per year (mrem/yr)
Gross alpha particle activity	none[5]	15 picocuries per Liter (pCi/L)
Radium 226 and Radium 228 (combined)	none[5]	5 pCi/L
Microorganisms		
Giardia lamblia	zero	TT[8]
Heterotrophic plate count (HPC)	N/A	TT[8]
Legionella	zero	TT[8]
Total Coliforms (including fecal coliform and *E. coli*)	zero	5.0%[10]
Turbidity	N/A	TT[8]
Viruses (enteric)	zero	TT[8]

Notes

1. Maximum Contaminant Level Goal (MCLG)—The level of a contaminant in drinking water below which there is no known or expected risk to health. MCLGs allow for a margin of safety and are non-enforceable public health goals.
2. Maximum Contaminant Level (MCL)—The highest level of a contaminant that is allowed in drinking water. MCLs are set as close to MCLGs as feasible using the best available treatment technology and taking cost into consideration. MCLs are enforceable standards.
3. Treatment Technique (TT)—A required process intended to reduce the level of a contaminant in drinking water.
4. Units are in milligrams per Liter (mg/L) unless otherwise noted.
5. MCLGs were not established before the 1986 Amendments to the Safe Drinking Water Act. The standard for this contaminant was set prior to 1986. Therefore, there is no MCLG for this contaminant.
6. Lead and copper are regulated using a Treatment Technique which requires systems to control the corrosiveness of their water. The action level serves as a trigger for water systems to take additional treatment steps if exceeded in more than 10% of tap water samples. For copper, the action level is 1.3 mg/L, and for lead is 0.015mg/L.
7. Each water system must certify, in writing, to the state that when it uses acrylamide and/or epichlorohydrin to treat water, the combination (or product) of dose and monomer level does not exceed the levels specified, as follows: Acrylamide = 0.05% dosed at 1 mg/L (or equivalent); Ephichlorohydrin = 0.01% dosed at 20 mg/L (or equivalent).
8. The Surface Water Treatment Rule requires systems using surface water or ground water under the direct influence of surface water to (1) disinfect their water, and (2) filter their water or provide the same level of treatment as those who filter. Treatment must reduce the levels of *Giardia lamblia* (parasite) by 99.9% and viruses by 99.99%. *Legionella* (bacteria) has no limit, but EPA believes that if *Giardia* and viruses are inactivated, *Legionella* will also be controlled. At no time can turbidity (cloudiness of water) go above 5 nephelometric turbidity units (NTU) [systems that filter must ensure that the turbidity is no higher than 1 NTU (0.5 NTU for conventional or direct filtration) in at least 95% of the daily samples for any single month]; HPC—no more than 500 bacterial colonies per milliliter.
9. Legionnaire's disease occurs when aerosols containing *Legionella* are inhaled by susceptible persons, not when people drink water containing *Legionella*. (Aerosols may come from showers, hot water taps, whirlpools, and heat rejection equipment such as cooling towers and air conditioners.) Some types of *Legionella* can cause a type of pneumonia called Legionnaire's Disease. *Legionella* can also cause a much less severe disease called Pontiac Fever. The symptoms of Pontiac Fever may include muscle pain, headache, coughing, nausea, dizziness, and other symptoms.
10. No more than 5.0% of samples may be total coliform-positive in a month. (For water systems that collect fewer than 40 routine samples per month, no more than one sample may be total coliform-positive during a month). Every sample that has total coliforms must be alalyzed for either *E. coli* or fecal coliforms to determine whether human or animal fecal matter is present (fecal coliform and *E. coli* are part of the total coliform group).
11. Fecal coliform and *E. coli* are bacteria whose presence indicates that the water may be contaminated with human or animal wastes. Disease-causing microbes (pathogens) in these wastes can cause diarrhea, cramps, nausea, headaches, or other symptoms. These pathogens may pose a special health risk for infants, young children, and people with severely compromised immune systems.

Table 9.2 NCCLS reagent water specifications.

	Type I	Type II	Type III
Maximum microbial content, colony forming units per mL (CFU/mL)	10	1000	NS
pH	NS	NS	5.0–8.0
Minimum resistivity, megohm • centimeter (megohm • cm 25°C)	10 (inline)	1.0	0.1
Maximum silicate mg/L SiO2	0.05	0.1	1.0
Particulate matter*	0.22-μm filter	NS	NS
Organic contaminants*	Activated carbon or distillation or reverse osmosis	NS	NS

*This is a purification process requirement and is not measured by the end user.
NS: not specified.

From C3–A3, "Preparation and Testing of Reagent Water in the Clinical Laboratory; Approved Guideline—Third Edition," Wayne, PA; NCCLS, 1997, with permission.

Table 9.3 ASTM standard specification for reagent water.

	Type I[1]	Type II[2]	Type III[3]	Type IV[4]
Electrical conductivity, max, μS/cm at 298 K (25°C)	0.056	1.0	0.25	5.0
Electrical resistivity, min, MΩ-cm at 298 K (25°C)	18	1.0	4.0	0.2
pH at 298 K (25°C)	[A]	[A]	[A]	5.0–8.0
Total organic carbon (TOC), max, μg/L	100	50	200	no limit
Sodium, max, μg/L	1	5	10	50
Chlorides, max, μg/L	1	5	10	50
Total silica, max μg/L	3	3	500	no limit

Microbiological contamination—When bacterial levels need to be controlled, reagent grade types should be further classified as follows:

	Type A	Type B	Type C
Maximum heteretrophic bacteria count	10/1000 mL	10/100 mL	100/10 mL
Endotoxin, EU/ml[B]	<0.03	0.25	not applicable

[A] The measurement of pH in Type I, II, and III reagent waters has been eliminated from this specification because these grades of water do not contain constituents in sufficient quantity to significantly alter the pH.

[B] EU = Endotoxin Units.

1. Type I grade of reagent water shall be prepared by distillation or other equal process, followed by polishing with a mixed bed of ion exchange materials and a 0.2-μm membrane filter. Feedwater to the final polishing step must have a maximum conductivity of 20 μS/cm at 298 K (25°C).
2. Type II grade of reagent water shall be prepared by distillation using a still designed to produce a distillate having a conductivity of less than 1.0 μS/cm at 298 K (25°C). Ion exchange, distillation, or reverse osmosis and organic adsorption may be required prior to distillation if the purity cannot be attained by single distillation.
3. Type III grade of reagent water shall be prepared by distillation, ion exchange, continuous electrodeionization reverse osmosis, or a combination thereof, followed by polishing with a 0.45-μm membrane filter.
4. Type IV grade of reagent water may be prepared by distillation, ion exchange, continuous electrodeionization reverse osmosis, electrodialysis, or a combination thereof.

Table 9.4 Purified water.

H_2O 18.02

Purified Water is water obtained by a suitable process. It is prepared from water complying with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations or comparable regulations of the European Union or Japan. It contains no added substance.

Notes—Purified Water is intended for use as an ingredient in the preparation of compendial dosage forms. Where used for sterile dosage forms, other than for parenteral administration, process the article to meet the requirements under *Sterility Tests* <71>, or first render the Purified Water sterile and thereafter protect it from microbial contamination. Do not use Purified Water in preparations intended for parenteral administration. For such purposes use Water for Injection, Bacteriostatic Water for Injection, or Sterile Water for Injection. The tests for *Total organic carbon* and *Conductivity* apply to Purified Water produced on site for use in manufacturing. Purified Water packaged in bulk for commercial use elsewhere meets the requirements of all of the tests under *Sterile Purified Water*, except *Labeling* and *Sterility* <71>.

USP Reference standards <11>—*USP 1,4–Benzoquinone RS. USP Sucrose RS.*

Total organic carbon <643>: it meets the requirements.

Water conductivity <645>: it meets the requirements.

Table 9.5 Water for injection.

Water for injection is water purified by distillation or by reverse osmosis. It is prepared from water complying with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations or comparable regulations of the European Union or Japan. It contains no added substance.

Note—Water for Injection is intended for use in the preparation of parenteral solutions. Where used for the preparation of parenteral solutions subject to final sterilization, use suitable means to minimize microbial growth, or first render the Water for Injection sterile and thereafter protect it from microbial contamination. For parenteral solutions that are prepared under aseptic conditions and are not sterilized by appropriate filtration or in the final container, first render the Water for Injection sterile and, thereafter, protect if from microbial contamination. The tests for *Total organic carbon* and *Conductivity* apply to Water for Injection produced on site for use in manufacturing. Water for Injection packaged in bulk for commercial use elsewhere meets the requirements of all the tests under *Sterile Purified Water*, except *Labeling*.

USP Reference standards <11>—*USP Endotoxin RS. USP 1, 4-Benzoquinone RS. USP Sucrose RS.*

Bacterial endotoxins <85>—It contains not more than 0.25 USP Endotoxin Unit per mL.

Other requirements—It meets the requirements of all of the tests under *Purified Water*.

Deionization, reverse osmosis, distillation, ultraviolet radiation, and ultrafiltration are all methods of water purification that in different combinations can be purchased in a benchtop design for a laboratory. A glossary is at the end of this chapter to help clarify some of the terms used in water treatment technology. The benchtop design was intended to further purify (or "polish") water originating from any source, and provide a minimal flow or quantity of available treated water.

Modern laboratory benchtop water purification systems are commonly designed as turnkey-type systems with multiple capabilities, such as: combinations of organic removal, removal of chlorine, deionization, measurement of resistivity and temperature, and bacterial reduction. Other design considerations that are available are ultrafiltration and distillation, which remove additional contaminants as required by the intended use of the water. A basic and very common system design includes removable cartridges for carbon filtration, deionization and final filtration (0.22 micron). The most technologically advanced systems of the new century have electrodeionization (EDI) in place of resin cartridges. Most new turnkey systems have monitoring capabilities for temperature and resistivity (or conductivity). Since resistivity is a measurement of the ionic

removal capability of a purification system, it has become a critical online design feature from the late 1990's. Some resistivity monitors include temperature compensation as well.

It is important that a laboratory be consistent in the use of terms such as "purified water" or "reagent-grade water" and define them in its written procedure(s). This will prevent confusion between the different compendial terms for purified water that already exist. A water polishing system, benchtop or wall-mounted in a laboratory, will "purify" water from any original source-feeding system. Some laboratories use potable water (meeting local drinking water standards) from municipalities or a well as the source water to the polishing system. Many laboratories in regulated industries use deionized water or softened water as the source water. The quality attributes of the source water should be known, from internal or external testing, to ensure that a laboratory water purifying system is chosen with a design that can appropriately produce water of the desired quality.

A standard operating procedure (SOP) should be written for each system. The SOP should include the system identification, design and operation, intended use and quality attributes measured, frequency of sampling, calibration frequency, and a preventative maintenance schedule. It is important that the procedure state, in sufficient detail, how the system is actually used for drawing water. For example, rinse or flush volume/time is an important detail. Another detail might be stating what the resistivity (if available) should be before drawing the water for use.

Sampling water is a critical activity and must be given due consideration when writing procedures. It is very important that a sampling plan and technique is chosen that has a useful purpose. A sampling plan for determining the consistency of water quality produced by a benchtop system can be quite different than sampling water intended for immediate use. The effect of a bacterial filter on microbial bioburden in water can be indicated by comparing samples from before and after the filter. Quality of water for use is commonly checked by sampling water by the identical technique used for drawing water. If a bacterial filter is used when drawing water for use, then it should also be in place when sampling the water. If water is stored in a carboy before use, then carboy water should be sampled and tested previous to actual use. Consistency of water quality produced by the system can be trended from samples taken daily or weekly. As you can see, a number of different sampling plans are possible. The best approach is to match your sampling plan with its intended purpose, logically and scientifically.

A logbook must be used to record the date and person performing calibrations and preventative maintenance, including sanitization and replacement of cartridges and filter(s). The logbook must be kept in a safe, waterproof area near the system. Logbook entries should be dated and initialed, and the details written legibly.

Calibration should occur at a frequency to ensure that readings of water quality are accurate for water usage frequency. Each calibration should be recorded in the logbook. The calibration date, recalibration date, and system identification number should also be conspicuously visible on the system using waterproof labels or something similar.

Analytical and/or microbiological water test results should be kept in a file or laboratory notebook. A periodic review or trend analysis of these results will help determine if the frequency of cartridge and filter replacement or sanitization is adequate for the desired quality of the water.

Some quality concerns are based on system design and frequency of use. Stagnant water in cartridges prior to filtration can be a source of microbial proliferation and reduce the effectiveness of bacterial retentive filters. Hose extensions, added for convenience, can develop microbial or chemical problems if not rinsed, sanitized, or replaced frequently. Be aware that bacterial retentive filters used in laboratory water systems will only be effective if maintained well and replaced at an appropriate frequency. That frequency can be determined by trend analysis of routine microbial test results. Devices for dispensing water should prevent backflow at the use-tip and minimize stagnant water at any point past the final filtration when the system is not in use. If ultraviolet lamps exist, the hours of usage time should be tracked to assure that lamps are replaced prior to reduction of their effectiveness. Manufacturers usually provide criteria for replacement.

Some water systems are subsequently designed in a laboratory to fill a carboy for routine as-needed use. Purified water can lose many of its acceptable attributes when stored in a nonairtight container. Take into account that water stored in a container (or even a dispensing container) that is not airtight can lose resistivity over time, and become subject to post-treatment microbial contamination. A study can be performed to determine how long the stored water maintains acceptable attributes that are critical to its use. Giving the stored water an expiration date would help protect the laboratory from using out-of-specification water. The best practice, although maybe not as efficient, is to use water directly from the treatment system as immediately as possible.

A RECAP OF KEY AUDIT POINTS

- Written procedure of system operation, complete and detailed.
- Calibration label, complete and up-to-date.
- Logbook records, complete and up-to-date.
- Cartridge/filter replacement frequency meets SOP.
- Ultraviolet lamp replacement frequency.
- Test results on file indicate that quality criteria are being met per intended use.
- If water storage container is used, expiration dating is followed.

An appropriately designed, well-maintained water system will consistently produce water meeting the required quality attributes for its intended use(s). How it is used, or how the water is dispensed, is just as critical as the water quality.

A MINI-GLOSSARY OF WATER PURIFICATION TERMS

bacterial retentive filter—a membrane filter capable of removing bacteria by adsorption or sieving through membrane pores; usually 0.22 microns pore size distribution or smaller.

carbon filter—carbon/charcoal acts as a filter and adsorbant for removal of organics and free chlorine.

conductivity—ability to transmit electricity; inverse of resistivity; measured in microSiemens/cm or micromhos/cm.

deionization—ionized salts in water are exchanged for hydrogen or hydroxyl ions which are attached to ion exchange resins; hydrogen ions exchange with cations, and hydroxyl ions exchange with anions.

distillation—the act of boiling water and condensing the steam on a cooled surface, then collecting and storing the condensate; "most" contaminants remain behind and do not pass to the distillate.

electrodeionization—combines electrolysis and ion exchange to deionize water while continuously regenerating the ion exchange resins.

ion exchange—a process in which ions are exchanged by adsorption from a solution (water) for equivalently charged ions attached to bead-like materials (resins); two common types of ion exchange are softening and deionization.

multimedia filter—granular adsorbant materials or a cartridge filter used to remove solid contaminants, as a pretreatment step before deionization.

potable water—drinking water as specified by the EPA National Primary Drinking Water Standards.

resistivity—property of a substance to resist flow of electricity; inverse of conductivity; measured in ohm-cm.

reverse osmosis—membrane-type method of removing 90–99 percent of all water contaminants; pressure is applied to counteract osmotic pressure across the membrane, thus driving pure water from a concentrated solution, and collecting it downstream.

softening—reducing water hardness by exchanging sodium ions for calcium or magnesium ions.

ultrafiltration—membrane filters produce a molecular sieve-type removal of macromolecules such as micro-organisms, endotoxins, and colloids.

ultraviolet irradiation—ultraviolet (UV) light is generated at 185 nm and 254 nm wavelengths to photo-oxidize and reduce total organic contaminants; UV generated at 254 nm wavelength has bactericidal properties, by reacting with and damaging microbial cell DNA (deoxyribonucleic acid).

10

Methods Validation

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OVERVIEW

It is the responsibility of the analytical scientist to implement appropriate controls on methods and associated laboratory activities to ensure that test results accurately reflect the quality of the sample being analyzed. The value of analytical method validation is to demonstrate the effectiveness of these controls; to characterize the extent of variability or bias in a test procedure. Analytical methods are typically validated for selectivity (or specificity), linearity (or working concentration range), accuracy, precision, reproducibility (ruggedness), and robustness. In addition, for determinations involving low levels of analyte, lower limits of quantitation (LOQ), and/or detection (LOD) must also be established. In this chapter a general description of these validation tests is included, followed by an example of how to perform the validation studies. Application to the validation of methods for various analyses and requirements for revalidation of methods as changes occur are also discussed.

KEY WORDS

- Analytical method validation
- Selectivity
- Specificity
- Linearity
- Working concentration range
- Accuracy
- Precision
- Reproducibility
- Ruggedness
- Robustness
- Limit of quantitation (LOQ)
- Limit of detection (LOD)
- Validation test plan
- Acceptance criteria
- Change control

INTRODUCTION

The validation of analytical methods is a requirement in many regulated industries, and therefore is the focus of attention for scientists and quality assurance professionals throughout the drug, food, and cosmetic businesses. As a consequence, validation is often looked at as regulatory-driven and not as an analytical or scientific responsibility. However, from a practical perspective, validation of an analytical method makes good scientific sense in building confidence in a measurement. The data generated by analytical scientists may rightfully be questioned by the customer or quality assurance auditor, particularly if a result is outside of specifications or normal ranges: If the result is low, perhaps the component of interest was not extracted thoroughly. If the result is high, perhaps a bias was introduced during analysis. If lot-to-lot results for an analysis are variable, perhaps the method variability is high. Looked at from this perspective, it is the responsibility of the analytical scientist to proactively ask these questions, challenging all phases of the analysis process. If methods are properly validated, analytical staff should be able to respond to customer comments on methods with hard supportive data.

Consider the following series of six stability results, not presented in any specific order:

100.8% 97.8% 93.3% 99.3% 102.3% 96.3%

Asked to interpret these results, an analytical scientist may remark (correctly) that an interpretation is not possible without knowing the sample history—are these the results for various stability time points? Multiple samples for the same time point? And so on. Without this knowledge, several "explanations" for the results are possible, including but not limited to the following:

1. Six repeat tests for the same sample, demonstrating method (or within-sample) variability;
2. Six tests on the same sample, each performed by a different analyst or laboratory, demonstrating analyst-to-analyst or lab-to-lab variability;
3. Six results for different stability time points, demonstrating variable recovery of the analyte from the sample matrix; or
4. If data is ordered from highest to lowest, these could be test results for six stability time points, demonstrating sample instability.

These explanations reflect just a few of the product and method variables that can affect test results. In the first three instances, the results may not truly reflect the sample quality due to analytical factors. It is the responsibility of the analytical scientist to control the method or laboratory aspects of testing so that results accurately reflect the sample being analyzed. The value of analytical method validation is to demonstrate the effectiveness of these controls, or at least to characterize the extent of variability of or bias in the test procedure. Validation results (for example, analyst-to-analyst or lab-to-lab) could help to identify details of methods that need clarification or greater detail, or identify specific method factors that must be controlled to achieve reproducible results (for

example, filter selection, shaking times, etc.). For the third explanation listed, variable results are due to poor recovery from the sample matrix. This example also demonstrates the need for a constant reevaluation of the suitability of a method. Alternatively, it may be that these physical changes in the test material are themselves unacceptable. In either event, a thorough understanding of the analytical factors affecting the test results is essential. Finally, the fourth explanation points out the need for careful assessment of the scope of a method or the need for additional supportive methods. If an assay result has decreased more than 7 percent, are the products of degradation identified and are they quantitated? Is the method for breakdown products validated for these determinations? Is mass balance achieved? If not, is there an understanding of why? All of these questions need to be answered by the chemist (or biologist) responsible for the analytical procedure.

Guidelines for the validation of analytical methods have been published in a variety of forums. Many of these are now accessible through the internet. Guidance regarding the validation of methods for pharmaceutical products can be found in the current USP,[1,2] in FDA guidelines,[3–6] as well as regulatory guidelines from Europe[7] and Canada.[8] Consensus texts on method validation definitions and terminology[9] and methodology[10] have also been issued from the International Conference on Harmonisation. Related guidance regarding validation of analytical procedures for the testing of bioanalytical samples has also been published.[11–18] While many literature references are available for the validation of chromatographic methods, discussions of validation principles applied to capillary electrophoresis,[19–21] other nonchromatographic procedures,[22–24] biological samples,[17,25–26] biologically-based tests such as immunoassays,[18] or microbiological[27–28] assays have also been published. Each of these sources provides definitions of terms useful in carrying out methods validation. While the details of the method validation activities for these various types of methods will differ, the principles of validation remain the same. In each instance, validation requirements must be matched to the scope and objectives of the method under evaluation.

The discussion below is intended to apply to most validation studies. A general description of each validation test is described, followed by an example of how to perform the validation study. For clarity, examples in the text focus on methods used for testing pharmaceutical products, where regulatory scrutiny is high. Although specific approaches to completing methods validation are described, many more alternatives exist. The chemist and laboratory manager should agree on the appropriate approach to be followed for a specific method before validation studies begin. As described later in this chapter, not all aspects of validation listed below are applicable to individual methods under evaluation.

VALIDATION TERMINOLOGY AND REQUIREMENTS

As required by compendial and regulatory guidelines, analytical methods are typically validated for selectivity (or specificity), linearity (or working concentration range), accuracy, precision, reproducibility (ruggedness), and robustness. In addition, for

determinations involving low levels of analyte, limits of quantitation (LOQ) and/or detection (LOD) must also be established. Selectivity, linearity, and LOD/LOQ studies primarily measure the suitability of equipment set-up and use, including the reagents, chromatographic columns, and instrumentation used. The accuracy (recovery) assessment can be viewed as a measure of the effectiveness of the sample preparation process. Precision, reproducibility (ruggedness), and robustness studies assess variability in both equipment and test preparation aspects of a method. Definitions of these terms are provided in the USP, FDA, and ICH guidelines.[1,5,9] Their application to the validation of methods for various analyses is discussed below. For pharmaceutical products, the validation tests required for various analytical procedures have been identified.[1,9]

Selectivity

Selectivity or *specificity* is the ability of a procedure to measure or distinguish the analyte of interest in the presence of other components that may be present in the sample matrix. Chromatographic and other techniques that rely on separation of components are generally referred to as selective. In contrast, a specific test will measure one analyte to the exclusion of others, the ultimate level of specificity. An example of a specific test may be a colorimetric reaction in which the reagent reacts with only one component of a mixture, or an infrared identification test, for which specific absorption bands must be matched. Immunoassay procedures are examples of biologically-based procedures intended to be specific;[18] the degree of cross-reactivity, if any, will need to be established during validation. Selectivity or specificity is demonstrated by testing the components of the sample matrix, chemically (or biochemically) related substances, potential degradation products of the analyte and, as appropriate, impurities generated in the synthesis or preparation of the analyte. Consideration should also be given to the impact of matrix degradation under conditions of normal sample or product storage and handling. If the sample matrix is of biological origin, the potential for interspecies or within species variability must be considered.

To perform the selectivity assessment, samples of potentially interfering substances are prepared for analysis in the amounts or concentrations that will be present during routine analysis. For example, for a test procedure that specifies that the content of 10 dosage units be used for an assay potency test, the selectivity assessment is performed by preparing a mixture of the components of the drug product formulation (minus the drug substance) in amounts equivalent to 10 dosage units. This sample is then prepared and tested exactly according to the proposed test procedure. The results of the selectivity test are examined for a response indicative of the analyte. Similar samples would also be prepared and tested for any additional potential interfering substances such as impurities or degradation products. Early in product development, samples of potential degradation products may not be available in sufficient amounts to prepare weighed samples. In these instances, the selectivity of a method for degradation products may be established by forcing degradation using acid, alkali, oxidizing agents, and intense light. Generally, degradation should be limited to the approximate extent permitted for the method; that is, for a drug product, potency test conditions should be chosen to limit

degradation to about 10 percent. By limiting degradation to the maximum extent that will be tolerated during routine testing, formation of secondary and tertiary breakdown products that will not be observed routinely will be avoided.

For separation techniques, method validation studies should demonstrate that potentially interfering substances are baseline resolved from the primary analyte. For chromatographic methods, it is common to further assess peak purity by evaluating the response for the primary analyte (for example, UV spectrum or mass spectral fragmentation pattern) at the upslope, apex, and downslope of the analyte peak. Differences in the pattern of response would be expected if interfering substances with different properties were coeluting. For procedures intended to be specific, the response of the primary analyte should be clearly distinguishable from that of other potential sample components. The levels of interference permissible will depend on the objectives of the method. For example, for pharmaceutical products, USP procedures for content uniformity and dissolution tests permit low level interferences.[1] From the results of selectivity determinations, a meaningful resolution test can be established for routine system suitability analysis. Typically, a closely eluting related substance would be identified during selectivity studies for use in a resolution test preparation.

Linearity

Linearity studies demonstrate the ability of a method (within a given concentration range) to produce test results directly proportional to the concentration (amount) of analyte in the sample. For some tests, of course, the standard curve may not be linear or only a portion of the curve may be linear. In these instances, which are common for biologically-based tests, sample response should be examined either to define the concentration range where linearity is approached, or to derive the required curve-fitting equations to be used for routine testing. A *working range* assessment defines the upper and lower levels of analyte (including these levels) for which the procedure has been demonstrated as suitable with regard to precision, accuracy, and linearity using the method as written. In some laboratories, a linearity assessment is performed in the presence of the sample matrix, effectively combining elements of the working range assessment. Caution must be exercised in analyzing the results of such a study, since deviation from linearity may be due to either the measurement technique employed or to interferences or poor recovery from the sample matrix.

To determine the working linear range, at least six samples of increasing concentration are prepared within the concentration range anticipated during routine analysis; the same preparation solvent to be employed for routine sample preparations should be used. The concentration range evaluated should be established prior to or during method development based on the intended application of the method. Concentrations should be selected to cover the full range of results expected during routine analysis. For example, for a drug product dissolution test where individual percent dissolved values between 25 percent and 115 percent may be encountered during routine testing, linearity studies should bracket these concentrations. Three to six replicate samples should be tested at each concentration as a preliminary assessment of the precision component

of working range. Separate studies which assess the working range will be necessary for tests where the targeted concentrations or sample solvents are different. From the mean responses obtained, a best fit linear regression analysis is typically performed and a linearity plot prepared comparing the actual data points and data calculated from linear regression parameters (for example, slope and intercept values).

For many analytical procedures, it is common to utilize single point standard calibration to cover the full linear range; that is, a single concentration of reference standard is tested to determine the concentration of test samples. In these instances, it will be necessary to look carefully for any bias or deviation from linearity, particularly at the low end of the concentration range. A useful way of assessing this is to determine the response factor (response divided by concentration) for each point in the calibration or linearity curve. A consistent response factor (absorptivity for direct UV measurements) gives confidence in the true proportionality of response. A comparison with the typical linear regression assessment demonstrates the value of the response factor assessment. The data in Table 10.1 represent typical peak area responses from an HPLC linearity study. Original data obtained are shown on the left side of the table, while to the right the response at only the lowest concentration has been artificially increased by 10 percent. Examination of the regression parameters and the typical linearity plots (Figure 10.1) reveals no significant differences caused by the response change. However, examination of the response factors calculated from the same data clearly reveals a clear difference at the lowest concentration (Table 10.1). A plot of the response factor data can also be constructed, including tolerance limits around the targeted standard response, providing clear graphic definition of the working range of the method.[29–30] An example of such a plot is shown in Figure 10.2. As a further illustration,

Table 10.1 Sample data for linearity determinations.

Concentration	Original Data		Modified Data	
	Response Factor[A]	Response	Response Factor[A]	Response
25.1	358.3	14.27 (100.7)	394.1	15.70 (110.7)
60.2	850.2	14.12 (99.6)	850.2	14.12 (99.6)
100.3	1422.5	14.18 (——)	1422.5	14.18 (——)
120.3	1709.8	14.21 (100.2)	1709.8	14.21 (100.2)
160.4	2271.8	14.16 (99.9)	2271.8	14.16 (99.9)
200.5	2861.3	14.27 (100.6)	2861.3	14.27 (100.6)
Y-intercept	–5.0		17.6	
Slope	14.25		14.10	
R^2	1.0000		0.9997	

The sample data demonstrate the effect of a change in response for low concentrations on linear regression parameters and the response factor: representative values from a chromatographic linearity assessment are shown as *Original Data*; the same results are shown as *Modified Data*, but with the response for only the lowest concentration increased artificially by 10%.

[A] Numbers in parentheses are percentages of the response factor for the 100.3 concentration.

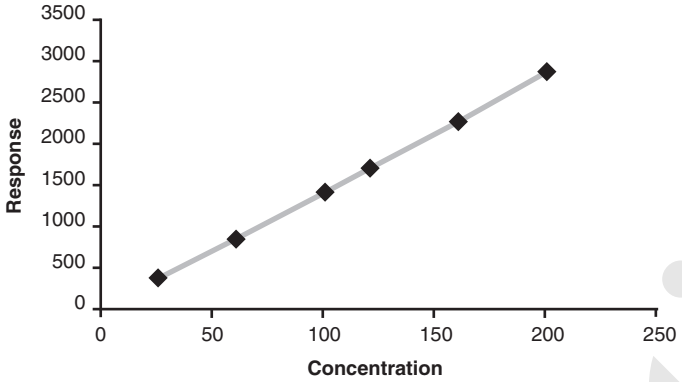

Figure 10.1 Overlapping linearity plots for the two sets of data in Table 10.1, demonstrating that a 10% higher response for the lowest concentration is not easily detected.

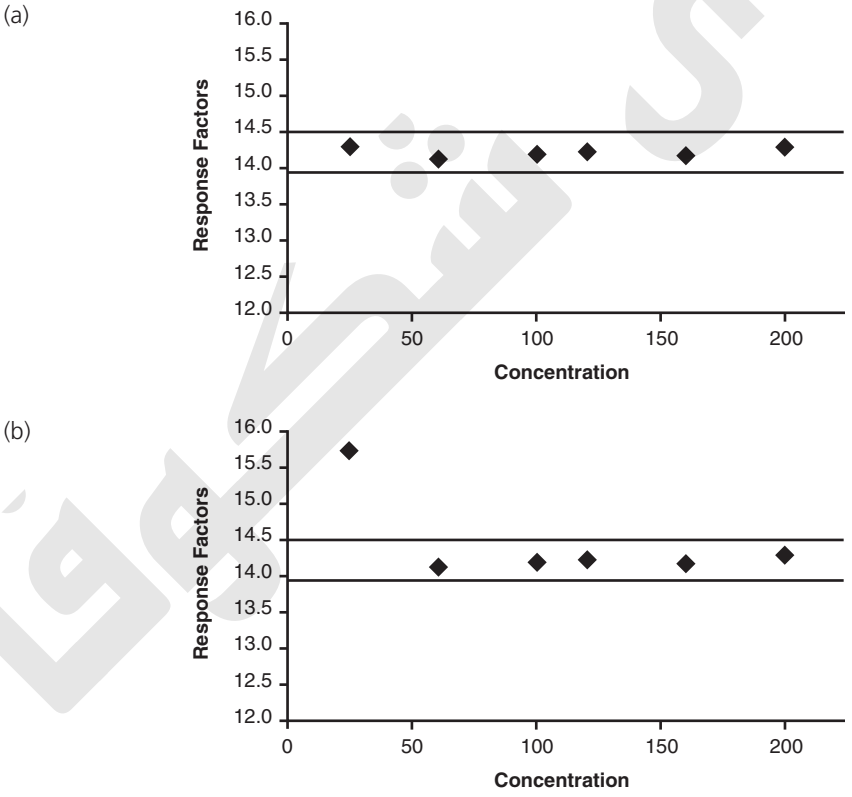

Figure 10.2 Response factor plots for the two sets of data in Table 10.1: (a) response factors for the original data set; (b) same data with an artificial 10% increase in response for the lowest concentration. Parallel lines represent response Factors ±2% above and below that for the concentration at about 100.

the data shown in Table 10.2 demonstrate acceptable linearity when assessed by the typical linearity plot (Figure 10.3) or the regression parameters, but clearly show curvature when response factors are analyzed. (See Table 10.2 and Figure 10.4.)

Table 10.2 Sample data for a linearity determination.

Concentration	Response	Response Factor[A]
20.0	49731.5	2484 (95.2)
40.0	101460.1	2534 (97.2)
60.1	153670.2	2559 (98.1)
80.1	206882.9	2584 (99.0)
100.1	261090.2	2608 (——)
120.1	311816.3	2596 (99.5)
140.1	358563.9	2559 (98.1)
160.2	405840.5	2534 (97.2)
180.2	447583.2	2484 (95.2)
200.2	498307.3	2489 (95.4)
Y-intercept	5273	
Slope	2490	
R^2	0.9988	

The data demonstrate the effect of curvature in response in the linear regression parameters and the response factors.
[A] Numbers in parentheses are percentages of the response factor for the 100.3 concentration.

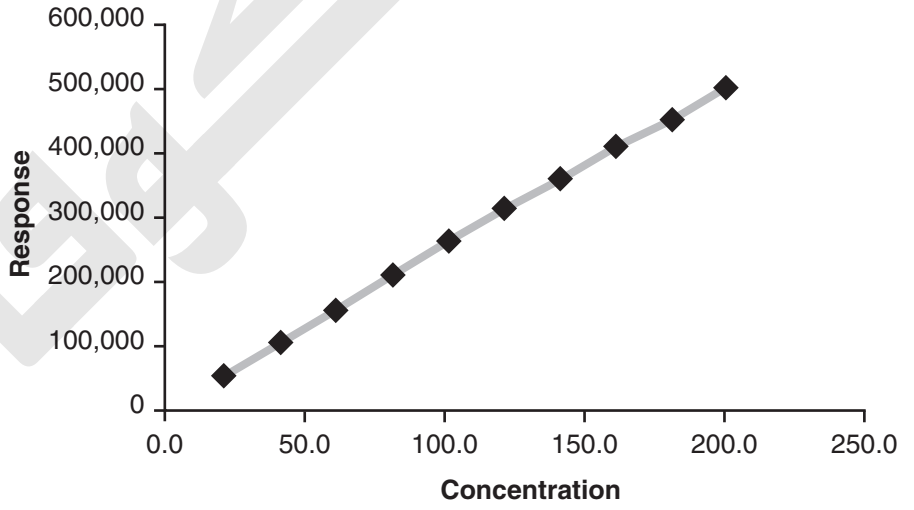

Figure 10.3 Linearity plot for the sample data in Table 10.2 illustrating that curvature in response exhibited by the data cannot be easily observed.

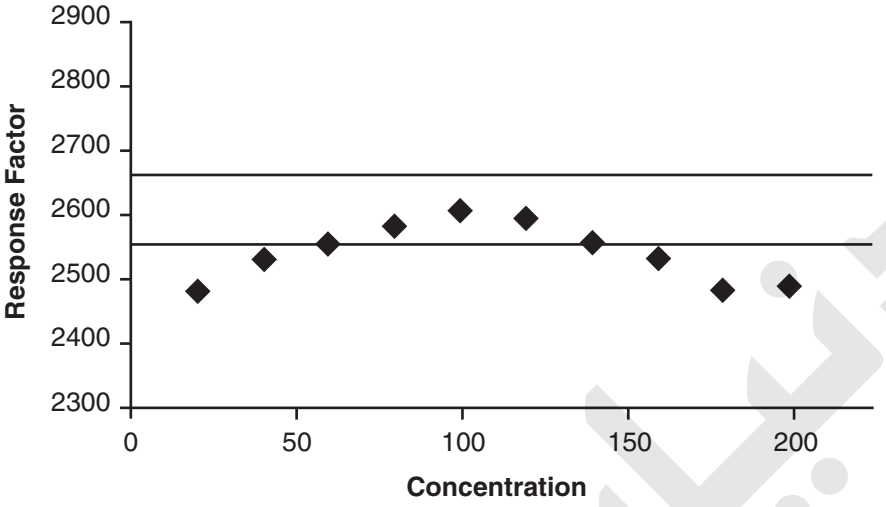

Figure 10.4 Response factor plot for the sample data in Table 10.2 illustrating the curvature in response. Parallel lines represent response factors ±2% above and below that for the concentration at about 100.

Limit of Detection and Limit of Quantitation

The *limit of detection* (LOD) is the lowest amount of an analyte in a sample which can be detected but not quantitated as an exact value. An estimate of LOD can be made based on the noise level of the test response. For example, for chromatographic analyses LOD may be defined as that concentration giving a peak height response three times greater than the baseline noise level. The LOD value may be critical for those tests (for example, limit tests) where response need only be lower than a specified value.

To determine the LOD value the background noise can often be estimated from an analysis of sample blanks. A concentration of analyte that will yield a response approximately three times this noise level can then be determined. To validate a limit test, the LOD is first determined or estimated. Frequently this value will be used to set the specification limit for the test. Methods validation studies should establish that samples spiked with analyte concentrations lower than the specification limit give no discernable response, while samples spiked with concentrations equal to and above the limit give a detectable response. Generally, quantitation at these low levels should not be attempted since response at or slightly above the LOD will be highly variable.

For quantitative procedures, the limit of detection assessment is routinely performed in many laboratories as well, but this adds little value since any value reported close to the LOD will not be reliable. The more critical assessment is the *limit of quantitation* (LOQ) or *lower limit of quantitation* (LLOQ), the lowest amount of an analyte in a sample which can be quantitatively determined with precision and accuracy under the stated experimental conditions. For instrumented methods, LOQ has variously been defined as the concentration giving a signal-to-noise ratio of at least 10:1 and

precision ≤ 10 percent RSD, adequate for impurity or degradation product analysis, or 20:1 signal-to-noise with precision ≤ 5 percent RSD, which may be more appropriate for bioanalytical samples. Various approaches to establishing LOQ have been described.[31] Regardless of the approach followed, the validating scientist should be certain that both required elements (accuracy and precision) are assessed. As an example, LOQ can be determined experimentally by estimating the concentration that will yield a response approximately 10 times greater than the background noise (for example, from method development studies). If the LOD value is known, the LOQ can be estimated by multiplying the LOD by a factor of three. Three to six replicate spiked samples at and above this level can then be assessed for linearity and precision of response; it may be useful to perform this assessment during accuracy studies. If specimens of impurities or degradation products are not available, a diluted sample of the primary analyte can be used to establish the LOQ value.

Establishing the upper and lower limits of quantitation is a critical feature of the working range assessment. The lower limit of quantitation is critical for the measurement of analyte degradation products and impurities. For drug substances and products, ICH guidance is available which defines thresholds for the reporting, identification, and safety qualification of impurities and degradation products based upon the expected daily dose of the drug.[32–33] These values are summarized for drug product analyses in Table 10.3. During method development and validation the anticipated reporting threshold can guide establishing acceptance criteria for LOQ. Validation studies must ensure that acceptable accuracy and precision data are available to include or bracket that value.

Accuracy/Recovery

The *accuracy* of an analytical method is the closeness of a test result obtained by that method to the true value. Together with the linearity and precision determinations, the accuracy study will define the overall working range of the method. Indeed, if studies using high, low, and intermediate concentrations of analyte are conducted in the presence of matrix components and replicate samples are analyzed, the results will define the

Table 10.3 A summary of reporting, identification, and safety qualification thresholds.

Daily Dose[1]	Reporting Threshold[2]	Identification Threshold[2]	Safety Qualification Threshold[2]
< 1 mg	0.1%	1.0%	1.0%
1 mg–10 mg	0.1%	0.5%	1.0%
> 10 mg–100 mg	0.1%	0.2%	0.5%
> 100 mg–1 g	0.1%	0.2%	0.2%
> 1 g–2 g	0.05%	0.2%	0.2%
> 2 g	0.05%	0.1%	0.1%

The thresholds are for impurities and degradation products in new drug products. (See reference 33 for details).
[1] The amount of drug administered per day.
[2] Threshold values are based on the drug substance content.

range. Accuracy may be expressed in some instances as a test of method *bias*, or reported as a percent *recovery*. In the latter instance, accuracy is determined by spiking the analyte into the sample matrix. Accuracy may also be determined by comparing test results with those obtained using another validated method. Comparative testing is particularly valuable for established products where methods have been in use for some time. It may be appropriate to test fresh and aged samples using both the old and new procedures and perform a statistical comparison of results. This assessment allows a better measure of the consistency in the product by allowing a comparison of results obtained using both the old and new methodologies. If substantial differences in results are obtained, however, an investigation will be required to determine whether the difference results from the product characteristics or the performance characteristics (validity) of the new method. In some instances, results from method comparisons may be challenging to assess, since the selectivity of the new procedure may have been improved.

Upon close examination, if method selectivity has already been established it should be clear that recovery assessments are designed to measure the effectiveness of the sample preparation procedure and to confirm that no bias is introduced. Therefore careful experimental design is important to obtain meaningful results that provide confidence in the actual sample preparation procedures.

For pharmaceutical products, recovery studies are most often performed by spiking the analyte into the sample matrix (for example, a mixture of formulation excipients, or a specimen of biological fluid), performing the analysis as intended, then comparing the observed result with the theoretical value. The sample matrix (excipient mixture) prepared for selectivity studies can also be used for recovery experiments. Three to six samples should be prepared and tested for high, low, and intermediate amounts of analyte. Concentrations or amounts selected may represent the outer specification boundaries plus the target value, or the upper and lower quantitation limits plus an intermediate level. Care should be taken to mimic the actual sample preparation as closely as possible. Otherwise results may not be predictive of recovery from the actual sample. For example, adding a large volume of a drug-containing solution to a mixture of inactive matrix components cannot provide a meaningful assessment of methods for use with products where the analyte is intimately mixed with matrix components in the solid state. Similarly, adding a large (> 10 percent) volume of a standard solution to biological samples (plasma, urine, etc.) may provide misleading recovery results. Matrix samples used for these studies should match as closely as possible the composition in the expected samples. For the validation of impurity or degradation product analysis, recovery studies should be performed by spiking small quantities of authentic materials into preparations containing the primary analyte; standard addition procedures using actual product samples may be the most meaningful. Recovery studies for all tests should examine the accuracy of the method at the low and high ends of the working range.

Recovery results within ± 2 percent of the target value are acceptable for pharmaceutical potency assays; ± 10 percent may be acceptable for impurity determinations; and ± 15–20 percent acceptable for bioanalytical methods, particularly at the LLOQ level.

Recovery studies are useful in assessing any interference caused by inactive components of the matrix or loss of analyte due either to binding with matrix components or to sample handling. In some instances, for example, certain biological tests or impurity assessments, a matrix sample cannot be obtained without endogenous analyte present. Under these circumstances, accuracy can be assessed through a standard addition method, where the values obtained will be offset by the amount of the analyte in the starting material used.

In some instances, innovative accuracy studies must be designed to truly reflect recovery of the drug from a pharmaceutical product. For example, for transdermal delivery devices or sustained release products, simply spiking a drug into a dry mixture of excipients provides no useful recovery information. Only adsorption of the analyte by matrix components or interference with the final measurement can be determined with these spiking studies. By design, a sustained release formulation is intended to shield the drug from rapid release. This illustrates the importance of interactions between analytical chemist and the internal or external customer or sample originator (for example, drug product formulator) during test-plan design.

The chemical and physical characteristics of the product must be taken into consideration in designing and validating test procedures. As an example, meaningful accuracy studies for a coated extended-release product might involve two experiments. In the first, drug recovery could be established for the uncoated product in the classical manner by spiking a drug into a mixture of components, excluding the sustaining polymer. Secondly, during the preparation of one or more batches of a product, replicate analysis of the core pellets or tablets could be obtained; these results can then be compared with subsequent results for the finished coated product. This combination of studies provides maximum confidence that the sample preparation procedure can adequately extract the drug from the product. Table 10.4 shows results from such a study, illustrating the presentation of results for six replicates and the assessment of percent recovery and precision for each data set. Other acceptable approaches more applicable to the product being tested could also be designed.

Table 10.4 Presentation of precision and recovery data for a coated extended release product.

Drug Recovery (40 mg Theoretical)			
Uncoated Product	**SR Coating Level 1**	**SR Coating Level 2**	**SR Coating Level 3**
39.4 mg	39.7 mg	39.8 mg	39.5 mg
40.1 mg	39.5 mg	38.9 mg	40.0 mg
40.3 mg	39.2 mg	39.3 mg	39.4 mg
38.8 mg	39.2 mg	39.4 mg	39.3 mg
39.8 mg	39.6 mg	39.4 mg	39.4 mg
39.2 mg	39.5 mg	39.7 mg	39.9 mg
Mean 39.6 mg %RSD 1.44	Mean 39.5 mg %RSD 0.51 Recovery 99.7%	Mean 39.4 mg %RSD 0.80 Recovery 99.5%	Mean 39.6 mg %RSD 0.73 Recovery 100.0%

Comparative results for the uncoated and three separate coated products manufactured from the same core batch.

Precision—System Precision, Repeatability, Intermediate Precision, and Reproducibility

The *precision* of an analytical method is the degree of agreement among individual test results when the procedure is applied repeatedly to multiple aliquots of a homogeneous sample. For pharmaceutical analysis, precision can be divided into four components: *system precision*, the reproducibility of the final measurement (for example, HPLC injection), *repeatability* (method precision), *intermediate precision*, and *reproducibility* (Ruggedness).

System precision may be assessed as part of linearity studies if multiple replicates are tested. Typically, six replicate analyses at the target concentration should be available for review. This data can be used to establish the precision component of a routine system suitability assessment.[1] This determination provides the basis for any other reproducibility assessment; poor system precision will inevitably lead to poor reproducibility in sample analysis.

Other precision measurements combine the equipment-related aspects of linearity and selectivity with the sample preparation considerations of accuracy studies. *Repeatability* (or *method precision*) provides an initial assessment of the reproducibility of sample preparation. Typically six aliquots from a homogeneous sample mixture are prepared and analyzed according to the test procedure. Although repeatability can also be assessed from recovery data if six replicates at the target concentration were tested, data from artificially prepared spiked samples may not be representative of the test reproducibility for actual samples. It is best to prepare six replicates from actual samples to perform the repeatability assessment. For dosage-form testing, particularly late in the product development cycle, method precision data should ideally be available using both fresh and aged or stressed samples (for example, initial and stability samples) of each unique formulation. At least the highest and lowest dosage strengths of a particular product should also be tested. Without supportive data, chemists should never assume that a method will work equally well with all samples.

With most methods involving analysis of traditional pharmaceutical products, repeatability results (for example, percent RSD) should be 2 percent or better; product-specific acceptance criteria should be specified in the validation test plan or standard operating procedures for the laboratory. For samples in which a drug may need to be extracted from a biological matrix, or for the cell-based testing of biological samples, acceptable precision may be in the 15–20 percent range, or 20–25 percent at the LLOQ level.[18] In certain instances, an internal standard will be required to control variability inherent to the measurement technique or the extraction/concentration of the analyte from the sample matrix.

To complete the initial assessment of method performance, additional day-to-day precision studies should be carried out. These studies are ideally performed using the same samples of homogeneous material used for the repeatability assessment. The analysis procedure should be conducted by the same chemist on the same equipment on each of three to five days, using fresh samples, standards, mobile phase, and reagent

preparations each day. By adding day-to-day studies to the typical method precision assessment, greater information can be obtained regarding the reproducibility of standard preparations, reagent or mobile phase preparation, and equipment set-up. These studies should provide an accurate assessment of the idealized long-term reproducibility of a method. No better reproducibility should be expected from the method than those obtained under these well-controlled conditions. It is tempting to skip this single analyst study and proceed directly to day-to-day studies using multiple chemists (intermediate precision). However, knowledge of the variability observed for a single analyst is critical to the effective interpretation of the data and to minimize experimental variables. If day-to-day variablity is assessed as a nested component of a statistically designed study which also incorporates chemist-to-chemist and perhaps lab-to-lab variability,[34–35] the study should be designed to allow the day-to-day variability for a single analyst to be deciphered from the data.

Early in the development cycle for a new product in a research and development environment, validation studies may end at day-to-day precision studies. This is appropriate if a single analyst will be performing all tests using the same analytical equipment. In these instances, the reliability of a method can be assessed further as routine sample testing is performed. This testing may identify method variables or details that must be optimized before a method is shared with other analysts or additional laboratories. An excellent way to establish the long-term variability for a method is the use of control (or quality control) samples. Ideally, samples of the same homogeneous product used to establish method repeatability would be retained and periodically analyzed. Results obtained can be assessed using control charts that link the validation studies with routine implementation of the method. Any variation observed over time should then be controlled further, if appropriate, through better definition and control of the critical factors of the method (see *robustness* studies). The need to blind the control samples to avoid special treatment by analysts should be considered by laboratory management.

Intermediate precision is a term currently used to describe an assessment of the analyst-to-analyst as well as day-to-day variability of a method.[9] Intermediate precision studies should also evaluate the impact of using different equipment. As for robustness studies, the timing of these studies should be determined on a case-by-case basis depending on the scope of the implementation plan. If the method will be implemented only for limited testing, or by a single analyst, intermediate precision studies may not be a value-added activity.

The intermediate precision test is carried out as an extension of repeatability and day-to-day trials; different analysts are assigned to different equipment to test multiple replicates of the same homogeneous samples. Ideally, each analyst should prepare separate reagents, standard preparations, and test preparations. Intermediate precision studies are optimally performed as part of a statistically designed study,[34–35] although the impact of changing analysts or equipment can be evaluated separately.

Reproducibility is the term used in ICH guidelines to describe collaborative interlaboratory validation studies.[9] These studies have also been referred to as *ruggedness* studies.[1] Reproducibility studies extend the intermediate precision evaluation to include additional laboratories. Successful completion of this work will provide the

final convincing evidence of the reliability of the test methods. However, if only one laboratory will be performing the test, reproducibility studies are not required, or may be performed later when a method is transferred to a new lab. Prior to testing samples in a new laboratory, method-specific performance qualification of equipment should be undertaken. Interlaboratory studies may not be successful unless equipment-specific validation factors are verified in the new laboratory. Typically this will consist of an assessment of the upper and lower limits of quantitation. A system suitability assessment, including performance factors established during earlier method validation studies, should also be performed. Once the performance of the equipment has been shown to match that observed during initial validation studies, interlaboratory testing can be carried out. Methods should be explained and demonstrated for new analysts, following which samples should be tested independently. Reproducibility is best established in the new laboratory by performing the repeatability test as previously described. Further intermediate precision studies may be carried out in the new laboratory to provide maximum confidence in the reliability of subsequent results. The samples used for these studies must have been tested previously by an experienced analyst to eliminate the product itself as a potential variable. If possible, control samples of the drug product should be used in these studies so that a history of results can be obtained in assessing the acceptability of reproducibility data. By carefully defining the steps necessary to transfer a method in a transfer test plan, including the acceptance criteria to be applied, the results of reproducibility studies can be deciphered into equipment-specific and analyst-specific factors. Follow-up actions can then be taken to obtain the appropriate equipment or to clarify the written test procedures to enable new analysts to obtain results consistent with those generated by experienced scientists.

In some instances, it may be appropriate to combine various elements of a method precision assessment (day-to-day, instrument-to-instrument, column-to column, and lab-to-lab) in a single statistically designed study. This may be particularly true if two laboratories collaborate in the development of a method. While efficient, the design of such a study is critical to ensure that the data can be deconvoluted to identify the cause for any variability observed. Even with data from these studies in hand, it will be necessary to ensure that any additional new lab can generate acceptable and consistent results.

Robustness

A thorough assessment of method variables can be accomplished by performing *robustness* studies. While precision and reproducibility studies will measure the impact of unintended variations in method parameters as part of day-to-day testing, robustness studies assess the impact of intentional variations. Method robustness is a measure of the capability of a method to remain unaffected by small but deliberate variations in method parameters. These studies will further define the analytical procedure itself, leading to clarifications in the method description. With these refinements, a method can be further assessed in different laboratories, by different analysts, using different instruments, etc.

The timing of robustness studies largely depends on the application of the method being validated and could follow two approaches. For methods employed early in an R&D process, the time spent in performing robustness studies may not provide substantial added value. In some instances, the product being tested may still be evolving; in other situations, the method may only need to be utilized a few times. In these instances it may be best to evaluate method performance through the actual implementation of a method for routine testing. As necessary and appropriate, once critical variables have been defined through this experience, well designed robustness studies can be performed. On the other hand, if multiple analysts will quickly be implementing a method for commercial or other critical samples, it is likely best to perform robustness studies during the initial validation stages. These different approaches to validation staging reflect differences in the lifecycle of a method that must be considered.[30,36]

In methods validation for NDA submissions, regulatory agencies will expect results from detailed, well-planned robustness studies. It is expected that these studies will be used to identify the critical variables of the procedure and that the final detailed written analytical procedure will reflect adequate control of these variables. Method robustness information should be generated prior to any attempt to transfer a method to a new laboratory. A discussion of the value added in performing robustness studies for HPLC methods has previously been published.[37]

To obtain the most meaningful results, robustness assessments should be performed as part of a statistically designed multifactor analysis,[20,34,38] not one factor at a time, which may fail to identify interactions between factors. To characterize the critical variables of a method, the robustness testing process should be broken down into unit operations, similar to the assay sequence shown in Figure 10.5. Variations or potential

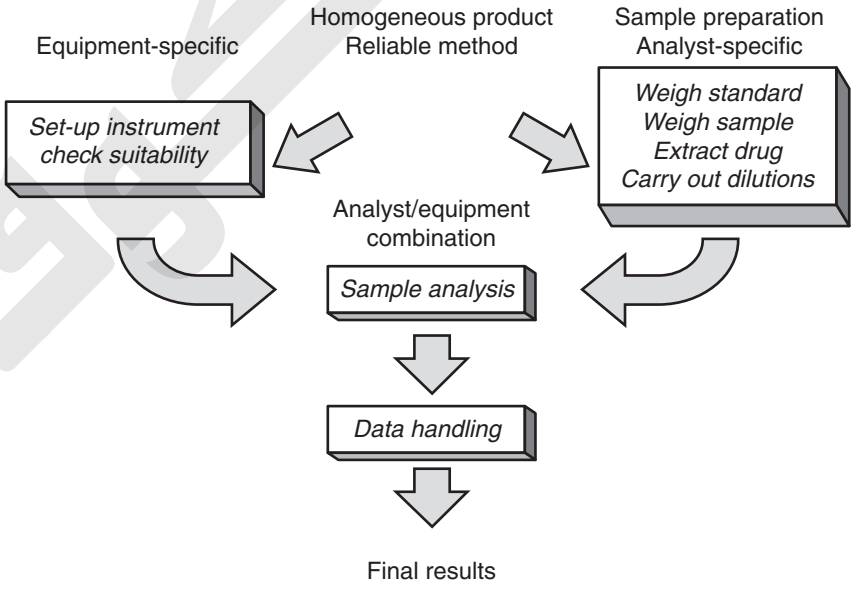

Figure 10.5 Relationships between equipment, method, techniques, and sample in a typical analysis sequence for drug product analysis.

variability in each of the unit operations should be assessed. For the sample and standard preparation steps, variables such as the amount of standard and sample weighed, the volumes used, the shaking or sonication time required for effective drug extraction (also the manufacturer/model of sonicator or shaker used), and any filters employed (that is, brand, type) should be considered. Potential product variability such as changes due to product aging must also be critically assessed. For the analysis step, variables to be assessed for a chromatographic test may include the equipment model and/or vendor, the wavelength and flow rate used, and the pH, ionic strength and organic modifier content of the chromatographic mobile phase. Similar lists can be created for other instrumented methods. Slight modifications should be made in many or all of these variables as part of a matrix designed statistical study to determine the resilience of the method to small changes. From the results of these studies, details should be added to the analytical procedure which define and fix the critical variables.

The importance of robustness studies cannot be overstated. Although they will take time and resources to perform, thorough robustness studies will help avoid subsequent unexpected results. Numerous examples can be cited of inconsistencies in results attributed to technicians using different procedures to grind tablets into a composite for testing, different shakers or shaking times, or different filters for final sample preparation. Proper definition of the test procedures in the form of detailed step-by-step instructions, together with thorough training of the chemists, biologists, or technicians involved, is the only effective way to minimize analyst-related laboratory errors during routine application of the method.

THE VALIDATION PROCESS PLANNING, EXECUTION, AND DOCUMENTATION

For any validation project to be successful, an appropriate plan needs to be in place beforehand. As an initial step prior to methods validation, the scope of analytical procedures should be determined. It is essential that a validation program closely match the intended objectives or purpose of the method. Based upon the chemical or biochemical nature of the analytes involved, and the product/dosage form/matrix involved, different aspects of validation testing will be required. As an example, questions need to be answered regarding the extent of analyte degradation expected. What is the expected content of impurities and degradation products? Have specifications/limits for these related compounds been proposed? Method validation studies should bracket the range of degradation product and impurity content expected to be encountered during routine analysis, from the results expected for initial release testing, through results anticipated during long-term stability testing, up to and including the upper specification limits. As noted above, ICH guidelines are available for reporting, identification, and safety qualification thresholds for new drug substances and products.[32–33] These guidelines should be consulted before or during the method development stage to determine the appropriate range for the method. If release of the analyte from a sample matrix over 8–24 hours must be measured (for example, drug release from a transdermal device of dissolution studies for extended-release drug products), validation studies must define drug stability in the test medium at the appropriate temperature for the appropriate time interval.

For bioanalytical testing, different pharmacokinetic studies will be performed at various stages of the pharmaceutical development process.[13] Attention to these plans will also dictate the scope of method development and the validation required. Interferences from the components of biological fluids may differ depending on the animal species to be studied preclinically, which in turn may differ from human samples. The stability of samples for bioanalytical analysis must also be assessed before samples are collected and stored for analysis, even if they will be frozen before testing. These factors must be built into the method development plan, as well as into the validation plan.

During the method development phase, the preliminary performance characteristics of a method will be determined. These studies should define the approximate linear range and detection limits of a method and help to shape the formal validation experiments. Once the scope of the analytical procedures has been defined, and preliminary information assessed regarding the performance of methods during development, a validation test plan should be prepared. The plan should define the tests necessary to characterize the reliability of the test procedures and the acceptance criteria for all studies to be performed. A test plan need not be an elaborate document—tabular or fill-in-the-blanks forms could be used. Alternatively, some laboratories may specify the validation tests required and the acceptance criteria in an SOP or a departmental policy document. The test plan or standard laboratory policy/procedure should identify follow-up action steps, anticipating those instances where validation data may fail to meet the pre-set acceptance criteria. This process avoids the retrospective fitting of acceptance limits to the data obtained. Validation acceptance criteria may be established on a test-by-test basis, from local laboratory SOPs, or through a statistical approach.[39] An excellent review of appropriate acceptance criteria for various methods has been published.[40]

In some fashion, which could be verbal communication, or written agreement in a test plan or SOP, it is essential that there be communication between the validating chemist or biologist and the laboratory or project manager regarding the how, what, why, and when of the validation studies. The scope of the studies to be performed, how these studies should be run, and the acceptance criteria for the validation tests should be clarified before studies commence. A laboratory manager should not assume that all of these factors are understood.

At the conclusion of initial validation work, a detailed report should be prepared which documents the equipment, supplies and samples tested, the results of each validation test, and an assessment of results against the acceptance criteria established in the validation test plan. The preliminary validation report should also note those items (for example, intermediate precision, reproducibility, or robustness studies) that may be performed later, once additional information for a method or for a new drug product is obtained. Furthermore, the report should also address any potential weaknesses in a method used early in product development that may require attention as development proceeds. The information provided in this report would serve both to provide supportive documentation for the existing procedure and to provide a guideline for future work. The validation report should be reviewed and approved by senior analytical management and be made available to new analysts and supervisors assigned to the project.

CHANGES AND THE NEED FOR REVALIDATION

Analytical method validation is a dynamic process, extending further as additional information is obtained and the application of test procedures expands to new products or new analytical staff in additional laboratories. By dividing validation steps into those which assess equipment, sample preparations, and both (Figure 10.6), clearer definition can be obtained regarding the requirements for revalidation of methods as changes occur. Comparing the scheme shown in Figures 10.5 with that in Figure 10.6, the overlap between routine testing activities and method validation becomes clear. Reliable analytical results can be obtained only if generated by well-trained chemists, biologists, or technicians, using good laboratory technique, valid methods, and qualified equipment. If all of these variables are controlled, then the results will truly reflect the quality of the product. If the appropriate controls are missing, however, the results will not be meaningful. If any changes are made in the method, equipment, or product, then revalidation is likely required. In making these decisions, assumptions must be avoided regarding the definition of a "major" change. Some examples are cited on the following pages.

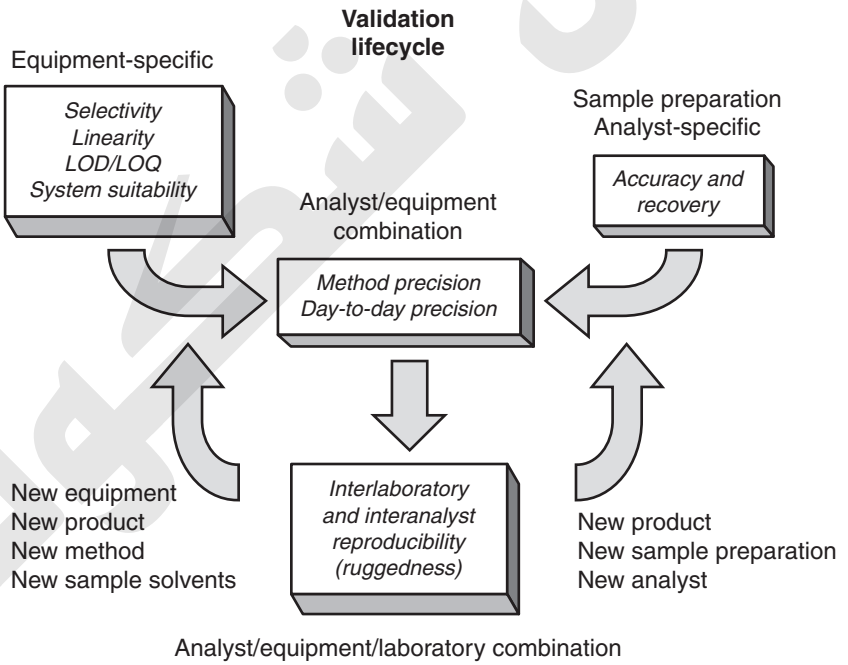

Figure 10.6 Equipment- and analyst-specific steps in analytical method validation for drug products.

Instrumentation Changes

In many instances, a laboratory manager may want to use newly purchased equipment to run validated methods, applied by qualified chemists, for products manufactured using the established manufacturing process. As shown in Figure 10.6, before applying the new method on this instrumentation, equipment-specific validation factors, such as the upper and lower quantitation limits and system precision, should be reconsidered and checked as needed. This is true even if the instrumentation is purported to be the same (or identical) as existing qualified equipment. Surprisingly, this product-specific performance qualification often uncovers minor changes in the equipment that might not have been apparent at the time of purchase or were considered "insignificant" by the instrument vendor. Ideally, new equipment will first be assessed against the manufacturer's specifications through installation qualification. Control chromatograms, often supplied by the instrument vendor, may be run as a measure of performance verification. Operational qualification is also essential, demonstrating that the equipment conforms to the typical pattern of use within a laboratory. To complete the process, however, some form of product-specific performance qualification studies should be performed prior to using the equipment for routine testing. In most instances, the dynamic range of the instrument (working range) is the critical factor of interest, particularly for samples that may approach the upper or lower limits of the range.

Product Changes

During the research and development stage it is not uncommon for product composition to change during development. Changes may also occur after product launch. In many instances, a change in the sample matrix will require validation of selectivity, accuracy, and precision. As previously noted, changes in drug products or bioanalytical samples due to prolonged storage must be assessed early in the development program. If major changes in sample composition occur, the method validation cycle must start anew. However, debate may occur regarding whether a "minor" composition or process change requires additional analytical validation. The final decision should be based upon the potential for influence of the change on the detailed step-by-step methodology. For example, a change in a dye component of a coated tablet or gelatin capsule formulation would not be expected to affect drug recovery, and therefore have no anticipated effect on method precision. However, selectivity studies would clearly be required. A change in the shape of a tablet or the dimensions of a capsule product would clearly require demonstration of comparative dissolution profiles, but ordinarily would not be expected to influence drug recovery, particularly if the tablets are ground or capsules emptied for analysis. If additional tablet or capsule strengths are developed which utilize the same composition as that for previously validated products (for example, composition-proportional formulations), the details of the method need to be examined. Are the tablets ground and a composite used, or does the method (for example, content uniformity or assay) use the intact tablet or capsule? In the latter instance, comparative accuracy studies, designed to evaluate recovery from the intact

dosage unit, will be necessary to provide confidence in subsequent test results. Frequently, it is assumed that such changes will not affect test results. These assumptions must be avoided.

Method Modification

A change in the analytical procedure should be assessed in the same detailed fashion as would changes in product. If a chromatographic procedure is modified, but the sample and standard preparation process is unchanged, then only equipment-specific items (selectivity, linearity, LOD/LOQ, system precision) require revalidation. If a change is made in the sample preparation procedure, but the same concentration range and preparation solvent is used, then only analyst-specific factors (accuracy/recovery, precision, reproducibility) need to be assessed. Changes in sample preparation involving changes in the extraction procedure and the sample preparation solvent will require complete revalidation of the procedure unless already covered in the course of robustness studies.

Analyst Changes

No assumption should ever be made that a method can be applied equally well by multiple analysts. Likewise, it should never be assumed that an experienced chemist or technician can start applying an unfamiliar method without prior training. The temptation exists in many laboratories to assume that one interanalyst study provides license to transfer the method to any other analyst. Often, such assumptions will result in subsequent analytical test failures. To minimize these occurrences, the qualification of every new chemist assigned to a project should be verified through a training review, a discussion of relevant experimental details, and in some instances, experimental studies. The qualification process could consist of testing control samples and comparing results with historical trends.

OUTDATED TECHNOLOGY

As a final step in the lifecycle of a method, new technology will eventually be developed which will make a method obsolete. For example, spectrophotometric assay tests developed in the 1960s will likely not withstand the same level of validation scrutiny that a selective, sensitive HPLC or capillary electrophoresis method would. In such cases, development of methods using the new technology should be pursued, initiating a new method validation lifecycle. Based upon the history of the product, an appropriate validation test plan should be prepared, with strong emphasis on building a high level of confidence in the new procedures prior to their implementation. Results obtained using both the old and the new procedures must be compared to allow long-term assessment of the manufacturing process performance. Indeed, the effect on the supportive data for the product must be considered before any changes in an analytical method are approved. Only when significant new information characterizing the product, or when improved

reliability in results will be obtained, should a change be permitted. In either instance, before any new method is implemented, method validation data should be generated to provide convincing evidence that an advantage will be gained by changing.

CONCLUSIONS

To fully understand the importance of method validation, analysts and supervisors should assume that all results will be 100 percent of the target value and will not change during the course of a stability program. Of course this assumption will likely never be true. However, only by starting with this assumption can the reasons for the variability observed be deciphered. Result variability will always be due to a combination of personnel, method, equipment, and product factors. The professional responsibility of the analytical scientist is to investigate, understand, and control the first three factors so that results for product testing reflect the fourth.

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Appendix B

ICH Guidelines on Validation of Analytical Procedures

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

TEXT ON VALIDATION OF ANALYTICAL PROCEDURES

Recommended for Adoption

at Step 4 of the ICH Process

on 27 October 1994

by the ICH Steering Committee

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

TEXT ON VALIDATION OF ANALYTICAL PROCEDURES

ICH Harmonised Tripartite Guideline

Having reached Step 4 of the ICH Process at the ICH Steering Committee meeting on 27 October 1994, this guideline is recommended for adoption to the three regulatory parties to ICH

1. Introduction

This document presents a discussion of the characteristics for consideration during the validation of the analytical procedures included as part of registration applications submitted within the EC, Japan, and USA. This document does not necessarily seek to cover the testing that may be required for registration in, or export to, other areas of the world. Furthermore, this text presentation serves as a collection of terms, and their definitions, and is not intended to provide direction on how to accomplish validation. These terms and definitions are meant to bridge the differences that often exist between various compendia and regulators of the EC, Japan, and USA.

The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose. A tabular summation of the characteristics applicable to identification, control of impurities and assay procedures is included. Other analytical procedures may be considered in future additions to this document.

2. Types of Analytical Procedures to be Validated

The discussion of the validation of analytical procedures is directed to the four most common types of analytical procedures:

- Identification tests.
- Quantitative tests for impurities' content.
- Limit tests for the control of impurities.
- Quantitative tests of the active moiety in samples of drug substance or drug product or other selected component(s) in the drug product.

Although there are many other analytical procedures, such as dissolution testing for drug products or particle size determination for drug substance, these have not been addressed in the initial text on validation of analytical procedures. Validation of these additional analytical procedures is equally important to those listed herein and may be addressed in subsequent documents.

A brief description of the types of tests considered in this document is provided below.

- Identification tests are intended to ensure the identity of an analyte in a sample. This is normally achieved by comparison of a property of the sample (e.g., spectrum, chromatographic behavior, chemical reactivity, etc.) to that of a reference standard.

- Testing for impurities can be either a quantitative test or a limit test for the impurity in a sample. Either test is intended to accurately reflect the purity characteristics of the sample. Different validation characteristics are required for a quantitative test than for a limit test.

- Assay procedures are intended to measure the analyte present in a given sample. In the context of this document, the assay represents a quantitative measurement of the major component(s) in the drug substance. For the drug product, similar validation characteristics also apply when assaying for the active or other selected component(s). The same validation characteristics may also apply to assays associated with other analytical procedures (e.g., dissolution).

The objective of the analytical procedure should be clearly understood since this will govern the validation characteristics which need to be evaluated. Typical validation characteristics which should be considered are listed below:

Accuracy

Precision

Repeatability

Intermediate Precision

Specificity

Detection Limit

Quantitation Limit

Linearity

Range

Each of these validation characteristics is defined in the attached Glossary. The table lists those validation characteristics regarded as the most important for the validation of different types of analytical procedures. This list should be considered typical for the analytical procedures cited but occasional exceptions should be dealt with on a case-by-case basis. It should be noted that robustness is not listed in the table but should be considered at an appropriate stage in the development of the analytical procedure.

Furthermore revalidation may be necessary in the following circumstances:

- changes in the synthesis of the drug substance;
- changes in the composition of the finished product;
- changes in the analytical procedure;

The degree of revalidation required depends on the nature of the changes. Certain other changes may require validation as well.

TABLE

Type of analytical procedure	IDENTIFICATION	TESTING FOR IMPURITIES		ASSAY
				- dissolution (measurement only)
				- content/potency
characteristics		quantitat.	limit	
Accuracy	-	+	-	+
Precision				
Repeatability	-	+	-	+
Interm.Precision	-	+ (1)	-	+ (1)
Specificity (2)	+	+	+	+
Detection Limit	-	- (3)	+	-
Quantitation Limit	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+

- \- signifies that this characteristic is not normally evaluated
- \+ signifies that this characteristic is normally evaluated

(1) in cases where reproducibility (see glossary) has been performed, intermediate precision is not needed

(2) lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s)

(3) may be needed in some cases

GLOSSARY

1. ANALYTICAL PROCEDURE

The analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include but is not limited to: the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc.

2. SPECIFICITY

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradants, matrix, etc.

Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedure(s).

This definition has the following implications:

Identification: to ensure the identity of an analyte.

Purity Tests: to ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte, i.e. related substances test, heavy metals, residual solvents content, etc.

Assay (content or potency):
to provide an exact result which allows an accurate statement on the content or potency of the analyte in a sample.

3. ACCURACY

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found.

This is sometimes termed trueness.

4. PRECISION

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision and reproducibility.

Precision should be investigated using homogeneous, authentic samples. However, if it is not possible to obtain a homogeneous sample it may be investigated using artificially prepared samples or a sample solution.

The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements.

4.1. Repeatability

Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision .

4.2. Intermediate precision

Intermediate precision expresses within-laboratories variations: different days, different analysts, different equipment, etc.

4.3. Reproducibility

Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology).

5. DETECTION LIMIT

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

6. QUANTITATION LIMIT

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products.

7. LINEARITY

The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.

8. RANGE

The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.

9. ROBUSTNESS

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

VALIDATION OF ANALYTICAL PROCEDURES: METHODOLOGY

Recommended for Adoption
at Step 4 of the ICH Process
on 6 November 1996
by the ICH Steering Committee

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

VALIDATION OF ANALYTICAL PROCEDURES: METHODOLOGY

ICH Harmonised Tripartite Guideline

Having reached Step 4 of the ICH Process at the ICH Steering Committee meeting on 6 November 1996, this guideline is recommended for adoption to the three regulatory parties to ICH

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VALIDATION OF ANALYTICAL PROCEDURES: METHODOLOGY

INTRODUCTION

This document is complementary to the parent document which presents a discussion of the characteristics that should be considered during the validation of analytical procedures. Its purpose is to provide some guidance and recommendations on how to consider the various validation characteristics for each analytical procedure. In some cases (for example, demonstration of specificity), the overall capabilities of a number of analytical procedures in combination may be investigated in order to ensure the quality of the drug substance or drug product. In addition, the document provides an indication of the data which should be presented in a registration application .

All relevant data collected during validation and formulae used for calculating validation characteristics should be submitted and discussed as appropriate.

Approaches other than those set forth in this guideline may be applicable and acceptable. It is the responsibility of the applicant to choose the validation procedure and protocol most suitable for their product. However it is important to remember that the main objective of validation of an analytical procedure is to demonstrate that the procedure is suitable for its intended purpose. Due to their complex nature, analytical procedures for biological and biotechnological products in some cases may be approached differently than in this document.

Well-characterized reference materials, with documented purity, should be used throughout the validation study. The degree of purity necessary depends on the intended use.

In accordance with the parent document, and for the sake of clarity, this document considers the various validation characteristics in distinct sections. The arrangement of these sections reflects the process by which an analytical procedure may be developed and evaluated.

In practice, it is usually possible to design the experimental work such that the appropriate validation characteristics can be considered simultaneously to provide a sound, overall knowledge of the capabilities of the analytical procedure, for instance: specificity, linearity, range, accuracy and precision.

1. SPECIFICITY

An investigation of specificity should be conducted during the validation of identification tests, the determination of impurities and the assay. The procedures used to demonstrate specificity will depend on the intended objective of the analytical procedure.

It is not always possible to demonstrate that an analytical procedure is specific for a particular analyte (complete discrimination). In this case a combination of two or more analytical procedures is recommended to achieve the necessary level of discrimination.

1.1. Identification

Suitable identification tests should be able to discriminate between compounds of closely related structures which are likely to be present. The discrimination of a procedure may be confirmed by obtaining positive results (perhaps by comparison with a known reference material) from samples containing the analyte, coupled with negative results from samples which do not contain the analyte. In addition, the identification test may be applied to materials structurally similar to or closely related to the analyte to confirm that a positive response is not obtained. The choice of such potentially interfering materials should be based on sound scientific judgement with a consideration of the interferences that could occur.

1.2. Assay and Impurity Test(s)

For chromatographic procedures, representative chromatograms should be used to demonstrate specificity and individual components should be appropriately labelled. Similar considerations should be given to other separation techniques.

Critical separations in chromatography should be investigated at an appropriate level. For critical separations, specificity can be demonstrated by the resolution of the two components which elute closest to each other.

In cases where a non-specific assay is used, other supporting analytical procedures should be used to demonstrate overall specificity. For example, where a titration is adopted to assay the drug substance for release, the combination of the assay and a suitable test for impurities can be used.

The approach is similar for both assay and impurity tests:

1.2.1 Impurities are available

For the assay, this should involve demonstration of the discrimination of the analyte in the presence of impurities and/or excipients; practically, this can be done by spiking pure substances (drug substance or drug product) with appropriate levels of impurities and/or excipients and demonstrating that the assay result is unaffected by the presence of these materials (by comparison with the assay result obtained on unspiked samples).

For the impurity test, the discrimination may be established by spiking drug substance or drug product with appropriate levels of impurities and demonstrating the separation of these impurities individually and/or from other components in the sample matrix.

1.2.2 Impurities are not available

If impurity or degradation product standards are unavailable, specificity may be demonstrated by comparing the test results of samples containing impurities or degradation products to a second well-characterized procedure e.g.: pharmacopoeial method or other validated analytical procedure (independent procedure). As appropriate, this should include samples stored under relevant stress conditions: light, heat, humidity, acid/base hydrolysis and oxidation.

- for the assay, the two results should be compared.
- for the impurity tests, the impurity profiles should be compared.

Peak purity tests may be useful to show that the analyte chromatographic peak is not attributable to more than one component (e.g., diode array, mass spectrometry).

2. LINEARITY

A linear relationship should be evaluated across the range (see section 3) of the analytical procedure. It may be demonstrated directly on the drug substance (by dilution of a standard stock solution) and/or separate weighings of synthetic mixtures of the drug product components, using the proposed procedure. The latter aspect can be studied during investigation of the range.

Linearity should be evaluated by visual inspection of a plot of signals as a function of analyte concentration or content. If there is a linear relationship, test results should be evaluated by appropriate statistical methods, for example, by calculation of a regression line by the method of least squares. In some cases, to obtain linearity between assays and sample concentrations, the test data may need to be subjected to a mathematical transformation prior to the regression analysis. Data from the regression line itself may be helpful to provide mathematical estimates of the degree of linearity.

The correlation coefficient, y-intercept, slope of the regression line and residual sum of squares should be submitted. A plot of the data should be included. In addition, an analysis of the deviation of the actual data points from the regression line may also be helpful for evaluating linearity.

Some analytical procedures, such as immunoassays, do not demonstrate linearity after any transformation. In this case, the analytical response should be described by an appropriate function of the concentration (amount) of an analyte in a sample.

For the establishment of linearity, a minimum of 5 concentrations is recommended. Other approaches should be justified.

3. RANGE

The specified range is normally derived from linearity studies and depends on the intended application of the procedure. It is established by confirming that the analytical procedure provides an acceptable degree of linearity, accuracy and precision when applied to samples containing amounts of analyte within or at the extremes of the specified range of the analytical procedure.

The following minimum specified ranges should be considered:

- for the assay of a drug substance or a finished (drug) product: normally from 80 to 120 percent of the test concentration;
- for content uniformity, covering a minimum of 70 to 130 percent of the test concentration, unless a wider more appropriate range, based on the nature of the dosage form (e.g., metered dose inhalers), is justified;

- for dissolution testing: +/–20 % over the specified range;

e.g., if the specifications for a controlled released product cover a region from 20%, after 1 hour, up to 90%, after 24 hours, the validated range would be 0–110% of the label claim.

- for the determination of an impurity: from the reporting level of an impurity[1] to 120% of the specification;

  for impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the detection/quantitation limit should be commensurate with the level at which the impurities must be controlled.

  Note: for validation of impurity test procedures carried out during development, it may be necessary to consider the range around a suggested (probable) limit;

- if assay and purity are performed together as one test and only a 100% standard is used, linearity should cover the range from the reporting level of the impurities[1] to 120% of the assay specification;

4. ACCURACY

Accuracy should be established across the specified range of the analytical procedure.

4.1. Assay

4.1.1 Drug Substance

Several methods of determining accuracy are available:

a) application of an analytical procedure to an analyte of known purity (e.g. reference material);

b) comparison of the results of the proposed analytical procedure with those of a second well-characterized procedure, the accuracy of which is stated and/or defined (independent procedure, see 1.2.);

c) accuracy may be inferred once precision, linearity and specificity have been established.

4.1.2 Drug Product

Several methods for determining accuracy are available:

a) application of the analytical procedure to synthetic mixtures of the drug product components to which known quantities of the drug substance to be analysed have been added;

b) in cases where it is impossible to obtain samples of all drug product components , it may be acceptable either to add known quantities of the analyte to the drug product or to compare the results obtained from a second, well characterized procedure, the accuracy of which is stated and/or defined (independent procedure, see 1.2.).

c) accuracy may be inferred once precision, linearity and specificity have been established.

---

[1] see chapters “Reporting Impurity Content of Batches” of the corresponding ICH-Guidelines: “Impurities in New Drug Substances” and “Impurities in New Drug Products”

4.2. Impurities (Quantitation)

Accuracy should be assessed on samples (drug substance/drug product) spiked with known amounts of impurities.

In cases where it is impossible to obtain samples of certain impurities and/or degradation products, it is considered acceptable to compare results obtained by an independent procedure (see 1.2.). The response factor of the drug substance can be used.

It should be clear how the individual or total impurities are to be determined e.g., weight/weight or area percent, in all cases with respect to the major analyte.

4.3. Recommended Data

Accuracy should be assessed using a minimum of 9 determinations over a minimum of 3 concentration levels covering the specified range (e.g. 3 concentrations/3 replicates each of the total analytical procedure).

Accuracy should be reported as percent recovery by the assay of known added amount of analyte in the sample or as the difference between the mean and the accepted true value together with the confidence intervals.

5. PRECISION

Validation of tests for assay and for quantitative determination of impurities includes an investigation of precision.

5.1. Repeatability

Repeatability should be assessed using:

a) a minimum of 9 determinations covering the specified range for the procedure (e.g. 3 concentrations/3 replicates each)

or

b) a minimum of 6 determinations at 100% of the test concentration.

5.2. Intermediate Precision

The extent to which intermediate precision should be established depends on the circumstances under which the procedure is intended to be used. The applicant should establish the effects of random events on the precision of the analytical procedure. Typical variations to be studied include days, analysts, equipment, etc. It is not considered necessary to study these effects individually. The use of an experimental design (matrix) is encouraged.

5.3. Reproducibility

Reproducibility is assessed by means of an inter-laboratory trial. Reproducibility should be considered in case of the standardization of an analytical procedure, for instance, for inclusion of procedures in pharmacopoeias. These data are not part of the marketing authorization dossier.

5.4. Recommended Data

The standard deviation, relative standard deviation (coefficient of variation) and confidence interval should be reported for each type of precision investigated.

6. DETECTION LIMIT

Several approaches for determining the detection limit are possible, depending on whether the procedure is a non-instrumental or instrumental. Approaches other than those listed below may be acceptable.

6.1. Based on Visual Evaluation

Visual evaluation may be used for non-instrumental methods but may also be used with instrumental methods.

The detection limit is determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be reliably detected.

6.2. Based on Signal-to-Noise

This approach can only be applied to analytical procedures which exhibit baseline noise.

Determination of the signal-to-noise ratio is performed by comparing measured signals from samples with known low concentrations of analyte with those of blank samples and establishing the minimum concentration at which the analyte can be reliably detected. A signal-to-noise ratio between 3 or 2:1 is generally considered acceptable for estimating the detection limit.

6.3 Based on the Standard Deviation of the Response and the Slope

The detection limit (DL) may be expressed as:

$$DL = \frac{3.3\ \sigma}{S}$$

where σ = the standard deviation of the response

S = the slope of the calibration curve

The slope S may be estimated from the calibration curve of the analyte. The estimate of s may be carried out in a variety of ways, for example:

6.3.1 Based on the Standard Deviation of the Blank

Measurement of the magnitude of analytical background response is performed by analyzing an appropriate number of blank samples and calculating the standard deviation of these responses.

6.3.2 Based on the Calibration Curve

A specific calibration curve should be studied using samples containing an analyte in the range of DL. The residual standard deviation of a regression line or the standard deviation of y-intercepts of regression lines may be used as the standard deviation.

6.4 Recommended Data

The detection limit and the method used for determining the detection limit should be presented. If DL is determined based on visual evaluation or based on signal to noise

ratio, the presentation of the relevant chromatograms is considered acceptable for justification.

In cases where an estimated value for the detection limit is obtained by calculation or extrapolation, this estimate may subsequently be validated by the independent analysis of a suitable number of samples known to be near or prepared at the detection limit.

7. QUANTITATION LIMIT

Several approaches for determining the quantitation limit are possible, depending on whether the procedure is a non-instrumental or instrumental. Approaches other than those listed below may be acceptable.

7.1. Based on Visual Evaluation

Visual evaluation may be used for non-instrumental methods but may also be used with instrumental methods.

The quantitation limit is generally determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be quantified with acceptable accuracy and precision.

7.2. Based on Signal-to-Noise Approach

This approach can only be applied to analytical procedures that exhibit baseline noise.

Determination of the signal-to-noise ratio is performed by comparing measured signals from samples with known low concentrations of analyte with those of blank samples and by establishing the minimum concentration at which the analyte can be reliably quantified. A typical signal-to-noise ratio is 10:1.

7.3. Based on the Standard Deviation of the Response and the Slope

The quantitation limit (QL) may be expressed as:

$$QL = \frac{10\,\sigma}{S}$$

where σ = the standard deviation of the response

S = the slope of the calibration curve

The slope S may be estimated from the calibration curve of the analyte. The estimate of s may be carried out in a variety of ways for example:

7.3.1 Based on Standard Deviation of the Blank

Measurement of the magnitude of analytical background response is performed by analyzing an appropriate number of blank samples and calculating the standard deviation of these responses.

7.3.2 Based on the Calibration Curve

A specific calibration curve should be studied using samples, containing an analyte in the range of QL. The residual standard deviation of a regression line or the standard deviation of y-intercepts of regression lines may be used as the standard deviation.

7.4 Recommended Data

The quantitation limit and the method used for determining the quantitation limit should be presented.

The limit should be subsequently validated by the analysis of a suitable number of samples known to be near or prepared at the quantitation limit.

8. ROBUSTNESS

The evaluation of robustness should be considered during the development phase and depends on the type of procedure under study. It should show the reliability of an analysis with respect to deliberate variations in method parameters.

If measurements are susceptible to variations in analytical conditions, the analytical conditions should be suitably controlled or a precautionary statement should be included in the procedure. One consequence of the evaluation of robustness should be that a series of system suitability parameters (e.g., resolution test) is established to ensure that the validity of the analytical procedure is maintained whenever used.

Examples of typical variations are:

- stability of analytical solutions,
- extraction time

In the case of liquid chromatography, examples of typical variations are

- influence of variations of pH in a mobile phase,
- influence of variations in mobile phase composition,
- different columns (different lots and/or suppliers),
- temperature,
- flow rate.

In the case of gas-chromatography, examples of typical variations are

- different columns (different lots and/or suppliers),
- temperature,
- flow rate.

9. SYSTEM SUITABILITY TESTING

System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analyzed constitute an integral system that can be evaluated as such. System suitability test parameters to be established for a particular procedure depend on the type of procedure being validated. See Pharmacopoeias for additional information.

11

Out-of-Specification Results

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OVERVIEW

This chapter is intended to give the reader an overview and understanding of how an out-of-specification (OOS) result is investigated to assure that all aspects are included and documented and a valid conclusion is reached. The procedures and steps that should be covered, as well as the responsibility to determine the root cause and implement corrective actions, are described. The responsibilities and roles of the QC laboratory for the OOS and any failure investigation are detailed, including the key areas to be covered: standards and controls, the analyst, the SOP, the equipment, the sample, the reagents, the assay, the glassware, and the analysis of the data generated. Methods to assure the investigation is timely and unbiased are emphasized.

KEY WORDS

- Barr decision
- CLIA
- Failure investigation
- OOS
- SOP for OOS

INTRODUCTION

Integrity of laboratory testing and the records that document the testing are considered by the FDA to be of "fundamental importance during drug manufacturing."[1] Laboratory results that can lead to the generation of out-of-specification (OOS) results can include both chemical/assay-based testing and computer/instrument-generated results. Out-of-specification results can also be generated from a monitoring and trending perspective. Any type of OOS result, regardless of its origin, must be thoroughly investigated and documented.

Laboratory testing and the investigation of suspect results have basis in cGMP regulations, mandated both from the FDA and worldwide authorities. Laboratory testing is required to assure the conformance to specifications for raw materials, in-process materials, finished product, containers, and closures.[2] Interpretation of results only allows for exclusion of failing results if the results can be determined to be invalid.

Thorough investigation of OOS results should not just be limited to the GMP environment. Development of products can be seriously impacted by unexpected results that are not properly investigated and documented, costing untold time in delays or misplaced effort spent pursuing false avenues based on questionable analytical results. The burden of documentation may be lessened in such a non-GMP environment, but the degree of investigation into the assay performance and accuracy should not be any less rigorous.

Since assay results are so fundamental to the process of developing and producing safe and effective products, the investigations need to be conducted from a sound scientific basis. The investigations need to be timely, unbiased, and result in assessments that are scientifically defensible. This chapter will address OOS investigations, what they are, when they occur, responsibility for performing these investigations, and how resolution is achieved.

WHAT IS AN OOS?

An out-of-specification (OOS) result is any result which falls outside of acceptance criteria, expected results, or specifications as written in test plans or test procedures. The FDA has proposed one definition of specification as "the quality standard (i.e., tests, analytical procedures and acceptance criteria) . . . to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents and other components . . . acceptance criteria refers to numerical limits, ranges, or other criteria for the tests described . . . To determine if material being tested complies with a specification, there must be predetermined criteria."[3]

Unexpected results can occur for obvious and not so obvious reasons. Obvious reasons for an unexpected result can include spilling of the sample, insufficient sample volume, or failure of an assay standard or reference sample, any of which may render the test invalid. Analysts should be trained such that testing is not continued when events occur which may cause an assay to be invalidated. This must be documented at

the time of the incident. In addition, errors in the performance of any assay should always be documented. When an unexpected result occurs and the analyst cannot determine an obvious reason for the result, all of the testing materials should be retained, the laboratory supervisor must be informed, and a thorough investigation is initiated.

For any unexpected result, an OOS investigation must be performed and that investigation must be documented. The individual designated to perform the investigation must initiate a thorough and timely assessment to determine whether or not the OOS resulted from laboratory error. This assessment must be prompt and may include:

- Review of the test data, including raw data and any charts or instrument printouts for errors;
- Review of test system suitability, including review of: test instrument or equipment performance: equipment or instrument calibration records; assay/method control charts; the preparation of solutions, reagents, and standards and controls used in the assay; glassware used, etc.;
- Review of sample suitability including sample identity or sample integrity; and
- Interview of analyst to verify proper knowledge and training adequacy in the performance of the test procedure or assay.

Each step of the above assessment must be fully documented in an investigation report. It has been recommended that the investigation be completed within 30 days.

In order to conclude that the OOS was due to laboratory error, one often needs to have a hypothesis that can be proved. For instance, interview the analyst and determine that a dilution error may have occurred. This theory may be tested when one is able to examine the original sample and repeat the test.

Laboratory error should be rare since trained analysts and validated procedures must be utilized. If it is determined that an analyst is inadequately trained or a procedure is not properly validated (for example, the assay may be validated but the SOP does not reflect the validation or is not clearly written), you must correct these errors and document this in the investigation. Keeping track of the completion of the corrective action is essential to your investigation and provides valuable history of good laboratory operations.

SOP FOR OOS

In order to assure that investigations into OOS results follow a standard approach, are timely, and are properly documented, it is necessary to develop an SOP covering this process. In developing this SOP, one must take into consideration the roles and responsibilities of the individuals involved in the laboratory environment. An awareness of any preconceived assumptions that are likely is also helpful, so that the procedure can address the elimination of these prejudices. Development of the SOP governing OOS investigations should also take into consideration the degree of involvement of other departments and the roles they might play.

The quality unit should develop the procedure and lead the OOS investigations. Any procedure covering these investigations should state the minimum requirement of such an investigation, list the responsible areas and define their responsibilities, provide guidance on determining the scope of the investigation, identify possible or probable causes, document requirements, and determine the mechanism for concluding the investigation. It is helpful to have some type of form or checklist to use in the investigation, although it must be understood that the investigation should not be limited to steps delineated in the SOP. The investigation may uncover other areas not on the checklist that need to be investigated.

The SOP should also specify levels of approval needed to conclude the investigation. These levels may be different based on the scope and impact of the suspect result, or the scope and impact of the corrective actions identified through the investigation. Approval levels may also differ for "laboratory centered" investigations and full failure investigations that impact the manufacturing process or actual product.

At the onset of an OOS investigation, the initial responsibility for the investigation is with the analyst. Clear guidance in the responsibilities of the analyst should be embodied in the SOP. These responsibilities include initial unbiased review of suspect results, accurate recording of any unusual events, errors, or malfunctions that occurred during the testing of the original sample, and performing any retesting allowed by specific SOPs as warranted. Some organizations have special individuals or groups responsible for overseeing the investigation and assuring its adequacy, timeliness, and completion.

Responsibilities of the supervisor should be differentiated from the analyst in the SOP. Such responsibilities would include: assessment of the assay data to ascertain if laboratory error is the cause, authorizing re-examination of test samples as warranted, verification of appropriate test procedure and analyst training, documentation of the initial OOS investigation, and notification to other individuals or groups if the investigation extends beyond the individual laboratory.

Approval of all investigations, OOS and failure, should be clearly defined in the SOP. As mentioned before, approval levels may differ given different circumstances, but all should be approved at a minimum by the quality unit. Some organizations have two separate procedures, one for laboratory investigations and one for full product investigations.

OOS Methodology

The methodology used for the OOS investigation is critical to the operation of the QC laboratory, the good manufacturing practice (GMP) compliance of the company, and the final safety and efficacy of the products produced. As previously indicated, the same methodology can and should be expanded to non-GMP situations in preclinical areas and process development. This can be helpful to both the design of the processes and the testing methodologies used.

Although the investigations can include all aspects of production, this only happens after the initial OOS investigation in the quality control laboratory. It must first be determined that a valid result has been obtained before proceeding to the next steps. The first area of discussion is related to the QC laboratory aspects of an OOS. See Figure 11.1

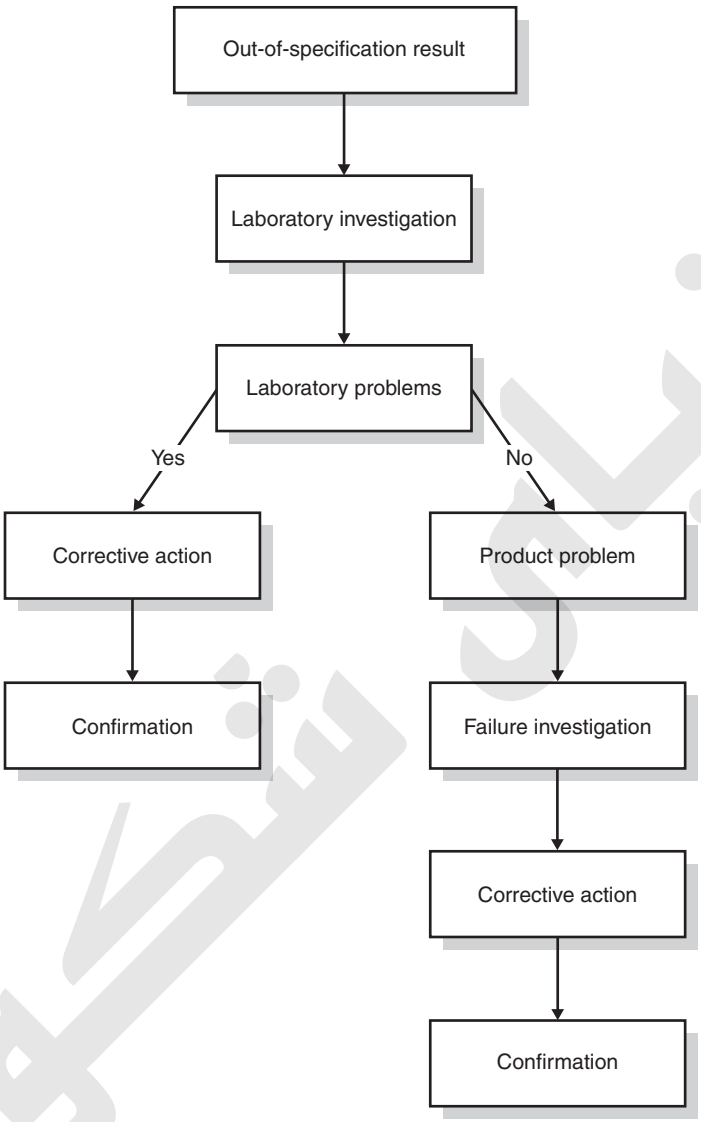

Figure 11.1 Overview of OOS.

for an algorithm of the steps regarding all aspects of an OOS investigation. Once an OOS result is generated, the QC laboratory must first determine whether or not it is a laboratory error. If laboratory error is determined, the follow-up and corrective action is laboratory oriented. If the OOS is not a result of laboratory error, a full-scale failure investigation is undertaken with the laboratory playing a supporting role.

The investigation and related activities must not just be a formality that the technician thinks is a "have to do," but should be done with both the timeliness and insight to identify

any problems, root causes, or areas that the QC laboratory must address. In the Barr decision, 30 days was indicated to be a reasonable time for completion of an investigation, including both the laboratory and the full-scale investigation. It is important that a consistent process is utilized, and that this process is documented from a GMP standpoint and from an operational standpoint. This should include an ability to trend any significant laboratory problems. In addition, if other similar incidents occur in the future, these investigations must be clear and available as a resource for this additional investigation.

An assay can only be invalidated after a complete and scientific investigation. If there is lack of definitive proof, it must be assumed that the problem is process or product related. In many instances, technicians will note a problem during an assay but continue with the hope that the result will be acceptable. If an assay is not invalidated at the time of the problem and is carried to completion, it will be necessary to perform a complete OOS investigation.

As indicated earlier, the SOP that has been approved for this process should be used as a guide. The better the SOP, the better the guide. No SOP can replace the knowledge and experience of the technician running that assay. The investigation must be done with an open mind and with clear thinking. The purpose of the OOS investigation should never be forgotten: is there a product problem or an assay problem? The assay problem could be the result of a single incident and/or technician error, a sample problem, an equipment problem or malfunction, dirty glassware, an inconsistent assay that is not reproducible, or an assay that is not appropriate for the intended use. The investigation must be clear, concise, and thorough. It must be scientifically sound and not open to individual biases.

Time limits for the initiation of the investigation should be in the SOP. This will obviously be dependent upon the stability of the product and the type of sample. For example, an assay of a microbiological sample will necessitate a much faster turnaround then a chemical assay on a stable sample. Sampling tables will indicate how the product should be stored and this document should be consulted immediately. The ideal situation, in the event of a laboratory OOS, is to test the same material originally tested. This may not always be possible but should be the first choice. The assay SOPs should clarify what and how any additional tests should be run. Good QC SOPs also include criteria to determine the validity of the assay and any system suitability parameters. The time limits necessitate the need to review test results in a timely manner. If the test results are not reviewed for days or weeks, then there is an increased possibility that there will not be appropriate samples for additional testing or accurate recollection of the event that occurred, which may have contributed to the unexpected result. An easily resolvable situation could become an untenable issue causing the rejection of a lot.

At the start of the investigation the technician should remember that s/he is trying to determine whether or not there is an assay problem or a product problem. The atmosphere in the laboratory should strive for open-mindedness, thus ensuring that technician error will be accepted within the realm of normal operation. General laboratory GMP operations are covered in 21CFR part 211 subparts I and J. Even if a lot is rejected, a written OOS must still be undertaken.[4] In a GMP environment, it would be expected that there should not be a large number of laboratory errors. If this is not the case, further investigation into the operation of the lab and the general quality of procedures, training, SOPs, and techniques is mandated.

There are at least nine areas that should be covered in a laboratory OOS investigation: standards and controls, technicians, SOPs, equipment, samples, reagents, assays, glassware, and raw data. Figure 11.2 shows an algorithm of these steps and some of the questions that must be addressed. This is a suggested order for these steps, but experience with the assay and product might suggest a different order. Once started, it is important to go through all steps because there may be multiple reasons for a problem. If one stops an investigation prematurely, the lab could encounter other problems later.

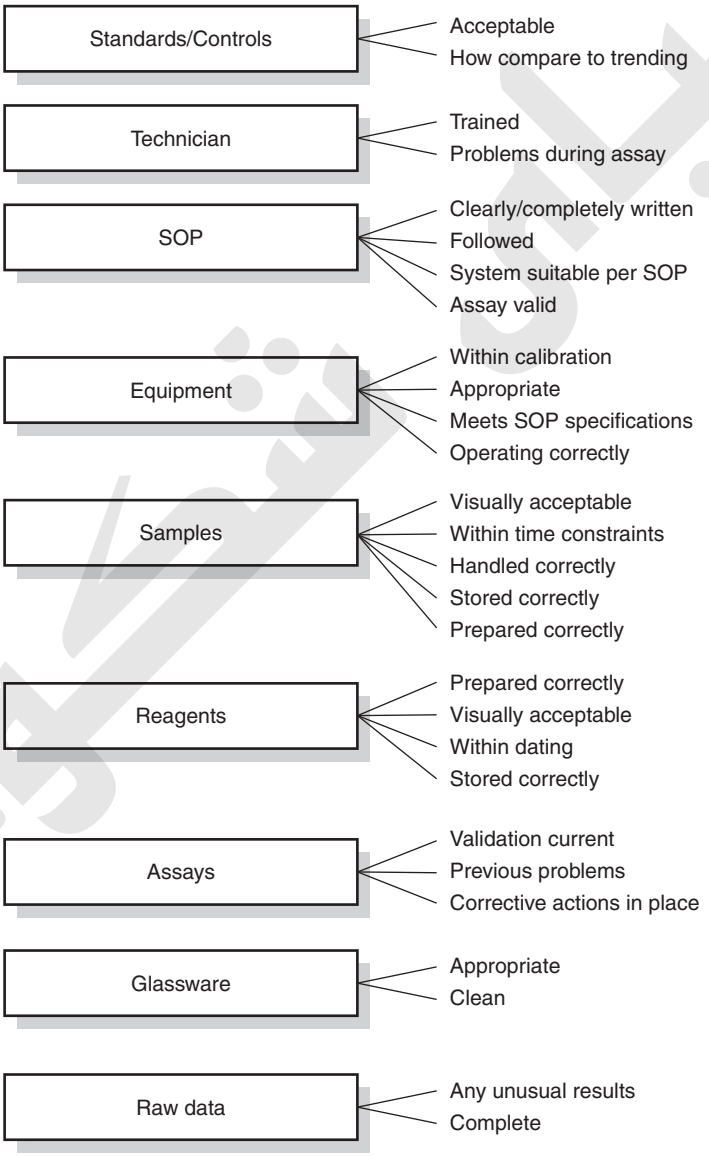

Figure 11.2 Steps in laboratory OOS investigation.

Standards/Controls

The validity of the assay is easily determined from the standards or controls that are utilized. The SOP should clarify what values must be obtained. These controls should be trended and have set values. The control should normally follow the total test process and not just parts of the test. It is important that the laboratory also have stability data on their controls. Many assays have problems because the controls are not stable and, as a result, give erroneous information. In the event of an OOS, the values of the controls or standards obtained should be compared to the trend charts. Are the controls changing over time? Is the control value significantly different from the norm? These are good indications of a problem.

Technician

The training and knowledge of the technician running the assay should be reviewed. How long have they been running the assay and what experience do they have? They should be asked about the assay and any problems/changes or concerns that might have come up during the test. It is important to have an open and honest atmosphere so the technician will feel free to share information. A trained technician is one of the best sources for sharing potential problem areas. This is also true in the event of a full-scale investigation; the operators performing the activity are one of the best sources of information for potential problem areas. They should always be interviewed during any investigation.

SOP

Is the test or equipment operation SOP clearly written so there is no confusion? Does it clearly delineate all steps and actions necessary? Did the technician follow the SOP as written? Were the system suitability parameters clear, and did the assay met these requirements? Was the assay valid according to the SOP?

Equipment

Was the equipment used for the assay as specified? Was the equipment operated per SOP or operator's manual? Was it within calibration? Did it meet the SOP requirements? Was it operated correctly? Did it operate in a consistent manner as expected? Was the equipment designed and validated for its intended use?

Samples

Are the samples visually acceptable? Were they taken as required? Have they been handled as required, including storage? Was the assay run in the required time? Was the correct sample tested? Many microbiological assays have specific time requirements to assure that the data represent the product and not the storage condition of the samples. Were the samples prepared correctly? Inadequate handling of samples is one of the key reasons for laboratory OOS results.

Reagents

Reagents are critical to an assay and must be prepared correctly. There should be SOPs for the preparation of the reagents and controls. There should be stability data for the allowed storage time and temperatures. They should be visually inspected to assure that they have not been contaminated or degraded.

Assays

Is there data to justify that this assay is valid for its intended purpose? Have there been previous problems with the assay, and what corrective actions have been taken? Are the indicated corrective actions in place? Assays that continuously have OOS situations may indicate that the assay is not appropriate for the intended purpose.

Glassware/Containers

Was the correct glassware or container used? Was it visually inspected for acceptability? Was the glassware prepared as required (for example, for pyrogen testing, was it adequately depyrogenated)? If one-time-use containers, were they procured from the correct vendor? Did they meet the required standards prior to use? Was the glassware/container clean prior to testing?

Raw Data

Review the raw data to determine if there were any anomalies. Did anything unusual happen or is the information incomplete? Were there any calculation errors? If prepared by computer, are the controls for the computer adequate and has the computer or spreadsheet been validated for its intended function?

The investigation should be done by the individual performing the assay in conjunction with a second independent person. In most situations this is a supervisor, but it is possible to have a special individual in a laboratory whose responsibility is investigations. This helps for a consistent, unbiased approach. Obviously, this individual must be trained and have an open mind. Each step of the investigation should be documented as it is undertaken, not at the end. If one waits until the end in a complicated situation, many of the facts may be missed. The SOP should supply a form or format for this documentation. It should be remembered that it is extremely difficult to prepare sound scientific data to prove that an OOS is laboratory related.

At the conclusion of the investigation if there is sound proof that the result was due to a laboratory error, then the result can be invalidated. There should be a manager's signature required on these reports because of their impact and to assure valid conclusions. If the suspect test result is invalidated due to laboratory error, the test may be rerun according to procedure. This is not a retest, because the first result was not valid. In the ideal situation this rerun test should be done on the same sample as the first test. There is an important distinction between an invalid test that is rerun and a retest. The laboratory SOP should clarify this and all technicians should clearly understand this

distinction. This invalid decision should be confirmed by Quality Assurance, either through an audit or review of the records.

If the investigation indicates that the problem is not laboratory related, then a failure investigation should be undertaken. The specific steps in this type of investigation have similarities to a laboratory investigation but will only be discussed in this chapter as they relate to the QC laboratory. Figure 11.3 is an algorithm for this full-failure investigation. The two areas of concern are to identify the scope of the problem and to determine the root cause. The steps and activities should be clarified the same as they would be for a laboratory investigation. In this failure investigation, it is often difficult to determine the root cause and necessary follow-up corrective actions.

Clear, appropriate, and implementable corrective actions must be identified at the conclusion of any investigation, OOS, or failure. These corrective actions should be agreed to and implemented by the appropriate individuals. SOPs should have guidelines for these steps. For obvious situations where no investigation is warranted beyond documentation of the contributing event, such as a spilled sample, identification of a corrective action is not usually required. For all other investigations this is key to correcting the problem and preventing reoccurrence. Corrective actions may be either short-term until a better system is put in place, or long-term. Examples of corrective actions can include adding clarity to a procedure, performing maintenance on an instrument, or in certain situations, revalidation may be required. All identified corrective actions need to address the identified "probable" or "root cause" of the failure. There should be approval or acceptance of the corrective action and a tracking system to assure the implementation and effectiveness of the corrective action.

OOS IMPLICATIONS

The implications of an OOS can vary depending on the product and stage of the product lifecycle where the unexpected result occurs. An OOS that is not attributable to laboratory error extends the investigation outside of the laboratory, to the manufacturing process. The supervisor of the manufacturing process or other designated individual should undertake an investigation similar to the one performed in the laboratory. As indicated, there are two major sections to this full-scale failure investigation: determination of the scope and determination of the root cause. The stage or step in the process is investigated to determine if there were any circumstances that contributed to an OOS. The batch records should be reviewed and the operator should be interviewed. As with the laboratory investigation, every step of this investigation must be fully documented. This latter investigation is more extensive than a laboratory investigation, although the laboratory plays a supporting part. The same parameters that apply to a laboratory investigation also apply to full-failure investigations in regard to timeliness, unbiased approach, scientific defensibility, and documentation.

The results of an investigation may determine that the process or the product does not meet the acceptance criteria, specification, or instructions in the batch record for that step. In the example of a raw material used in a process, the implication of an OOS may not be as severe as an OOS determined after a product is in the hands of

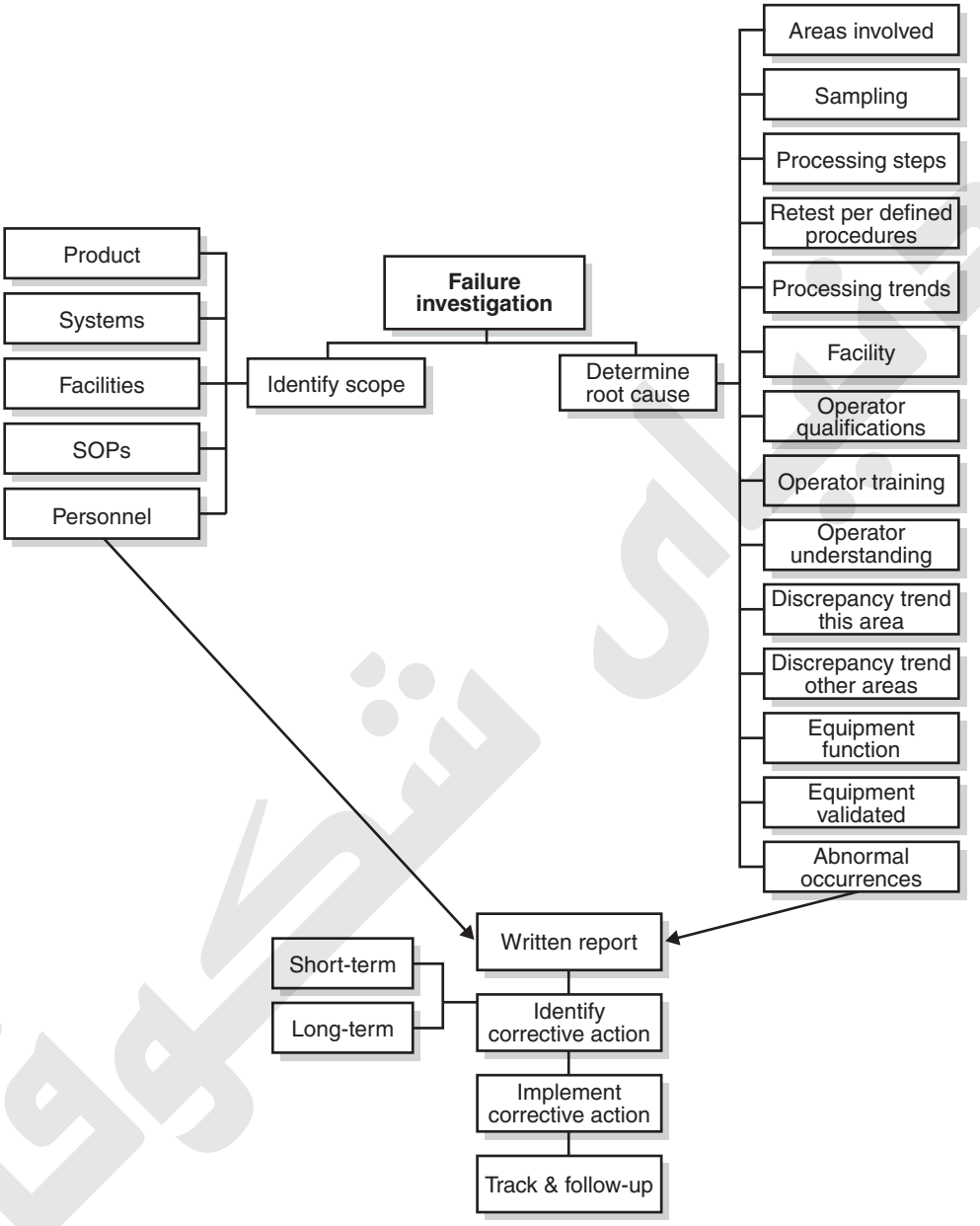

Figure 11.3 Investigation of a failure.

Modified from Jean F. Huxsoll, A Practical Approach to Investigating GMP Failures. *Biopharm* August, 1999, 40. Used by permission.

the consumer. One example of this latter situation is an OOS resulting from ongoing product stability studies.

An investigation of an OOS may determine that acceptability of the entire batch is now in question. Moreover, the investigation may expand to other batches, and again a greater risk is involved if other impacted batches have been released to the customer.

The implications of an OOS could be related to compliance issues, process capabilities, and/or safety. A GMP manufacturer must have compliance as the basis for daily processing and testing. An OOS could be an indication of a compliance breach. Thus, the investigation and completion of corrective action is critical to the normal operating environment. In the case of an OOS related to process capabilities, this could be an indication of a process that is not well-defined, not robust, not developed for routine manufacturing, or not sufficiently validated. The results could result in serious regulatory consequences, including such items as error and accident reports (Biological Product Deviation Reports), product withdrawal, product recall, assay, or process changes that necessitate regulatory approval or product availability. The safety issues are obvious to the end user and are discussed later. As with an OOS investigation, appropriate corrective actions need to be identified, approved, and implemented.

LIMITATIONS OF OOS

The results of an OOS investigation are only as good as the investigation process, and often not conclusive in regard to the determination of a root cause. One faces the challenges of having insufficient information to perform a complete investigation. It may be determined that a series or combination of events may have occurred; however, no single event is assignable. This is a compelling reason for completing an investigation prior to making any corrective actions. It may require multiple corrective actions and still not address the complete cause of the OOS. It is possible that in some cases no cause will be found. There will be indications of a problem but no definitive proof. The corrective actions should be taken in a systematic manner with systematic follow-up to assure that the end result is as desired.

The disposition of the batch may be for further processing at the end of the OOS investigation, but one must always take the OOS into consideration in the evaluation of the release of the batch.

Quality Control Laboratory Responsibilities in Failure Investigations

If a full-scale failure investigation is necessary, the laboratory has certain responsibilities to assure the validity of the investigation. This primarily covers any retesting to be performed. The requirements for the retesting would include: how samples should be taken and stored, what samples should be tested, how many tests may be run, and how the data is interpreted. The quality control department not only has to have expertise in laboratory methods but they must stay current with product and process trend reviews. They must be actively involved with routine production and process changes.

SOPs must include the criteria for retesting. The number and types of allowable retests must be designated in the SOP, and must be specified as part of the normal testing process. The retesting is obviously dependent upon the type of assay being run; chemical assays are very different from microbiological. If the original results are valid, it is not acceptable to retest and ignore the initial test results. In addition, unless the SOP specifically allows for averaging, the values cannot be averaged especially to make

something meet specification. Thus, individual values that do not meet specifications cannot be averaged to bring the overall results into specification. This was a clear result of the United States versus Barr in 1993. Averaging will hide the variability that can be seen from individual values. It is acceptable to average in certain circumstances, provided those instances have been clearly defined in the test method SOP.

In some instances, retesting will be for investigation purposes only and not for the resolution of the disposition of the material. This is to help pinpoint the reason for the failure in order to take corrective action. This type of testing is as important as lot release because of the long-term implications for the company.

If at all possible, the retest should be on the same sample. The test should be done by a different technician from the technician who originally ran the test. If resampling is necessary, it should have also been designed in the SOP. It is important to have all parameters predetermined. The number of allowable retests should be statistically and scientifically valid. These must be indicated in the SOP and the number of seven from the Barr decision is often used.

The QC laboratory should have SOPs in place in regard to data interpretation and the statistical procedures acceptable for use. It is not acceptable to establish these criteria as part of an investigation; they also must be predetermined. In a rare instance, an outlier interpretation may be taken into account in the analysis of the data. In the 1993 Barr decision, the court allowed for the use of outliers for biological tests but not for chemical tests. This is again to be clarified in an SOP and should not be used in situations that may invalidate a valid result that was caused by product failures. During a full-scale investigation, it may be necessary to run additional tests for strictly investigation purposes. The QC laboratory should be involved in this decision and the types of tests that will clearly add to the investigation and corrective action plans. In these cases, these are not retests because they are not for the release of product, but are for resolution of the investigation. These assays may be critical to potential future corrective actions and should be run with the same care as a release test assay.

As with the laboratory OOS investigation, all steps of the failure investigation must be clearly documented and reported in a timely manner to those performing the investigation. Thus, QC must support these efforts by timely and documented responses to their parts of the investigation.

Consumer Safety/Expectation

The product consumers expect is a product that meets all the established specifications and quality standards. The consumer assumes that the product has been manufactured correctly. As a manufacturer, the responsibility is for the safety, purity, potency, identity, and quality of the product. In some cases, the Food and Drug Administration (FDA) oversees these attributes. The health, and sometimes the lives, of the customers depend on the procedures, controls, testing, and personnel engaged to manufacture the product. Failure of the laboratory to perform an adequate OOS investigation can lead to the release of product detrimental to the health and safety of the customer, and can place extraordinary financial burden on the manufacturer.

Financial Impact

In the example of an OOS determined for a batch of raw material versus an OOS that occurs during stability testing of a product which is already in the consumers' hands, the financial consequences can range from minimal to monumental. The results could vary from the formal recall of the material involved and its replacement, to the liabilities associated with product that may not function as designed. A rejected batch of raw material may cost you in terms of production time and product availability. The downtime could be limited to extensive, depending on the material, and the availability of additional acceptable raw material in inventory. It may be possible to eventually recover the cost of the rejected material from the vendor. If the problem results in vendor disapproval (for example, due to repeat failures of batches), this may incur the cost of qualifying another vendor and the downtime associated with the qualification.

The associated costs of correcting a problem with a batch that has already been distributed to your customer are not so easy. For instance, you must prepare your recall or market withdrawal announcement, complete with detailed information about the handling and return of product, and you must notify both the regulatory agencies involved and your customers quickly. Often, you offer the customer replacement material and you pick up the cost of replacing their product. You may have to develop special labeling and perform a field correction. You may suffer negative publicity and lose percentages of your market share. Lengthy litigation may follow on behalf of affected consumers. All of these activities are additional costs to your business that can result from an OOS on the magnitude of a recall or market withdrawal.

Regulations

Specific regulations and other general references that relate to OOS investigations are listed for your reference.

21 CFR 210.1 (a) The regulations set forth in this part and in parts 211 through 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacturing, processing, packing, or holding of a drug. This is to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

21 CFR 211.64 This is the requirement for performing laboratory testing to confirm that components, containers, and closures in process materials and finished products conform to specifications, including stability.

21 CFR 211.160 (a) The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and documented at the time of performance.

Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.

21 CFR 211.160 (b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

1. Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.
2. Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.
3. Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified.
4. The calibration of instruments, apparatus, gages, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gages, and recording devices not meeting established specifications shall not be used.

Clinical Laboratory Improvement Act (CLIA)—*42 CFR Part 493*

42 CFR 493.1425. The testing personnel are responsible for specimen processing, test performance, and for reporting test results.

b. Each individual performing moderate complexity testing must:
    1. Follow the laboratory's procedures for specimen handling and processing, test analyses, reporting, and maintaining records of patient test results;
    2. Maintain records that demonstrate that proficiency test samples are tested in the same manner as patient samples;
    3. Adhere to the laboratory's quality control policies; document all quality control activities, instrument, and procedural calibrations; and maintenance performed;

4. Follow the laboratory's established corrective action policies and procedures whenever test systems are within the laboratory's established acceptable levels of performance;
5. Be capable of identifying problems that may adversely affect test performance or reporting of test results, and either must correct the problems or immediately notify the technical consultant, clinical consultant, or director; and
6. Document all corrective actions taken when test systems deviate from the laboratory's established performance specifications.

***Quality System Regulation in 21 CFR Subpart I*—Nonconforming Product**

820.90 (a) Control of nonconforming product. Each manufacturer shall establish and maintain procedures to control product that does not conform to specified requirements. The procedures shall address the identification, documentation, evaluation, segregation, and disposition of nonconforming product. The evaluation of nonconformance shall include a determination of the need for an investigation and notification of the persons or organizations responsible for the nonconformance. The evaluation and any investigation shall be documented.

***United States v. Barr Laboratories, Inc.*, 812 F. Supp. 458, 464 (D.N.J. 1993)**

21 CFR 600.14 Reporting of Errors

21 CFR 600 and 605 Proposed Rule: Reporting of Errors and Accidents in Manufacturing. Federal Register Vol. 62, No. 184 Tuesday September 23, 1997.

21 CFR 600 and 605 Final Rule. Biological Products: Reporting of Biological Product Deviations in Manufacturing. Federal Register Vol. 65, No. 218, Thursday, November 9, 2000.

SUMMARY

For any laboratory, the primary operating principle is ultimate integrity of their testing and the records that document that testing. Thorough investigation of suspect results begins first in the laboratory with the assessment of the test data, the test system suitability, the sample suitability, and the interview with the analyst. The timely investigation into each of these aspects must be thoroughly documented. In general, the investigation should be completed within 30 days. It is important to remember that what you are looking for, the root cause, should be rare and possibly hard to find; after all, you are utilizing trained analysts and validated assays.

The SOP for OOS investigation should be developed and/or approved by the quality unit. The procedure should state the minimum requirements of OOS investigations, provide information regarding the scope of investigations, and define the roles and

responsibilities of those persons performing, reviewing, and approving investigations. The methodology used for the investigation is critical to the laboratory's operation and to the firm's compliance with GMP. The same methodology is beneficial in non-GMP areas such as the preclinical research and process development functions.

The OOS investigation must be scientifically sound and free from bias. The prime targets of investigation are the standards and controls used, the analyst/technician, the SOP, the equipment, the sample, the reagents, the assay, the glassware/containers used, and the raw data. The investigation of each of these target areas must be documented at the time it is performed.

At the conclusion of the OOS investigation you must have sound scientific proof to invalidate the test result. The assay can be run again as if for the first time, only it is desirable to test the original sample if available. If, however, the suspect result is valid, a failure investigation must be initiated. The two prime objectives of failure investigations are to define the appropriate scope of investigation and to determine the root cause of the failure. Though the focus of this information is related to laboratories, a diagram was presented to enumerate target areas of failure investigations.

The implications of an OOS can vary widely depending on the product and the step or stage of processing. Out-of-specification results can implicate your laboratory's compliance program, or indicate inadequate assays, or can point to inadequate process capability, or, the ultimate in concern, indicate lack of product safety assurance.

The main limitation of an OOS investigation is often that the investigation does not yield a definitive cause for the suspect result. You may end up with contributing causes and corrective actions yet still not address the cause of the OOS.

The QC laboratory plays an important role even after a conclusion that a suspect result is valid. Their part in a failure investigation primarily involves determination of any retesting, including any retesting requirements, how samples are taken and stored, what samples are tested, and how many tests should be run. Ultimately the QC unit must interpret the test data generated. The failure investigation should cover these responsibilities and the criteria for retesting, including the number and type of allowable retests.

Data interpretation and statistical procedures for use should be addressed in the QC SOPs and, like acceptance criteria, should be predetermined. It is never a good policy to establish this criteria during an investigation. In light of the Barr decision, the subject of averaging of results should be carefully defined in the SOPs. If possible, the retest should be on the original sample. In some cases, additional tests may be performed for investigation purposes only. These tests are not utilized in the decision to release the product. They are helpful to pinpoint problems and assist in corrective action determinations.

It is clear that the consumer expects a product that meets all of the established specifications. Failure to perform an adequate OOS investigation could lead to serious complications for the customer and your laboratory. The financial implications can vary; however there is additional cost with any OOS. A rejected raw material which never makes it into the batch is much easier to correct than an OOS generated for a batch already in the customer's hands.

CONCLUSION

The quality control laboratory is a key player in the manufacture and release of product to assure GMP compliance, regulatory specifications, safety, and efficacy. Although one cannot test quality into a product, test results can indicate that processes were followed according to standardized procedures. The QC test results are critical to the determination of the acceptability of the material before it is released to the consumer. There are three main reasons for batch failures: laboratory error, operator error either in the laboratory or the manufacturing environment, or process-related errors. The first of these, if proven and documented, can be overcome and additional testing performed. The latter two are identified as failures. In most cases, these failures cannot be overcome and the resulting batch or batches of product cannot be used as is.

The importance of an OOS investigation is critical. It must be completed within a reasonable time with an unbiased scientific approach. There needs to be clear distinct processes for the investigation with clear, distinct management approval on the results of the investigation. There should be sound, clear SOPs describing the steps and actions necessary for both laboratory and full-scale investigations. Since in many instances the expectations and uses by the consumer are based upon trust of the manufacturer, the investigations must be thorough. The results must reflect the data generated and cannot include assumptions without fact.

> *Each day with confidence and hope millions of people in the United States and other countries reach for pills, powders, capsules and syrups to relieve or prevent an infinite number of physical and mental ailments. The weighty task of ensuring the integrity of these products, frequently unquestioned by most consumers, falls to the Food and Drug Administration, which monitors the practices of the drug industry through a system of approvals and investigations. Built into this maze of often ambiguous rules, however, is the recognition that drug manufacturers are businesses, which must follow efficient as well as effective procedures.*[5]

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III.

Inspections

12

An FDA Approach to Laboratory Inspections

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OVERVIEW

The quality control laboratory has one of the most important functions in the manufacturing of regulated industry products. It provides the data and information related with the quality of in-process products, finished products, validation samples, and others. As such, it has been the object of increasing scrutiny in FDA audits, and laboratory data are routinely used as the basis for the rest of the GMP inspection. This chapter focuses on FDA current auditing approaches for laboratory systems, including ANDA, NDA postapproval, or general cGMP compliance-type inspections.

KEY WORDS

- FDA quality control auditing approach
- Regulatory status of laboratory quality systems
- Method validation and instrument qualifications
- Formal training program for laboratory personnel
- Sample controls
- Laboratory records and logbooks
- Quality program for laboratory reagents, standards, and test solutions
- Instrument maintenance and calibration program
- Instrument software validation program

INTRODUCTION

The demand to audit regulated facilities encompassing pharmaceutical, medical devices, biotechnology, cosmetic, and food manufacturing has always been dynamic and challenging. New auditing techniques are constantly being developed and successfully applied to such industries in order to prevent major manufacturing disasters.

The quality control laboratory has been the object of increasing scrutiny in FDA audits, and laboratory data are routinely used as the basis for the rest of the GMP inspection. Growing concern with poor laboratory practices has led to a vast amount of governmental regulations relating to good laboratory practices. Applying the necessary controls requires not only a thorough knowledge of laboratory operations but also the dedication and commitment of management staff.

The contents of this chapter will guide the reader into the current thinking of an FDA auditor while executing his/her investigation. This approach will be the same for laboratory systems, independent from the type of inspection: ANDA, NDA, or general cGMP compliance.

QUALITY CONTROL LABORATORY

The quality control laboratory has one of the most important functions in the manufacturing of regulated industry products. It provides the data and information related with the quality of in-process products, finished products, validation samples, and others.

The quality control unit is responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company. Adequate laboratory facilities should be available for the testing and approval or rejection of components, drug products, containers, closures, packaging materials, in-process materials, and drug products.

The quality control laboratory is a complex organizational system dealing with a wide range of critical factors, such as:

- Appropriate training;
- Human motivation;
- Handling of sensitive instrumentation;
- Performing wet chemistry reactions;
- Providing documentation;
- Performing calibrations and preventive maintenance; and
- Handling regulatory compliance operations related to OSHA, FDA, DEA, ISO, and other regulations or standards.

On occasion, such services deal with limitations in budget, bench space, instrumentation resources, analysts, and testing time. It takes creativity and commitment to improve the effectiveness and efficiency in the quality control laboratory.

The scope of the FDA audit usually includes the analysis of documentation related to quality procedures, test methods, compliance in laboratory equipment including maintenance and calibration, training requirements, auditing, LIMS/LANs implementation, and legal precedents from U.S. Federal Courts applied to laboratories. The order of the audit steps may vary, but usually covers the following areas:

- Incoming raw material testing;
- In-process and finished products testing;
- Stability samples;
- Complaint samples;
- ANDA/NDA validation samples; and
- Microbiological and other special samples.

The auditor will verify the regulatory status of the laboratory quality system by looking at the organization structure, management and analysts' responsibilities, procedures, processes, and resources needed to provide accurate, precise, and reliable testing results that meet manufacturing specifications under a regulatory compliance environment. The laboratory quality program should have sufficient procedures to ensure effective control of all purchased equipment and materials, including a list of detailed specifications and quality requirements needed for the installation, operational, and performance qualifications.

One aspect that the FDA auditor would take into consideration is the involvement of management in laboratory operations. Laboratory management should be able to revise, on a frequent basis, the analysts' and supervisors' job descriptions in terms of the performed job functions. Management organizational structure should be clearly established, defining lines of authority, tasks, communication, and responsibilities of each unit within the organization. Normally this type of information is stated in the quality manual. An important aspect of this activity is the development of job functions to find out the resources and expertise needed.

It is important to notice that management should provide sufficient and appropriate resources to the execution of testing, calibrations, method validation, method transfer, and systems optimization. This is normally developed by creating different levels of analysts, that is, I, II, III, and so on, to motivate the personnel to reach higher goals and performance, with emphasis on problem prevention rather than the correction.

Written procedures should be available for the analysts' use at all times. The analyst should have next to him/her the analytical method applicable to the tests. The test methods, as well as the sampling procedures, should always be current, and old versions must be removed from the working area. It is important to have access to an historical file containing all obsolete test methods, SOPs, and specifications. Such a file should be properly identified and controlled.

All test methods should be properly validated before analyzing commercial product samples. The method validation is intended to provide a high level of confidence that the method is scientifically sound and that it serves its intended analytical purpose. The

firm must establish that the analytical methods it uses to assess or evaluate a manufacturing process accurately measure variables affecting process control. The suitability of a chosen method may be measured by analytical variables including precision, accuracy, limit of detection, limit of quantitation, selectivity, range, linearity, and ruggedness. Compendial methods reflect years of experience and, in most cases, do not need to be revalidated. However, proper qualifications of such methods should be in place to reflect accuracy and reproducibility of its intended function. Notice that any product modification may also lead to innovative analytical methods.

The analytical procedure should describe in detail the necessary steps to perform each analytical test including sample, reference standard and reagents preparations, the use of apparatus and equipment, use of formulas for calculation, and others.

Well-characterized reference materials, with documented purity, should be used throughout the validation study. The degree of purity required depends on the intended use. Table 12.1 summarizes the characteristics that should be evaluated when applied to identity, control of impurities, and assay procedures.[1] The table indicates that full method validation is required for quantitative analyses involving the assay, dissolution, and content uniformity. However, qualitative analysis just requires that the sample be properly identified by the specificity test.

Adequate laboratory facilities should be designed to avoid the possibility of cross-contamination between the laboratory, the manufacturing area, and also within the laboratory itself. There must be sufficient area, that is, eight feet of free space, for analytical work to function efficiently and safely. The handling and disposal of solvent waste and effluents should be carried out in a manner consistent with federal regulatory requirements.

Defined and controlled space should be provided for storage of incoming samples as well as for the storage of retention samples of raw materials and finished products. There should be provisions for safety equipments such as laboratory hoods, eye wash

Table 12.1 Method validation parameters.

Type of Analytical Procedure: Parameters	Identification	Testing for Impurities		Assay; dissolution (measurement only); content/potency
		Quantitation	Limit	
Accuracy	–	+	–	+
Precision (Repeatability)	–	+	–	+
Intermediate Precision	–	+(a)	–	+(a)
Specificity (b)	+	+	+	+
Detection Limit	–	–(c)	+	–
Quantitation Limit	–	+	–	–
Linearity	–	+	–	+
Range	–	+	–	+

Notes:
+ = signifies that this characteristic is normally evaluated.
– = signifies that this characteristic is not normally evaluated.
a = In cases where reproducibility has been performed, intermediate precision is not needed.
b = Lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s).
c = May be needed in some cases.

stations, safety showers, fire extinguishers, and others. Perchloric acid titrations and the use of Karl Fisher with pyridine must be conducted inside a hood. The lab hoods must be calibrated under a preventive maintenance program.

The laboratory management should conduct internal audits periodically for independent review and evaluation of the system. The audit should be carried out by trained members of the laboratory management or by competent independent personnel. Audits review should consist of a well-structured evaluation containing the following elements: observations noted on past audits; the overall compliance with cGMP, ISO 9000, or other applicable standards; areas of opportunity or updating the quality management system in relation to improvements for new technology, more effective instruments, and/or analytical techniques.

Is important to remember that the purpose of any audit is to verify both compliance and performance, and to identify discrepancies when they exist. Problems should be addressed and remedied in an appropriate manner. The maintenance of a log of problems encountered and the corrective actions taken is essential if an auditing program is to be successful. This log should be reviewed for recurrence of the same problems and for the presence of patterns that could be symptoms of broader problems. There should be no carry-over from audit to audit. It should be noted, however, that the FDA will not review or copy audits results conducted according to a firm's written quality assurance program unless they are the result of a consent decree, judicial search warrant, or in a direct inspection of a clinical investigation.[2]

Areas that the FDA will be covering during laboratory inspections are: deviation reports, nonconformances, out-of-specifications (OOS), incident reports, and consumer complaints. It is expected that previous internal audits have addressed such deviations and failures, and corrective action plans are proactively developed by the firm.

The laboratory should have written procedures for dealing with the investigation of discrepancies, including their attempts to identify the cause of the failure or discrepancy. This involves the criteria for determining whether nonconformances or OOS results were caused by sampling or laboratory error. The FDA auditor will be particularly concerned for procedures involving the exclusion of any test data due to laboratory or sampling error, additional sampling and testing, extending the investigation to other batches or other products, the amount of retesting permitted, and the point at which testing ends and the product is evaluated.

Analyst Training

Laboratory management should define and organize a well-structured and formal training program for their personnel. Provisions should be in place to allocate time and resources for continuous training at all levels of the organization. Particular attention should be given to the selection and training of newly recruited personnel and personnel transferred to new assignments. An individual training record should contain evidence of competence, including: the curriculum vitae, academic degree, experience, seminars, courses, safety training, cGMPs, and others pertinent to the job.

Training should be specific for the particular laboratory operations and in cGMPs regulations. Qualified personnel should conduct cGMP trainings on a continuous basis to assure that the personnel remain familiar with the tests, methods, and regulations.

One program area that is moving beyond the basic training requirements is the adoption of an analyst certification program (ACP). Although not a legal requirement under cGMPs, it provides sufficient support for daily activities in the regulated industry. Laboratory management should ensure that all analysts and technicians are qualified to conduct the testing according to written testing procedures per cGMP and other international regulations (if applicable). Records of results of analysts' certification program should be kept together with analysts' training records as well as the analyst certification protocol.

Unknown test samples can be used to certify that analysts are following a written protocol. Unknown samples to test both the analyst and laboratory competence have been in use by FDA and EPA laboratories for a long time now.

Even though there are a great number of laboratories with internal certifications, deficiencies are still found belonging to the following areas:

- Unvalidated analytical methods used instead of those established by the firm. No evidence demonstrating analytical methods are stability indicating.
- Inadequate instrument calibration/validation programs.
- Lack of procedures for handling reagents, test solutions, and standards.
- Failure to record data into original records.
- Missing or incomplete raw data. No explanations for miscalculations and transposition errors.
- Failure to record analytical methods and/or instruments used.
- Lack of a second person responsible for checking the completeness and validity of the results for a particular test.

The FDA auditor will also be looking for changes in analytical methodology and new law requirements, and the impact of new products being analyzed with the current methods of analysis. He/she would identify changes in procedures involving vendor validation programs and the qualification of instruments/computers in laboratory facilities.

Sample Controls

Sample controls are extremely important since they address the quality attributes for the products being manufactured. Each laboratory that is responsible for collecting samples should have a detailed "sampling procedure," describing current procedures used to obtain samples. The procedure should also include sample size and storage conditions.

Special precautions must be taken for receiving, handling, storing, and shipping samples. Procedures should be in place protecting the identification, strength, purity, and quality of the sample. Management should make efforts to avoid mechanical injury,

loss, deterioration, degradation, contamination, and other type of damage to samples submitted to laboratory analyses.

Samples received by the laboratory should be logged into the incoming logbook as soon as possible, that is, no later than 24 hours after receipt, and should be stored in an organized manner to avoid their deterioration or loss of the analyte. This might involve refrigeration, freezing, controlled humidity, and protection from light. The storage facility must be adequate in order to avoid possible mix-ups of samples. It is important that samples be clearly identified at all times. Management should design a label system to identify the sample indicating "in-process" or "completed" status. Both the signature and date of completion should be included.

Traceability must be kept when transferences are conducted from one container to the other. The handling and storage must be conducted by authorized personnel following adequate practices, including the storage of samples in an organized location segregated by product.

Samples submitted for analysis or testing must be logged, identified by type, lot number, and source or origin. There must be provisions for the date, hour, sample signature, and special requirements, when applicable. The logbook should be hard cover, with numbered pages. This log is an official record that should be audited by management and could be subjected to FDA audits.

If the incoming log record is kept by using a computerized database, care must then be taken to follow computerized systems validation requirements under 21 CFR Part 11 *Electronic Records; Electronic Signatures*. Data integrity, data security, and meta data (data internal to the activity and not normally evidenced in a hard copy, that is, audit trails, calibration and integration tables, error logs, etc.) evidence in both human readable and electronic format should be taken into consideration on this type of system.

Laboratory Records

Laboratory records and logbooks represent a vital source of information that allows a complete overview of the technical ability of the staff and general quality control procedures of the company. The laboratory program should include a system to control the release, use, and change of documents that define the work to be performed. Laboratory test data must be recorded directly into notebooks. The use of scrap paper and loose paper must be avoided. All raw data calculations must be documented on the official laboratory record or notebook. It is not acceptable to document tests and results on scrap papers or paper towels, but if this is done, those scraps are to be kept as the official raw data and must be retained.

The distribution of laboratory records or notebooks used for raw data collection should be controlled. A log containing the analyst's name and the date when the notebook was given should be retained by management. Each notebook should be identified with a unique number and should have numbered pages. An index at the end of the notebook would facilitate the tracking of events. Notebook entries should be verified by a senior chemist or laboratory supervisor for all data and laboratory requirements prior to release of a product. All entries should be in indelible ink and blank pages should be

crossed out with a single diagonal line. All changes in data should be made by crossing a single line through the data being changed, recording the corrected information, the date of change, and the reason for the change. The person making the change must initial or sign the change with the actual date of the change. A double check of this entry should be made by a senior chemist or laboratory supervisor.

Furthermore, the verification of data should be conducted by a senior chemist or laboratory supervisor who knows the test and is qualified to verify the data. The verifier must get the actual specification, test method, and applicable references to check all raw data, graphs, chromatograms, readings, standardization logbook, calculations, and others. Prior to completing the check, the verifier must compare final results with the written specifications to assure compliance. All entries should be dated and signed with full legal signature (or following your written SOP) at least once per page.

It is recommended that the laboratory supervisor periodically evaluate the logbooks and document the "check-by" entry. A result of "zero" should never be reported. Instead the phrase "not detected" or the common "less than" sign with appropriate detection limits should be in place. Units of measurement should be carefully established in every determination.

All documentation should be legibly signed and dated in a clean, identifiable, and orderly manner. Data could be registered manually or as an electronic record in a durable medium such as a computer hard, floppy, or magneto-optical disk. Proper procedures should be in place to guarantee the integrity and security of such data.

An official list of applicable test methods should be documented including method title, test ID number, approval date, expiration, and effective date. Also another list of current SOPs should be available containing the SOP title, SOP identification, approval date, expiration, and effective date.

For instruments involving chromatographic separations and detection, chromatograms should be completely identified with sample identification, date, analyst, column identification, chromatographic conditions, integration parameters, calibration tables, reference standard, system suitability, and verification by a second analyst.

Laboratory Standards

The laboratory reference standard program should be organized in such a way to assure that all reference standards used by the quality control laboratory meet the criteria for identity, purity, strength, and quality. Standards should be certified through adequate means and certificates of analysis should be available for all standards used. Standard and stock solutions should be analyzed to ensure stability over a period of time. Proper storage conditions should be provided including inventory, standardization, and documentation. Such solutions should be prepared according to procedures described in the pharmacopoeia and/or method's specifications. The bottle should carry a label identifying the solution, concentration, and the expiration date.

When a new reference standard is purchased, its purity should be verified against a known reference standard unless obtained from the United States Pharmacopoeia (USP). When obtaining a reference standard, a certificate of analysis (COA) must be

requested from the originating company or supplier. The COA should contain standard ID, traceability, testing results, acceptance criteria, and expiration date.

Chemical Reagents

The quality program should include provisions to ensure that reagents and chemicals used in analytical work conform to physical, chemical, and other technical requirements as set forth in written specifications. Such materials should be stored in a safe manner in order to reduce damage and degradation. All reagents and solutions in the laboratory must be labeled to indicate its identity, titer or concentration, storage requirements, and expiration date. Deteriorated or outdated reagents and solutions should not be used.

The materials should show the date of receipt, date opened, expiration or shelf life, and safety code. This cGMPs practice is most desirable, especially for those chemicals that can undergo deterioration or decomposition after long storage, such as ether, hydrogen peroxide, and ammonium persulfate. These chemicals should be verified periodically for degradation to avoid explosions and damage in the laboratory.

Of utmost importance is the removal of particulates and contaminants from the glassware. The laboratory should have a written procedure for the cleaning of glassware. The method of cleaning should be of such nature that would be able to remove residues from analytical determinations being performed. Numerous unidentified and extraneous chemical entities are often associated with a poor cleansing technique. The method of cleaning should be validated through an adequate validation protocol and with final results and recommendations supported by management. Some cleaning agents commonly used are water, detergents, organic solvents, dichromate cleaning solution, nitric acid, and aqua regia. Microbiological glassware must be cleaned and kept separately from the chemical laboratory glassware to avoid contamination.

Substances posing a serious threat of contamination to humans or animals that show a particular sensitivity, even at extremely low levels, should be controlled through dedicated production processes such as dedicated facilities, air handling, and process equipment. Manufacturers should identify any drugs that they produce that present the risk of cross-contamination to implement the measures necessary to eliminate the risk. It is important to realize that a number of substances such as dust, dirt, debris, toxic substances, infectious agents, or residue of other drugs or drug components may contaminate drug products. The laboratory must have the capability of identifying and quantifying such contaminants.

Test Solutions (TS)

Test solutions may be purchased from reliable vendors and/or prepared as specified in the test method or SOP. Each bottle containing the TS should carry a label identifying the nature and concentration of the solution and its expiration date.

In some cases, the bottles and stoppers might be of an inert nature and manufactured as light-resistant containers. When the method requires standardization, such information should be recorded in an analytical book containing the method identification, date, analyst, and reference to the test or product name.

Instrument Maintenance and Calibration Programs

Instruments should be maintained and calibrated on a regular schedule. Results of maintenance and calibration records should be kept in appropriate notebooks, including dates and signatures. Each instrument should have its own calibration notebook kept in a close vicinity to the instrument. It is important to routinely record the instrument response to the standard and compare with previous standards run under the same conditions, to ensure that the system response is not degrading. A separate bound record could be used to record all instruments maintenance work, no matter how minor they might be. This record should also be kept in a close vicinity to the instrument to assure that maintenance work will be recorded.

The laboratory management has the responsibility of maintaining all measurement systems used in the analysis and testing of samples to ensure the required precision and accuracy. Laboratory equipment usage, maintenance, calibration logs, repair records, and maintenance SOPs should be routinely examined. The existence of the equipment specified in the analytical methods, and supplements to ANDA or NDA should be confirmed and its condition noted. Adequate controls are required over gages, analytical balances, HPLCs, GCs, UV, IR, Polarimeters, pH meters, ovens, automatic titrators, and other special test equipment, including computer software.

Throughout the FDA inspection, the firm should ensure that the instrumentation is working properly, that it was properly calibrated and under a preventive maintenance (PM) system. This PM, in general, should be accurate, precise, and reliable for the intended purpose of use. All analytical instruments require an operational written procedure (SOP) defining the steps needed to operate the instrument. Those instruments should be qualified before use by the development and execution of installation, operational, and performance qualification protocols.

A calibration and verification written procedure should be in place indicating the actions, requirements, and acceptance criteria for calibration and verification of instruments and equipment. Also, a preventive maintenance written procedure designed to assure a continuous operational status should be available.

The laboratory should employ a PM program in support of the calibration program. It should include the maintenance of chromatographic columns, pH meters, electrodes, hoods, and others. Keep in mind that the purpose of an orderly maintenance program is to increase the measurement system reliability and availability. A maintenance record as well as a repair file including outside servicing should be maintained for each instrument.

Quite important are history logs used to monitor instruments' response using statistical tools of analysis, such as control charts, precision and linearity tests, and others. Proper documentation should be in place involving the identification of instruments, frequency of recalibration, calibration status, and procedures for corrective actions. The firm should maintain traceability to reference standards of known accuracy and stability.

There should be a warning system able to identify failures of important equipment, that is, failure of a fan in the fume hood or an out-of-tolerance of an analytical balance.

Equipment Performance

FDA audits are now more focused on instrumentation due to the complex automated capabilities of such equipment while reporting analytical results. Analytical balances and other sensitive instruments should be protected from drafts, moisture, shock, vibration, electrical interference, and sudden temperature changes. Service contracts should provide certification of standards used and must include traceability up to the primary standard. Electronic balances with internal calibration should be checked and calibrated periodically.

UV/VIS spectrophotometers should include reproducibility and linearity tests. The data presented with the analysis should include the instrument used, solvent, reference standard, sample concentration, cell path, computer, integrator, absorbance range, and maximum wavelength of interest. In addition, there must be evidence of tests performed to determine the accuracy of the wavelength scale by using Holmium Oxide glass at ±1nm, dependant on the slit width. The accuracy of the absorbance scale, also called the photometric test, should also be conducted by using certified National Institute of Standards and Technology (NIST) standards. The UV Region is normally checked with Potassium Dichromate, NIST SRM 935 while the VIS Region is verified with high purity Cobalt and Nickel, NIST SRM 931.

Instruments such as pH meters are verified with a set of buffers to check accuracy. The FDA auditor would verify such documentation including expiration date, lot number, and the suitability, care, and maintenance of electrodes used during an analytical determination.

Chromatographic equipment, including HPLC and GC, are commonly audited in terms of their respective reproducibility and linearity tests. Other parameters such as theoretical plates, k', tailing, and resolution factors are also inspected.

For analytical computer systems, the FDA auditor is interested in the documentation pertaining to software validation. Such validation should be conducted with real samples at normal and stressed, boundary-limit conditions, commonly called worst-case. Considerations most be given to raw data, data manipulation, mathematical formulas, and data integrity.

Recent changes on federal regulations pertaining to electronic records have made the audit of laboratory-computerized equipment of utmost importance to FDA investigators. The law, effective since August 20, 1997, deals with electronic records and electronic signatures under Title 21 Code Federal Regulations (CFR) Part 11. Within the scope of this law requirement, software becomes the center of attention and the "heart" of the analytical instrument. Validation activities must incorporate the attributes of this software to the end use of the system.

Management should not assume that the manufacturer company has validated software just as they should never assume that incoming raw materials are within company specifications. The software validation of any analytical system should include: hardware and software specifications, system data flow, hardware and software interface documentation, input/output design documentation, security specifications, backups/archival procedures, data and file structure, data integrity, and audit trails.

The software validation format follows the software development lifecycle approach from international organizations that includes the following elements:

- Validation plan
- User requirements protocol
- Functional specifications protocol
- Vendor audits
- Installation qualification (IQ)
- Functional qualification (OQ)
  - testing under normal conditions
  - testing under stress conditions
  - testing under boundary limits
  - testing for data integrity
- Performance qualification (OQ)
- Traceability matrix
- Change control procedures

The software validation must clearly state the function to be performed under the user requirement's protocol. For example, the validation of a spectrophotometer must clearly demonstrate that a software program will control the spectrophotometer so that it scans at the same rate and produces the same spectrum for each scan. The specifications for this scan, as well as its tolerance level, are furthermore obtained from the ANDA, NDA, or official method. Parallel testing, or the comparison of a computer response with that of a known system or integrator, is unacceptable as the sole basis for validation because it is not normally designed to test the software source code at the boundary conditions, demonstrate program behavior when the program receives invalid inputs, and test program routines that may be infrequently used.

Sophisticated software is often used by firms to control laboratory robotics. The FDA auditor would be particularly interested in procedures identifying changes from the manual to automated procedure, including method validation. Management should ensure that proper qualification has been made to accessories and specialized equipment involving:

- Filters, pipet tips;
- Extraction columns;
- Sensors;
- Battery back-up, UPS system;

- Evaluation of critical modules;
  - precision syringe hand,
  - weighing station, and
  - vortex station.

CONCLUSION

This represents the current thinking of an FDA auditor while executing a laboratory investigation. Understanding of this approach combined with knowledge of good laboratory practices will enable a laboratory to meet its compliance requirements.

REFERENCES

1. Federal Register. 1995. *Text on Validation of Analytical Procedures* 60.
2. U.S. Food and Drug Administration. 1996. *FDA Compliance Policy Guides*. CPG 7151.02, Chapter 1, Subchapter 130, Sec. 130.300. (August): 19–20.

Appendix D

FDA Guide to Inspections of Pharmaceutical Quality Control Laboratories

Note: This document is reference material for investigators and other FDA personnel. The document does not bind FDA, and does not confer any rights, privileges, benefits, or immunities for or on any person(s).

1. INTRODUCTION

The pharmaceutical quality control laboratory serves one of the most important functions in pharmaceutical production and control. A significant portion of the cGMP regulations (21 CFR 211) pertain to the quality control laboratory and product testing. Similar concepts apply to bulk drugs.

This inspection guide supplements other inspectional information contained in other agency inspectional guidance documents. For example, Compliance Program 7346.832 requiring pre-approval NDA/ANDA inspections contains general instructions to conduct product specific NDA/ANDA inspection audits to measure compliance with the applications and CGMP requirements. This includes pharmaceutical laboratories used for in-process and finished product testing.

2. OBJECTIVE

The specific objective will be spelled out prior to the inspection. The laboratory inspection may be limited to specific issues, or the inspection may encompass a comprehensive evaluation of the laboratory's compliance with cGMP's. As a minimum, each pharmaceutical quality control laboratory should receive a comprehensive GMP evaluation each two years as part of the statutory inspection obligation.

In general these inspections may include

- the specific methodology which will be used to test a new product
- a complete assessment of laboratory's conformance with GMPs
- a specific aspect of laboratory operations

3. INSPECTION PREPARATION

FDA Inspection Guides are based on the team inspection approach and our inspection of a laboratory is consistent with this concept. As part of our effort to achieve uniformity and consistency in laboratory inspections, we expect that complex, highly technical and specialized testing equipment, procedures and data manipulations, as well as scientific laboratory operations will be evaluated by an experienced laboratory analyst with specialized knowledge in such matters.

District management makes the final decision regarding the assignment of personnel to inspections. Nevertheless, we expect investigators, analysts and others to work as teams and to advise management when additional expertise is required to complete a meaningful inspection.

Team members participating in a pre-approval inspection must read and be familiar with Compliance Program 7346.832, Pre-Approval Inspections/Investigations. Relevant sections of the NDA or ANDA should be reviewed prior to the inspection; but if the application is not available from any other source, this review will have to be conducted using the company's copy of the application.

Team members should meet, if possible, prior to the inspection to discuss the approach to the inspection, to define the roles of the team members, and to establish goals for completion of the assignment. Responsibilities for development of all reports should also be established prior to the inspection. This includes the preparation of the FDA 483.

The Center for Drug Evaluation and Research (CDER) may have issued deficiency letters listing problems that the sponsor must correct prior to the approval of NDA/ANDAs and supplements. The inspection team is expected to review such letters on file at the district office, and they are expected to ask the plant for access to such letters. The team should evaluate the replies to these letters to assure that the data are accurate and authentic. Complete the inspection even though there has been no response to these letters or when the response is judged inadequate.

4. INSPECTION APPROACH

A. General

In addition to the general approach utilized in a drug cGMP inspection, the inspection of a laboratory requires the use of observations of the laboratory in operation and of the

raw laboratory data to evaluate compliance with cGMP's and to specifically carry out the commitments in an application or DMF. When conducting a comprehensive inspection of a laboratory, all aspects of the laboratory operations will be evaluated.

Laboratory records and logs represent a vital source of information that allows a complete overview of the technical ability of the staff and of overall quality control procedures. SOPs should be complete and adequate and the operations of the laboratories should conform to the written procedures. Specifications and analytical procedures should be suitable and, as applicable, in conformance with application commitments and compendial requirements.

Evaluate raw laboratory data, laboratory procedures and methods, laboratory equipment, including maintenance and calibration, and methods validation data to determine the overall quality of the laboratory operation and the ability to comply with cGMP regulations.

Examine chromatograms and spectra for evidence of impurities, poor technique, or lack of instrument calibration.

Most manufacturers use systems that provide for the investigation of laboratory test failures. These are generally recorded in some type of log. Ask to see results of analyses for lots of product that have failed to meet specifications and review the analysis of lots that have been retested, rejected, or reworked. Evaluate the decision to release lots of product when the laboratory results indicate that the lot failed to meet specifications and determine who released them.

B. Pre-Approval

Documents relating to the formulation of the product, synthesis of the bulk drug substance, product specifications, analysis of the product, and others are examined during the review process in headquarters. However, these reviews and evaluations depend on accurate and authentic data that truly represents the product.

Pre-approval inspections are designed to determine if the data submitted in an application are authentic and accurate and if the procedures listed in the application were actually used to produce the data contained in the application. Additionally, they are designed to confirm that plants (including the quality control laboratory) are in compliance with cGMP regulations.

The analytical sections of drug applications usually contain only test results and the methods used to obtain them. Sponsors are not required to file all the test data because such action would require voluminous submissions and would often result in filing redundant information. Sponsors may deliberately or unintentionally select and report data showing that a drug is safe and effective and deserves to be approved. The inspection team must decide if there is valid and scientific justification for the failure to report data which demonstrates the product failed to meet its predetermined specifications.

Coordination between headquarters and the field is essential for a complete review of the application and the plant. Experienced investigators and analysts may contact the review chemist (with appropriate supervisory concurrence) when questions concerning specifications and standards arise.

Inspections should compare the results of analyses submitted with results of analysis of other batches that may have been produced. Evaluate the methods and note any exceptions to the procedures or equipment actually used from those listed in the application and confirm that it is the same method listed in the application. The analyst is expected to evaluate raw laboratory data for tests performed on the test batches (biobatches and clinical batches) and to compare this raw data to the data filed in the application.

5. FAILURE (OUT-OF-SPECIFICATION) LABORATORY RESULTS

Evaluate the company's system to investigate laboratory test failures. These investigations represent a key issue in deciding whether a product may be released or rejected and form the basis for retesting, and resampling.

In a recent court decision the judge used the term "out-of-specification" (OOS) laboratory result rather than the term "product failure" which is more common to FDA investigators and analysts. He ruled that an OOS result identified as a laboratory error by a failure investigation or an outlier test,* or overcome by retesting** is not a product failure. OOS results fall into three categories:

- laboratory error
- non-process related or operator error
- process related or manufacturing process error

A. Laboratory Errors

Laboratory errors occur when analysts make mistakes in following the method of analysis, use incorrect standards, and/or simply miscalculate the data. Laboratory errors must be determined through a failure investigation to identify the cause of the OOS. Once the nature of the OOS result has been identified it can be classified into one of the three categories above. The inquiry may vary with the object under investigation.

B. Laboratory Investigations

The exact cause of analyst error or mistake can be difficult to determine specifically and it is unrealistic to expect that analyst error will always be determined and documented. Nevertheless, a laboratory investigation consists of more than a retest. The inability to identify an error's cause with confidence affects retesting procedures, not the investigation inquiry required for the initial OOS result.

The firm's analyst should follow a written procedure, checking off each step as it is completed during the analytical procedure. We expect laboratory test data to be

* The court provided explicit limitations on the use of outlier tests and these are discussed in a later segment of this document.

** The court ruled on the use of retesting which is covered in a later segment of this document.

recorded directly in notebooks; use of scrap paper and loose paper must be avoided. These common sense measures enhance the accuracy and integrity of data. Review and evaluate the laboratory SOP for product failure investigations.

Specific procedures must be followed when single and multiple OOS results are investigated. For the single OOS result the investigation should include the following steps and these inquiries must be conducted before there is a retest of the sample:

- the analyst conducting the test should report the OOS result to the supervisor
- the analyst and the supervisor should conduct an informal laboratory investigation which addresses the following areas:
  1. discuss the testing procedure
  2. discuss the calculation
  3. examine the instruments
  4. review the notebooks containing the OOS result

An alternative means to invalidate an initial OOS result, provided the failure investigation proves inconclusive, is the "outlier" test. However, specific restrictions must be placed on the use of this test.

1. Firms cannot frequently reject results on this basis.
2. The USP standards govern its use in specific cases only.
3. The test cannot be used for chemical testing results. An initial content uniformity test was OOS followed by a passing retest. The initial OOS result was claimed the result of analyst error based on a statistical evaluation of the data. The court ruled that the use of an outlier test is inappropriate in this case.
4. It is never appropriate to utilize outlier tests for a statistically based test, i.e., content uniformity and dissolution.

Determine if the firm uses an outlier test and evaluate the SOP.

Determine that a full scale inquiry has been made for multiple OOS results. This inquiry involves quality control and quality assurance personnel in addition to laboratory workers to identify exact process or non-process related errors.

When the laboratory investigation is inconclusive (reason for the error is not identified) the firm:

1. Cannot conduct 2 retests and base release on average of three tests
2. Cannot use outlier test in chemical tests
3. Cannot use a re-sample to assume a sampling or preparation error
4. Can conduct a retest of different tablets from the same sample when a retest is considered appropriate (see criteria elsewhere)

C. Formal Investigations

Formal investigations extending beyond the laboratory must follow an outline with particular attention to corrective action. The company must:

1. State the reason for the investigation
2. Provide summation of the process sequences that may have caused the problem
3. Outline corrective actions necessary to save the batch and prevent similar recurrence
4. List other batches and products possibly affected, the results of investigation of these batches and products, and any corrective action. Specifically:
   - examine other batches of product made by the errant employee or machine
   - examine other products produced by the errant process or operation
5. Preserve the comments and signatures of all production and quality control personnel who conducted the investigation and approved any reprocessed material after additional testing

D. Investigation Documentation

Analyst's mistakes, such as undetected calculation errors, should be specified with particularity and supported by evidence. Investigations along with conclusions reached must be preserved with written documentation that enumerates each step of the investigation. The evaluation, conclusion and corrective action, if any, should be preserved in an investigation or failure report and placed into a central file.

E. Investigation Time Frames

All failure investigations should be performed within 20 business days of the problem's occurrence and recorded and written into a failure or investigation report.

6. PRODUCT FAILURES

An OOS laboratory result can be overcome (invalidated) when laboratory error has been documented. However, non-process and process related errors resulting from operators making mistakes, equipment (other than laboratory equipment) malfunctions, or a manufacturing process that is fundamentally deficient, such as an improper mixing time, represent product failures.

Examine the results of investigations using the guidance in section 5 above and evaluate the decision to release, retest, or rework products.

7. RETESTING

Evaluate the company's retesting SOP for compliance with scientifically sound and appropriate procedures. *A very important ruling in one recent court decision sets forth a procedure to govern the retesting program.* This district court ruling provides an excellent guide to use in evaluating some aspects of a pharmaceutical laboratory, but should not be considered as law, regulation, or binding legal precedent. The court ruled that a firm should have a predetermined testing procedure and it should consider a point at which testing ends and the product is evaluated. If results are not satisfactory, the product is rejected.

Additionally, the company should consider all retest results in the context of the overall record of the product. This includes the history of the product. The court ordered a recall of one batch of product on the basis of an initial content uniformity failure and no basis to invalidate the test result and on a history of content uniformity problems with the product, type of test performed, and in-process test results. Failing assay results cannot be disregarded simply on the basis of acceptable content uniformity results.

The number of retests performed before a firm concludes that an unexplained OOS result is invalid or that a product is unacceptable is a matter of scientific judgment. The goal of retesting is to isolate OOS results but retesting cannot continue ad infinitum.

In the case of non-process and process related errors, retesting is suspect. Because the initial tests are genuine, in these circumstances, additional testing alone cannot contribute to product quality. The court acknowledged that some retesting may precede a finding of non-process or process based errors. Once this determination is made, however, additional retesting for purposes of testing a product into compliance is not acceptable.

For example, in the case of content uniformity testing designed to detect variability in the blend or tablets, failing and non-failing results are not inherently inconsistent and passing results on limited retesting do not rule out the possibility that the batch is not uniform. As part of the investigation firms should consider the record of previous batches, since similar or related failures on different batches would be a cause of concern.

Retesting following an OOS result is ruled appropriate only after the failure investigation is underway and the failure investigation determines in part whether retesting is appropriate. It is appropriate when analyst error is documented or the review of analyst's work is "inconclusive," but it is not appropriate for known and undisputed non-process or process related errors.

The court ruled that retesting:

- must be done on the same, not a different sample
- may be done on a second aliquot from the same portion of the sample that was the source of the first aliquot
- may be done on a portion of the same larger sample previously collected for laboratory purposes

8. RESAMPLING

Firms cannot rely on resampling to release a product that has failed testing and retesting unless the failure investigation discloses evidence that the original sample is not representative or was improperly prepared. The court ordered the recall of one batch of product after having concluded that a successful resample result alone cannot invalidate an initial OOS result.

Evaluate each resampling activity for compliance with this guidance.

9. AVERAGING RESULTS OF ANALYSIS

Averaging can be a rational and valid approach when the object under consideration is total product assay, but as a general rule this practice should be avoided. The court ruled that the firm must recall a batch that was released for content uniformity on the basis of averaged test results because averages hide the variability among individual test results. This phenomenon is particularly troubling if testing generates both OOS and passing individual results which when averaged are within specification. Here, relying on the average figure without examining and explaining the individual OOS results is highly misleading and unacceptable.

Content uniformity and dissolution results never should be averaged to obtain a passing value.

In the case of microbiological turbidimetric and plate assays an average is preferred by the USP. In this case, it is good practice to include OOS results in the average unless an outlier test (microbiological assays) suggests the OOS is an anomaly.

10. BLEND SAMPLING AND TESTING

The laboratory serves a vital function in blend testing which is necessary to increase the likelihood of detecting inferior batches. Blend uniformity testing cannot be waived in favor of total reliance on finished product testing because finished product testing is limited.

One court has ruled that sample size influences ultimate blend test results and that the sample size should resemble the dosage size. Any other practice would blur differences in portions of the blend and defeat the object of the test. If a sample larger than the unit must be taken initially, aliquots which resemble the dosage size should be carefully removed for the test, retests, and reserve samples. Obviously, the initial larger sample should not be subjected to any additional mixing or manipulation prior to removing test aliquots as this may obscure non-homogeneity.

Multiple individual blend uniformity samples taken from different areas cannot be composited. However when variation testing is not the object of assay testing, compositing is permitted.

If firms sample product from sites other than the blender, they must demonstrate through validation that their sampling technique is representative of all portions and

concentrations of the blend. This means that the samples must be representative of those sites that might be problems; e.g. weak or hot spots in the blend.

11. MICROBIOLOGICAL

The review of microbiological data on applicable dosage forms is best performed by the microbiologist (analyst). Data that should be reviewed include preservative effectiveness testing, bioburden data, and product specific microbiological testing and methods.

Review bioburden (before filtration and/or sterilization) from both an endotoxin and sterility perspective. For drug substance labs evaluate methods validation and raw data for sterility, endotoxin testing, environmental monitoring, and filter and filtration validation. Also, evaluate the methods used to test and establish bioburdens.

Refer to the Microbiological Inspection Guide for additional information concerning the inspection of microbiological laboratories.

12. SAMPLING

Samples will be collected on pre-approval inspections. Follow the sampling guidelines in CP 7346.832, Part III, pages 5 and 6.

13. LABORATORY RECORDS AND DOCUMENTATION

Review personal analytical notebooks kept by the analysts in the laboratory and compare them with the worksheets and general lab notebooks and records. Be prepared to examine all records and worksheets for accuracy and authenticity and to verify that raw data are retained to support the conclusions found in laboratory results.

Review laboratory logs for the sequence of analysis versus the sequence of manufacturing dates. Test dates should correspond to the dates when the sample should have been in the laboratory. If there is a computer data base, determine the protocols for making changes to the data. There should be an audit trail for changes to data.

We expect raw laboratory data to be maintained in bound (not loose or scrap sheets of paper) books or on analytical sheets for which there is accountability, such as prenumbered sheets. For most of those manufacturers which had duplicate sets of records or "raw data," non-numbered loose sheets of paper were employed. Some companies use discs or tapes as raw data and for the storage of data. Such systems have also been accepted provided they have been defined (with raw data identified) and validated.

Carefully examine and evaluate laboratory logs, worksheets and other records containing the raw data such as weighings, dilutions, the condition of instruments, and calculations. Note whether raw data are missing, if records have been rewritten, or if correction fluid has been used to conceal errors. Results should not be changed without explanation. Cross reference the data that has been corrected to authenticate it. Products cannot be "tested into compliance" by arbitrarily labeling out-of-specification lab results as "laboratory errors" without an investigation resulting in scientifically valid criteria.

Test results should not have been transcribed without retention of the original records, nor should test results be recorded selectively. For example, investigations have uncovered the use of loose sheets of paper with subsequent selective transcriptions of good data to analyst worksheets and/or workbooks. Absorbance values and calculations have even been found on desk calendars.

Cut charts with injections missing, deletion of files in direct data entry systems, indirect data entry without verification, and changes to computerized programs to override program features should be carefully examined. These practices raise questions about the overall quality of data.

The firm should have a written explanation when injections, particularly from a series are missing from the official work-sheets or from files and are included among the raw data. Multiple injections recorded should be in consecutive files with consecutive injection times recorded. Expect to see written justification for the deletion of all files.

Determine the adequacy of the firm's procedures to ensure that all valid laboratory data are considered by the firm in their determination of acceptability of components, in-process, finished product, and retained stability samples. Laboratory logs and documents when cross referenced may show that data has been discarded by company officials who decided to release the product without a satisfactory explanation of the results showing the product fails to meet the specifications. Evaluate the justification for disregarding test results that show the product failed to meet specifications.

14. LABORATORY STANDARD SOLUTIONS

Ascertain that suitable standards are being used (i.e. in-date, stored properly). Check for the reuse of stock solutions without assuring their stability. Stock solutions are frequently stored in the laboratory refrigerator. Examine the laboratory refrigerators for these solutions and when found check for appropriate identification. Review records of standard solution preparation to assure complete and accurate documentation. It is highly unlikely that a firm can "accurately and consistently weigh" to the same microgram. Therefore data showing this level of standardization or pattern is suspect and should be carefully investigated.

15. METHODS VALIDATION

Information regarding the validation of methods should be carefully evaluated for completeness, accuracy and reliability. In particular, if a compendial method exists, but the firm chooses to use an alternate method instead, they must compare the two and demonstrate that the in-house method is equivalent or superior to the official procedure. For compendial methods firms must demonstrate that the method works under the actual conditions of use.

Methods can be validated in a number of ways. Methods appearing in the USP are considered validated and they are considered validated if part of an approved ANDA.

Also a company can conduct a validation study on their method. System suitability data alone is insufficient for and does not constitute method validation.

In the review of method validation data, it is expected that data for repetitive testing be consistent and that the varying concentrations of test solutions provide linear results. Many assay and impurity tests are now HPLC, and it is expected that the precision of these assays be equal or less than the RSD's for system suitability testing. The analytical performance parameters listed in the USP XXII, <1225>, under the heading of Validation of Compendial Methods, can be used as a guide for determining the analytical parameters (e.g., accuracy, precision, linearity, ruggedness, etc.) needed to validate the method.

16. EQUIPMENT

Laboratory equipment usage, maintenance, calibration logs, repair records, and maintenance SOPs also should be examined. The existence of the equipment specified in the analytical methods should be confirmed and its condition noted. Verify that the equipment was present and in good working order at the time the batches were analyzed. Determine whether equipment is being used properly.

In addition, verify that the equipment in any application was in good working order when it was listed as used to produce clinical or biobatches. One would have to suspect the data that are generated from a piece of equipment that is known to be defective. Therefore, continuing to use and release product on the basis of such equipment represents a serious violation of cGMPs.

17. RAW MATERIAL TESTING

Some inspections include the coverage of the manufacturer of the drug substance. The safety and efficacy of the finished dosage form is largely dependent on the purity and quality of the bulk active drug substance. Examine the raw data reflecting the analysis of the drug substance including purity tests, charts, etc.

Check the impurity profiles of the BPC used in the biobatch and clinical production batches to determine if it is the same as that being used to manufacture full scale production batches. Determine if the manufacturer has a program to audit the certificate of analysis of the BPC, and, if so, check the results of these tests. Report findings where there is substantial difference in impurity profiles and other test results.

Some older compendial methods may not be capable of detecting impurities as necessary to enable the control of the manufacturing process, and newer methods have been developed to test these products. Such methods must be validated to ensure that they are adequate for analytical purposes in the control and validation of the BPC manufacturing process. The drug substance manufacturer must have complete knowledge of the manufacturing process and the potential impurities that may appear in the drug substance. These impurities cannot be evaluated without a suitable method and one that has been validated.

Physical tests such as particle size for raw materials, adhesion tests for patches, and extrusion tests for syringes are essential tests to assure consistent operation of the production and control system and to assure quality and efficacy. Some of these tests are filed in applications and others may be established by the protocols used to manufacture the product. The validation of methods for such tests are as important as the test for chemical attributes.

Physical properties tests often require the use of unique equipment and protocols. These tests may not be reproducible in other laboratories, therefore, on-site evaluation is essential.

18. IN-PROCESS CONTROLS AND SPECIFICATIONS

Evaluate the test results from in-process tests performed in the production areas or laboratory for conformance with established sampling and testing protocols, analytical methods, and specifications. For example, evaluate the tests for weight variation, hardness, and friability. These tests may be performed every fifteen or thirty minutes during tableting or encapsulating procedures. All testing must comply with cGMPs.

The drug application may contain some of the in-process testing plan, including methods and specifications. The inspection must confirm that the in-process tests were done, as described in the plan, and ascertain that the results were within specifications. The laboratory work for the lengthier tests should also be reviewed.

The methods used for in-process testing may differ from those used for release testings. Usually, whether the methods are the same or different, the specifications may be tighter for the in-process tests. A product with a 90.0%–110.0% assay release specification may have a limit of 95.%–105.0% for the in-process blend. Some of the tests done may differ from those done at release. For example, a firm may perform disintegration testing as an in-process test but dissolution testing as a release test.

Expect to see consistent in-process test results within batches and between batches of the same formulation/process (including development or exhibit batches). If this is not the case, expect to see scientific data to justify the variation.

19. STABILITY

A stability-indicating method must be used to test the samples of the batch. If there is no stability-indicating assay additional assay procedures such as TLC should be used to supplement the general assay method. Evidence that the method is stability-indicating must be presented, even for compendial methods.

Manufacturers may be required to accelerate or force degradation of a product to demonstrate that the test is stability-indicating. In some cases the sponsor of ANDAs may be able to search the literature and find background data for the specificity of a particular method. This information may also be obtained from the supplier of the drug substance. Validation would then be relatively straightforward, with the typical parameters listed in the USP in chapter <1225> on validation of compendial methods addressed as applicable.

Evaluate the manufacturer's validation report for their stability testing. Again, review the raw laboratory data and the results of testing at the various stations to determine if the data actually reported matches the data found in on-site records.

Evaluate the raw data used to generate the data filed documenting that the method is stability-indicating and the level of impurities.

20. COMPUTERIZED LABORATORY DATA ACQUISITION SYSTEMS

The use of computerized laboratory data acquisition systems is not new and is addressed in the following cGMP guidance documents:

- Compliance Policy Guide 7132a.07 Computerized Drug Processing: Input/Output Checking.
- Compliance Policy Guide 7132a.08 Computerized Drug Processing: Identification of "Persons" on Batch Production and Control Records.
- Compliance Policy Guide 7132a.11 Computerized Drug Processing: cGMP Applicability to Hardware and Software
- Compliance Policy Guide 7132a.12 Computerized Drug Processing: Vendor Responsibility
- Compliance Policy Guide 7132a.15 Computerized Drug Processing: Source Code for Process Control Application Programs
- Guide to Inspection of Computerized Systems in Drug Processing.

It is important, for computerized and non computerized systems, to define the universe of data that will be collected, the procedures to collect it, and the means to verify its accuracy. Equally important are the procedure to audit data and programs and the process for correcting errors. Several issues must be addressed when evaluating computerized laboratory systems. These include data collection, processing, data integrity, and security.

Procedures should only be judged adequate when data are secure, raw data are not accidentally lost, and data cannot be tampered with. The system must assure that raw data are stored and actually processed.

The agency has provided some basic guidance on security and authenticity issues for computerized systems:

- Provision must be made so that only authorized individuals can make data entries.
- Data entries may not be deleted. Changes must be made in the form of amendments.
- The data base must be made as tamperproof as possible.
- The Standard Operating Procedures must describe the procedures for ensuring the validity of the data.

One basic aspect of validation of laboratory computerized data acquisition requires a comparison of data from the specific instrument with that same data electronically transmitted through the system and emanating on a printer. Periodic data comparisons would be sufficient only when such comparisons have been made over a sufficient period of time to assure that the computerized system produces consistent and valid results.

21. LABORATORY MANAGEMENT

Overall management of the laboratory work, its staff, and the evaluation of the results of analysis are important elements in the evaluation of a control laboratory. Span of supervisory control, personnel qualifications, turnover of analysts, and scope of the laboratory's responsibility are important issues to examine when determining the quality of overall management and supervision of work. Individually or collectively, these factors are the basis for an objection only when they are shown to result in inadequate performance of responsibilities required by the cGMPs.

Review laboratory logs for the sequence of analysis and the sequence of manufacturing dates. Examine laboratory records and logs for vital information about the technical competence of the staff and the quality control procedures used in the laboratory.

Observe analysts performing the operations described in the application. There is no substitute for actually seeing the work performed and noting whether good technique is used. You should not stand over the analysts, but watch from a distance and evaluate their actions.

Sometimes the company's employees have insufficient training or time to recognize situations that require further investigation and explanation. Instead they accept unexplained peaks in chromatograms with no effort to identify them. They may accept stability test results showing an apparent increase in the assay of the drug with the passage of time with no apparent question about the result. Also, diminishing reproducibility in HPLC chromatograms appearing several hours after system suitability is established is accepted without question.

Good manufacturing practice regulations require an active training program and the documented evaluation of the training of analysts.

The authority to delete files and override computer systems should be thoroughly examined. Evaluate the history of changes to programs used for calculations. Certain changes may require management to re-examine the data for products already released.

Appendix E

FDA Guide to Inspections of Microbiological Quality Control Laboratories

Note: This document is reference material for investigators and other FDA personnel. The document does not bind FDA, and does not confer any rights, privileges, benefits, or immunities for or on any person(s).

I. INTRODUCTION

The Guide to the Inspection of Pharmaceutical Quality Control Laboratories provided very limited guidance on the matter of inspection of microbiological laboratories. While that guide addresses many of the issues associated with the chemical aspect of laboratory analysis of pharmaceuticals, this document will serve as a guide to the inspection of the microbiology analytical process. As with any laboratory inspection, it is recommended that an analyst (microbiologist) who is familiar with the tests being inspected participate in these inspections.

II. MICROBIOLOGICAL TESTING OF NON-STERILE PRODUCTS

For a variety of reasons, we have seen a number of problems associated with the microbiological contamination of topical drug products, nasal solutions, and inhalation products. The USP Microbiological Attributes Chapter <1111> provides little specific guidance other than "The significance of microorganisms in non-sterile pharmaceutical products should be evaluated in terms of the use of the product, the nature of the product, and the potential hazard to the user." The USP recommends that certain categories be routinely tested for total counts and specified indicator microbial contaminants. For

example, natural plant, animal, and some mineral products for *Salmonella*, oral liquids for *E. Coli*, topicals for *P. aeruginosa* and *S. Aureus*, and articles intended for rectal, urethral, or vaginal administration for yeasts and molds. A number of specific monographs also include definitive microbial limits.

As a general guide for acceptable levels and types of microbiological contamination in products, Dr. Dunnigan of the Bureau of Medicine of the FDA commented on the health hazard. In 1970, he said that topical preparations contaminated with gram negative organisms are a probable moderate to serious health hazard. Through the literature and through our investigations, it has been shown that a variety of infections have been traced to the gram negative contamination of topical products. The classical example being the *Pseudomonas cepacia* contamination of Povidone Iodine products reported by a hospital in Massachusetts several years ago.

Therefore, each company is expected to develop microbial specifications for their non-sterile products. Likewise, the USP Microbial Limits Chapter <61> provides methodology for selected indicator organisms, but not all objectionable organisms. For example, it is widely recognized that *Pseudomonas cepacia* is objectionable if found in a topical product or nasal solution in high numbers; yet, there are no test methods provided in the USP that will enable the identification of the presence of this microorganism.

A relevant example of this problem is the recall of Metaproterenol Sulfate Inhalation Solution. The USP XXII monograph requires no microbial testing for this product. The agency classified this as a Class I recall because the product was contaminated with *Pseudomonas gladioli/cepacia*. The health hazard evaluation commented that the risk of pulmonary infection is especially serious and potentially life-threatening to patients with chronic obstructive airway disease, cystic fibrosis, and immunocompromised patients. Additionally, these organisms would not have been identified by testing procedures delineated in the general Microbial Limits section of the Compendia.

The USP currently provides for retests in the Microbial Limits section <61> however there is a current proposal to remove the retest provision. As with any other test, the results of initial test should be reviewed and investigated. Microbiological contamination is not evenly dispersed throughout a lot or sample of product and finding a contaminant in one sample and not in another does not discount the findings of the initial sample results. Retest results should be reviewed and evaluated, and particular emphasis should be placed on the logic and rationale for conducting the retest.

In order to isolate specific microbial contaminants, FDA laboratories, as well as many in the industry, employ some type of enrichment media containing inactivators, such as Tween or lecithin. This is essential to inactivate preservatives usually present in these types of product and provides a better medium for damaged or slow-growing cells. Other growth parameters include a lower temperature and longer incubation time (at least 5 days) that provide a better survival condition for damaged or slow-growing cells.

For example, FDA laboratories use the test procedures for cosmetics in the Bacteriological Analytical Manual (BAM), 6th Edition, to identify contamination in non-sterile drug products. This testing includes an enrichment of a sample in modified letheen broth. After incubation, further identification is carried out on Blood Agar Plates and MacConkey Agar Plates. Isolated colonies are then identified. This procedure allows FDA microbiologists to optimize the recovery of all potential pathogens and to quantitate and

speciate all recovered organisms. Another important aspect of procedures used by FDA analysts is to determine growth promotion characteristics for all of the media used.

The selection of the appropriate neutralizing agents are largely dependent upon the preservative and formulation of the product under evaluation. If there is growth in the enrichment broth, transfer to more selective agar media or suitable enrichment agar may be necessary for subsequent identification.

Microbiological testing may include an identification of colonies found during the Total Aerobic Plate Count test. Again, the identification should not merely be limited to the USP indicator organisms.

The importance of identifying all isolates from either or both Total Plate Count testing and enrichment testing will depend upon the product and its intended use. Obviously, if an oral solid dosage form such as a tablet is tested, it may be acceptable to identify isolates when testing shows high levels. However, for other products such as topicals, inhalants, or nasal solutions where there is a major concern for microbiological contamination, isolates from plate counts, as well as enrichment testing, should be identified.

III. FACILITIES, EQUIPMENT, AND MEDIA

Begin the inspection with a review of analyses being conducted and inspect the plates and tubes of media being incubated (caution should be exercised not to inadvertently contaminate plates or tubes of media on test). Be particularly alert for retests that have not been documented and "special projects" in which investigations of contamination problems have been identified. This can be evaluated by reviewing the ongoing analyses (product or environmental) for positive test results. Request to review the previous day's plates and media, if available, and compare your observations to the recorded entries in the logs. Inspect the autoclaves used for the sterilization of media. Autoclaves may lack the ability to displace steam with sterile filtered air. For sealed bottles of media, this would not present a problem. However, for non-sealed bottles or flasks of media, non-sterile air has led to the contamination of media. In addition, autoclaving less than the required time will also allow media associated contaminants to grow and cause a false positive result. These problems may be more prevalent in laboratories with a heavy workload.

Check the temperature of the autoclave since overheating can denature and even char necessary nutrients. This allows for a less than optimal recovery of already stressed microorganisms. The obvious problem with potential false positives is the inability to differentiate between inadvertent medium contamination and true contamination directly associated with the sample tested.

IV. STERILITY TESTING

On 10/11/91, the Agency published a proposed rule regarding the manufacture of drug products by aseptic processing and terminal sterilization. A list of contaminated or potentially contaminated drug products made by aseptic processing and later recalled

was also made available. Many of the investigations/inspections of the recalled products started with a list of initial sterility test failures. FDA review of the manufacturer's production, controls, investigations and their inadequacies, coupled with the evidence of product failure (initial sterility test failure) ultimately led to the action.

The USP points out that the facilities used to conduct sterility tests should be similar to those used for manufacturing product. The USP states, "The facility for sterility testing should be such as to offer no greater a microbial challenge to the articles being tested than that of an aseptic processing production facility." Proper design would, therefore, include a gowning area and pass-through airlock. Environmental monitoring and gowning should be equivalent to that used for manufacturing product.

Since a number of product and media manipulations are involved in conducting a sterility test, it is recommended that the inspection include actual observation of the sterility test even though some companies have tried to discourage inspection on the grounds that it may make the firm's analyst nervous. The inspection team is expected to be sensitive to this concern and make the observations in a manner that will create the least amount of disruption in the normal operating environment. Nevertheless, such concerns are not sufficient cause for you to suspend this portion of the inspection.

One of the most important aspects of the inspection of a sterility analytical program is to review records of initial positive sterility test results. Request lists of test failures to facilitate review of production and control records and investigation reports. Particularly, for the high risk aseptically filled product, initial positive sterility test results and investigations should be reviewed. It is difficult for the manufacturer to justify the release of a product filled aseptically that fails an initial sterility test without identifying specific problems associated with the controls used for the sterility test.

Examine the use of negative controls. They are particularly important to a high quality sterility test. Good practice for such testing includes the use of known terminally sterilized or irradiated samples as a system control. Alternatively, vials or ampules filled during media fills have also been used.

Be especially concerned about the case where a manufacturer of aseptically filled products has never found an initial positive sterility test. While such situations may occur, they are rare. In one case, a manufacturer's records showed that they had never found a positive result; their records had been falsified. Also, the absence of initial positives may indicate that the test has not been validated to demonstrate that there is no carryover of inhibition from the product or preservative.

Inspect robotic systems or isolation technology, such as La Calhene units used for sterility testing. These units allow product withdrawal in the absence of people. If an initial test failure is noted in a sample tested in such a system, it could be very difficult to justify release based on a retest, particularly if test controls are negative.

Evaluate the time period used for sterility test sample incubation. This issue has been recently clarified. The USP states that samples are to be incubated for at least 7 days, and a proposal has been made to change the USP to require a period of 14 days incubation. You are expected to evaluate the specific analytical procedure and the product for the proper incubation period. Seven days may be insufficient, particularly when slow growing organisms have been identified. Media fill, environmental, sterility test

results and other data should be reviewed to assure the absence of slow-growing organisms. Also, you should compare the methods being used for incubation to determine if they conform to those listed in approved or pending applications.

V. METHODOLOGY AND VALIDATION OF TEST PROCEDURES

Determine the source of test procedures. Manufacturers derive test procedures from several sources, including the USP, BAM and other microbiological references. It would be virtually impossible to completely validate test procedures for every organism that may be objectionable. However, it is a good practice to assure that inhibitory substances in samples are neutralized.

During inspections, including pre-approval inspections, evaluate the methodology for microbiological testing. For example, we expect test methods to identify the presence of organisms such as *Pseudomonas cepacia* or other *Pseudomonas* species that may be objectional or present a hazard to the user. Where pre-approval inspections are being conducted, compare the method being used against the one submitted in the application. Also verify that the laboratory has the equipment necessary to perform the tests and that the equipment was available and in good operating condition on the dates of critical testing.

The USP states that an alternate method may be substituted for compendial tests, provided it has been properly validated as giving equivalent or better results.

You may find that dehydrated media are being used for the preparation of media. Good practice includes the periodic challenge of prepared media with low levels of organisms. This includes USP indicator organisms as well as normal flora. The capability of the media to promote the growth of organisms may be affected by the media preparation process, sterilization (overheating) and storage. These represent important considerations in any inspection and in the good management of a microbiology laboratory.

VI. DATA STORAGE

Evaluate the test results that have been entered in either logbooks or on loose analytical sheets. While some manufacturers may be reluctant to provide tabulations, summaries, or printouts of microbiological test results, this data should be reviewed for the identification of potential microbial problems in processing. When summaries of this data are not available the inspection team is expected to review enough data to construct their own summary of the laboratory test results and quality control program.

Some laboratories utilize preprinted forms only for recording test data. Some laboratories have also pointed out that the only way microbiological test data could be reviewed during inspections would be to review individual batch records. However, in most cases, preprinted forms are in multiple copies with a second or third copy in a central file. Some companies use logbooks for recording data. These logbooks should also be reviewed.

Additionally, many manufacturers are equipped with an automated microbial system for the identification of microorganisms. Logs of such testing, along with the identification of the source of the sample, are also of value in the identification of potential microbial problems in processing.

The utilization of automated systems for the identification of microorganisms is relatively common in the parenteral manufacturer where isolates from the environment, water systems, validation, and people are routinely identified.

Microbiologists in our Baltimore District are expert on the use of automated microbic analytical systems. They were the first FDA laboratory to use such equipment and have considerable experience in validating methods for these pieces of equipment. Contact the Baltimore District laboratory for information or questions about these systems. Plants with heavy utilization of these pieces of equipment should be inspected by individuals from the Baltimore District laboratory.

VII. MANAGEMENT REVIEW

Microbiological test results represent one of the more difficult areas for the evaluation and interpretation of data. These evaluations require extensive training and experience in microbiology. Understanding the methodology, and more importantly, understanding the limitations of the test present the more difficult issues. For example, a manufacturer found high counts of *Enterobacter cloacae* in their oral dosage form product derived from a natural substance. Since they did not isolate *E. coli*, they released the product. FDA analysis found *E. cloacae* in most samples from the batch and even *E. coli* in one sample. In this case management failed to recognize that microbiological contamination might not be uniform, that other organisms may mask the presence of certain organisms when identification procedures are performed, and that microbiological testing is far from absolute. The inspection must consider the relationship between the organisms found in the samples and the potential for the existence of other objectionable conditions. For example, it is logical to assume that if the process would allow *E. cloacae* to be present, it could also allow the presence of the objectionable indicator organism. The microbiologist should evaluate this potential by considering such factors as methodology, and the growth conditions of the sample as well as other fundamental factors associated with microbiological analysis.

Evaluate management's program to audit the quality of the laboratory work performed by outside contractors.

VIII. CONTRACT TESTING LABORATORIES

Many manufacturers contract with private or independent testing laboratories to analyze their products. Since these laboratories will conduct only the tests that the manufacturer requests, determine the specific instructions given to the contractor. Evaluate these instructions to assure that necessary testing will be completed. For example, in a

recent inspection of a topical manufacturer, total plate count and testing for the USP indicator organisms were requested. The control laboratory performed this testing only and did not look for other organisms that would be objectionable based on the product's intended use.

Analytical results, particularly for those articles in which additional or retesting is conducted, should be reviewed. Test reports should be provided to the manufacturer for tests conducted. It is not unusual to see contract laboratories fail to provide complete results, with both failing as well as passing results.

Bacteriostasis/fungiostasis testing must be performed either by the contract lab or the manufacturer. These test results must be negative, otherwise any sterility test results obtained by the contractor on the product may not be valid.

IV.

An International Perspective

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Accreditation and Harmonization

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KEY WORDS

- Accreditation
- Mutual recognition agreement
- Quality systems
- Calibration

INTRODUCTION

The primary standard in use today for the accreditation of laboratories is ISO/IEC 17025 "General requirements for the competence of testing and calibration laboratories." The intent of the standard is to establish a framework of activities, procedures, and records systems that enhance the overall quality of the laboratory's test results. This standard replaces ISO Guide 25.

Many of the requirements found in ISO Guide 25 have simply been further augmented in ISO/IEC 17025. Some requirements are more prescriptive and there are many more explanatory notes. These explanatory notes serve as guidance. The incorporation of the ISO 9000 requirements increases the level of detail.

Mutual recognition arrangement (MRA) process is the means by which laboratory accreditation bodies develop confidence in their peers' abilities to determine a laboratory's competence to perform testing or calibrations. With its acceptance worldwide, ISO/IEC 17025 will be instrumental in the further development of mutual recognition agreements (MRA) between economies.

CONFORMITY ASSESSMENT

Conformity assessment is the determination of whether a product "conforms" to required standards, specifications, or other descriptors and the attestation of such conformity. The three major third-party tools related to conformity assessment are:

1. Laboratory Accreditation—the procedure by which an authoritative body gives formal recognition that a body or person is competent to carry out specific tasks.
2. Registration—the procedure by which a body indicates relevant characteristics of a product, process or service, or particulars of a body or person, on an appropriate publicly available list.
3. Product Certification—the procedure by which a third party gives written assurance that a product, process, or service conforms to specified requirements.

Each of these tools plays a distinct and significant role.

Quality Systems Registration

Quality systems registration (usually performed against the ISO 9000 series of standards) verifies that the organization providing a process, good, or service, has a quality system in place that meets the requirements of the standard. However, registration itself does not guarantee that the product produced meets conformity requirements. In fact, quality system registration only helps to ensure that a consistent process is being carried out. This process may indeed produce a bad product on a consistent basis. Being generic in nature, quality systems registrations tend to focus on broad product categories, and include no determination of specific competencies of the organization.

Laboratory Accreditation

Laboratory accreditation provides a means to verify that a laboratory is competent to carry out specific tasks. Competency may be defined as having all the necessary components to ensure that the test can be carried out correctly. These components include, for example:

- Trained and qualified staff;
- Equipment that is functioning properly;
- Well-defined methods;
- Proper environmental conditions;
- Procedures for feedback and corrective action; and
- Quality control systems.

But competency must not be confused with a guarantee. Accreditation makes no guarantee that a laboratory will perform the work correctly, nor does it guarantee the quality of the product or item tested. Accreditation only ensures that the laboratory has all the necessary means to be able to perform the work correctly.

Accreditation also differs from registration in terms of specificity. While quality systems registrations are broad in nature, accreditation seeks to determine the specific competencies of the organization. For a laboratory, this scope is usually expressed in various combinations of:

- Products (for example, specific electrical appliances);
- Parameters (for example, volts, ohms, etc);
- Ranges (for example, –40° to 70°C);
- Accuracy (best measurement capability or uncertainty of measurement);
- Type of test (electrical safety tests); and
- Test specification (IEC, etc.).

Product Certification

Product certification makes a definitive statement about the characteristics of a specific product. It ensures that there is a consistent production process (that is, it may require quality systems registration), that representative samples are taken, and that those samples are tested (that is, it may require accreditation) to offer verification that the rest of the batch meets the specified requirements.

ISO/IEC 17025

The primary standard in use today for the accreditation of laboratories is ISO/IEC 17025 "General requirements for the competence of testing and calibration laboratories," published in December 1999. This standard replaces ISO Guide 25 that has been in use since 1978. The intent of the standard is to establish a framework of activities, procedures, and records systems that enhance the overall quality of the laboratory's test results.

ISO/IEC 17025 is divided into two major sections: Management Requirements and Technical Requirements. Many of the ideas present in the Management Requirements are based upon those requirements listed in the ISO 9000 series of documents. At first glance, ISO/IEC 17025 appears to be vastly different from Guide 25. It has been reformatted to address the quality system requirements in one section and the technical requirements in another section; it has incorporated all of the ISO 9000 requirements, and it has added requirements to foster better client/laboratory interactions and service. The document is longer, leading one to believe that it holds many new requirements.

Actually, many of the requirements found in Guide 25 have just been further augmented in ISO/IEC 17025. Some requirements are more prescriptive and there are

many more explanatory notes. These explanatory notes serve as guidance but do not constitute any new requirements. The incorporation of the ISO 9000 requirements naturally increases the level of detail. For example, Guide 25 asked that the laboratory have "procedures for control and maintenance of documentation." ISO/IEC 17025 is more prescriptive because it not only calls for a document control procedure, but that procedure must address master lists, controlled distribution lists, and specific insertions into revised documents.

ISO/IEC 17025 does contain some new requirements, however. Requirements addressing the needs of the client are new. Incorporation of the ISO 9000 requirements adds a new preventive action requirement. There are new requirements for including opinions and interpretations in the test reports.

A brief review of each section of ISO/IEC 17025 is presented in the following section.

4. Management requirements

4.1 Organization

The premise of this section is to verify that the laboratory is able to produce a result that reflects the actual characteristics of the item tested. Several issues may evolve in a laboratory that prevent this "independence of judgement." This section seeks to minimize the effect of these issues by requiring the laboratory to identify what potential conflicts of interest might exist, and define its policies and procedures to avoid the possibility of impropriety. The laboratory is also required to define its organizational structure, key management personnel, and its place within any parent organization.

4.2 Quality system

The laboratory's quality system consists of its quality manual and all other documentation required by this standard. The minimum requirements for a quality manual are stated as:

a. A quality policy statement;

b. The roles and responsibilities of the technical management and the quality manager; and

c. The overall structure of the documentation, including references to supporting procedures.

This quality manual and related documentation is meant to serve as a repository of knowledge within the company. It describes the organization and scope of the laboratory, and its supporting documentation should provide all necessary information needed for the normal operational activities of the laboratory.

4.3 Documentation control

Documentation control's key goal is to ensure that all personnel have access to the up-to-date procedural information required in order to perform their functions. To make certain that all documentation is kept current, the standard requires a procedure to ensure that:

a. All documentation is periodically reviewed and revised, where necessary;

b. Obsolete documents are removed from use; and

c. When obsolete documents are retained, that they are suitably marked as such.

4.4 Review of requests, tenders, or contracts

Every test to be performed in the laboratory is initiated through a request. This request may take the form of a formal contract, a purchase order request, or in the case of an internal client, a simple submission of a test sample. Whatever form the request might take, the laboratory must define procedures for reviewing this scope of work to determine that:

a. The requirements of the contract are understood (method to be used, expectation in terms of reports and turnaround time, etc.);

b. The lab has the capability and resources to perform the test; and

c. That the test itself meets the clients needs.

4.5 Subcontracting

Subcontracting is defined as placing any part of the contracted scope of work (as defined in Section 4.4) with another laboratory. When a laboratory subcontracts any portion of the testing to another party, the laboratory must be able to demonstrate, through its record system, that the subcontractor is competent to perform the work in question and complies with ISO/IEC 17025.

4.6 Purchasing services and supplies

While often confused with subcontracting, this section deals with those items that support the actual testing. These items might include:

a. Calibration services;

b. Chemical purchases;

c. Maintenance contracts; and

d. Equipment purchases.

The suppliers of these services or products aren't being asked to perform the test directly; they are supplying necessary components to enable the laboratory to perform the test. These services must be evaluated to ensure that they are of adequate quality to sustain confidence in the laboratory's tests.

4.7 Service to the client

The laboratory must allow the clients the opportunity to clarify or make changes to their requested scope of work. The laboratory must also allow clients to monitor the performance of their work, as long as the confidentiality of other clients' work is not compromised.

4.8 Complaints

The laboratory must define its policies and procedures for handling of complaints received from clients or other parties.

4.9 Control of nonconforming testing and/or calibration work

It is clear that the work of the laboratory is the production of test data. Therefore, nonconforming work is test data that, for some reason, does not meet specifications. Test data may not meet specifications for a variety of reasons, including but not limited to:

a. Discovery of defective test equipment;

b. Errors in testing technique;

c. Improper storage of test item;

d. Improper test item preparation; and

e. Faulty environmental conditions during testing.

When it is discovered that nonconforming work exists, the laboratory must follow its established procedures to ensure that the deviation is evaluated for significance, and that the client is notified where necessary. It may also be necessary to halt further work in that area until the problem is eliminated.

4.10 Corrective action

Procedures or corrective actions shall be followed when is it determined that a situation that has resulted in nonconforming work (see Section 4.9) may occur again in the future, or where there is evidence of any other departures for quality or technical procedures defined in the quality manual. The corrective action system shall follow these steps:

a. Identify the root cause;

b. Select appropriate actions to eliminate the problem and prevent recurrence;

c. Monitor corrective actions to ensure effectiveness; and

d. Introduce special audits when circumstances cast doubt on compliance with its own procedures.

4.11 Preventive action

While control of nonconforming work (4.9) and corrective action (4.10) explains what happens after the occurrence of a departure, preventive action includes those steps taken to ensure that problems never occur. Preventive actions seek to identify what problems *might* occur, and attempt to put into place the necessary systems to prevent this future occurrence.

4.12 Control of records

The laboratory shall maintain all records relating to its technical and quality activities for a defined period (defined by the laboratory, however many accreditation bodies set minimal retention times). These records shall be legible, readily retrievable, held in confidence to the client, and provide an audit trail for all activities related to testing. For

those laboratories managing records by use of computers, procedures must exist for the security and backup of computer records.

4.13 Internal audits

The internal audit serves as the laboratory's way of determining the correct implementation of its quality system. This audit is carried out in accordance with a defined procedure, and is conducted at predetermined intervals (defined by the laboratory). The essential outcome is to determine that the laboratory *complies* with its own quality system and the requirements of ISO/IEC 17025.

4.14 Management review

Management reviews are the standard's way of ensuring that the laboratory is involved in continuous process improvement activities. Much like preventive action (see 4.11), management reviews tend to seek out areas for improvement rather than simply responding to issues of compliance, as would the corrective action (4.10) and internal audits (4.13) systems.

5. Technical Requirements

5.1 General

Many factors influence the date produced from a test or calibration. These factors include, but are not limited to:

a. Environmental conditions during the test;

b. Accuracy and condition of the equipment;

c. Adequacy of personnel training systems;

d. Storage, handling, and preparation of test items;

e. Sampling; and

f. Test methods and method validation.

When developing methods, designing test parameters, and training personnel, the laboratory should take account of these factors to ensure that they have the most appropriate systems.

5.2 Personnel

All personnel that are involved in any aspect of the testing must have been appropriately trained and shown to be competent in their appointed tasks. All personnel who perform any part of the testing, regardless of the employment status (permanent, contract, temporary, etc.) shall operate in accordance with the quality system of the laboratory.

The laboratory has to establish goals for the training system for all personnel, and develop a system or procedures to help to identify training needs and to provide a formal framework in which training is provided. The outcome of this training will, of course, be relevant to the current and anticipated tasks of the laboratory, and each training record will include a date on which competency is confirmed.

5.3 Accommodation and environmental conditions

The environment the testing is conducted in may play a critical role in the accuracy of the results. In addition to controlling and monitoring environmental conditions (temperature and humidity) as relevant to the specific method, the laboratory should also consider other accommodation issues (voltage, lighting, water pressure, etc.) that may have an effect on the overall test result. The laboratory is also required to take steps to prevent any type of cross-interference from adjacent areas which might invalidate the test results.

Security of the laboratory testing areas is also discussed, however it is important to note that the level of security established is dependent upon the laboratory's particular circumstances.

5.4 Test and calibration methods and method validation

The laboratory is required to use appropriate methods for all tests or calibration within its scope. However, one critical line in this section of the standard allows considerable variation in the detail contained in each method. The standard states, "The laboratory shall have instructions on the use and operation of all relevant equipment . . . where the absence of such instructions could jeopardize the results of tests or calibrations." This phrase allows the laboratory to determine the level of detail of the procedures provided to their staff. A laboratory with a very highly functioning training program may not need as much detail in a procedure when compared with a small laboratory with no formalized training program.

During the contract review phase (see Section 4.4) all requirements for the testing to be conducted, including the method to be used, should be discussed with and agreeable to the client. If the client has not specified a method to be used, the laboratory shall determine if there is a suitable method available from an international or a national standard, from reputable technical organizations, or from relevant scientific text of journals.

However, in many cases, there is no suitable method that meets the clients' needs. In these cases, the laboratory must develop its own methods. These methods must be agreeable to the client and validated to ensure that they are fit to meet the client's needs.

All laboratories, both testing and calibration, must now have a procedure for calculating measurement uncertainty. The rigor applied to this calculation is greater for calibration laboratories, however. If a testing laboratory is involved in testing where the results are purely qualitative, or the methods themselves specify the limits to major sources of uncertainty, no further calculations are needed to satisfy the standard.

During the conduct of testing, many laboratories use automated equipment to capture data, or utilize computers in some way to analyze data gathered by other means. When a laboratory is involved in either of these activities, the laboratory must have procedures that ensure the integrity of the data, the software, and the hardware. In addition, any code that is written or modified by the user must be documented in sufficient detail, and the user-written code must be validated as producing the correct output.

5.5 Equipment

All equipment in use by the laboratory must be properly maintained, calibrated (see measurement traceability, Section 5.6), and operated by authorized personnel (see personnel, Section 5.2). If the laboratory needs to borrow a piece of equipment from another area due to unforeseen circumstances, the laboratory still maintains the

responsibility to verify that this piece of borrowed equipment complies with the standard with respect to its use.

Proper records, including the calibration status and history, history of maintenance and malfunctions, manufacturer's instructions, unique identification, and current location must be maintained on all items of equipment that have an affect on the accuracy of the results. The laboratory must ensure that all equipment is calibrated before being put into use, and that if the equipment goes outside the direct control of the laboratory, the calibration status is checked to ensure that it is satisfactory for use.

5.6 Measurement traceability

A calibration laboratory or a testing laboratory performing its own calibrations shall ensure that its system for the calibration of equipment is designed to provide an unbroken chain of calibrations back to the International System of Units (SI). In most cases, maintaining traceability to the national standard of measurement or the national metrological institution ensures traceability to the SI unit.

Reference materials and standards shall also have direct traceability to the SI unit.

5.7 Sampling

Sampling is defined as the procedure whereby a part of a substance, materials, or product is taken for testing or calibration, and its results are meant to represent the properties of the whole, that is, water samples from a lake or samples from a bin at the end of a production line. When a laboratory is engaged in the sampling process, the laboratory must have a sampling plan (from where the sample is selected) and procedure (how the actual sample is taken), and these plans and procedures must be available at the location where the sampling is carried out. Since the environment in which the sampling is carried out may have a direct impact on the results, the laboratory must record any relevant data regarding the sampling process.

5.8 Handling of test and calibration items

The laboratory must design a system to ensure that all items received for testing or calibration are uniquely identified. All items must be stored under the proper conditions and must be held secure to the client.

If the laboratory receives a sample that is not suitable for testing or does not correspond with the description provided, the laboratory must contact the client before proceeding.

5.9 Assuring the quality of test and calibration results

In addition to all of the quality control measures found in the standard, there are additional ways to measure the accuracy of the data produced by the laboratory:

a. Use of certified reference materials;

b. Participation in proficiency testing and/or interlaboratory comparisons;

c. Replicate testing using the same or different methods;

d. Retesting of items; and

e. Correlation of results for different characteristics of the same item.

The laboratory may take part in any of these activities or may design a more rigorous activity. In all cases, the data shall be recorded or analyzed in such a way that trends are detectable for quality improvement purposes.

5.10 Reporting the results

The final section of the standard specifies a series of items to be included on a test report or calibration certificate. These items include, but are not limited to:

I. Standard information
   A. Name and address of laboratory
   B. Date of test
   C. Method used
   D. Name and address of client

II. Sampling information
   A. Date of sampling
   B. Location where sampling was carried out
   C. Reference to sampling plans and procedures
   D. Environmental conditions during sampling

III. Calibration certificate information
   A. Conditions during calibration
   B. Uncertainty of measurement
   C. Traceability information
   D. Before and after results

However, a laboratory may forego that specified format if they are servicing an internal client, or in the case of a written agreement with an external client. Laboratories that choose a simplified report are responsible for maintaining in their record system all information specified in 5.10.2 through 5.10.4.

HARMONIZATION

The mutual recognition arrangement (MRA) process is the means by which laboratory accreditation bodies develop confidence in their peers' abilities to determine a laboratory's competence to perform testing or calibrations. These accrediting bodies also agree to promote the acceptance of test or calibration data generated from the laboratories accredited by the MRA signatories, thereby fostering the reduction of technical barriers to trade. Verifying an accrediting body's compliance with ISO/IEC Guide 58, and its accredited laboratories' compliance with ISO/IEC 17025, is critical in establishing the needed level

of confidence to make the MRA process work. The means by which an accrediting body ensures that measurements made by the testing or calibration laboratories are traceable to the national measurement institute (whenever possible) is also of critical importance.

In the international conformity assessment structure, the evaluation and approval mechanism for the ISO 9000 registrar system is well known. The International Accreditation Forum (IAF) is recognized as the organization that formally evaluates and approves accreditors of ISO 9000 registrars. Within the United States, the Registrar Accreditation Board (RAB) is a signatory to the IAF multilateral agreement (MLA) for quality management systems. RAB in turn is recognized as the accreditor for ISO 9000 registrars in the United States. (They also accredit QS-9000 and AS 9000 registrars.) Similarly, within the United States, the American National Standards Institute (ANSI) is recognized as the accreditor of product certifiers. There is no mechanism at present to formally evaluate and approve the function provided by ANSI, but the IAF membership is looking at expanding their present MLA process to include evaluation and approval of the accreditors of product certifiers.

Evaluation at each of these levels of conformity assessment is performed against relevant international consensus standards. IAF uses ISO Guide 61, "General requirements for assessment and accreditation of certification/registration body assessment and accreditation systems" in its evaluation of RAB. (This same document could be used should IAF develop a program to evaluate and approve product certification accreditors.) RAB in turn evaluates registrars against ISO Guide 62, "General requirements for bodies operating assessment and certification/registration of quality systems." ANSI uses ISO Guide 65, "General requirements for bodies operating product certification systems" in its evaluation of product certifiers.

However, for the laboratory accreditation arm of conformity assessment, the structure and mechanism for evaluating and approving laboratory accreditation bodies is not as well-known or easily defined. Recently, a number of different sources have asked how laboratory accreditation bodies such as the American Association for Laboratory Accreditation (A2LA) or the National Voluntary Laboratory Accreditation Program (NVLAP) have established themselves as credible, internationally recognized laboratory accreditation bodies. This query is often followed up by questions concerning the means by which confidence between accrediting bodies is developed sufficiently to allow the accreditation bodies to promote worldwide acceptance of test and calibration data.

This credibility and confidence are developed through multilateral mutual recognition arrangements among various accreditation systems. This means that appointed representatives from the cooperating laboratory accreditation systems perform an evaluation of an applicant laboratory accreditation system on behalf of all the systems in the cooperation. If the requirements are met, then all systems party to the cooperative arrangement recognize accreditations issued by the applicant. Evaluations include time spent at the offices of the applicant system to determine the applicant's compliance with ISO Guide 58, "Calibration and testing laboratory accreditation systems—General requirements for operation and recognition." Additionally the evaluators also witness the performance of the applicant's assessors during actual assessments to determine if the laboratories are in compliance with ISO Guide 25 or ISO/IEC 17025, "General requirements for the competence of calibration and testing laboratories."

Structure of the International MRA Cooperations

The International Laboratory Accreditation Cooperation (ILAC) is the world's principal international forum for the development of laboratory accreditation practices and procedures. ILAC promotes laboratory accreditation as a trade facilitation tool, assists developing accreditation bodies, and recognizes competent test facilities around the globe. Membership to ILAC is open to mature, growing, and newly emerging accreditation bodies. Representatives from these bodies contribute to standing committees that develop accreditation policies, procedures, guidelines, and technical documents that are then approved through consensus. ILAC receives input from the laboratory community through a standing liaison committee.

There are a number of MRA regional cooperations operating, including the European Cooperation for Accreditation (EA), the Asia Pacific Cooperation for Laboratory Accreditation (APLAC), the Inter-American Accreditation Cooperation (IAAC) and the Southern Africa Development Conformity Assessment (SADCA). EA is the more mature regional cooperation, followed by APLAC. IAAC and SADCA are still in their infancy. The United States is fortunate (or unfortunate, depending on one's point of view) in having a vast number of private or public "laboratory accreditation systems" professing to offer some sort of "accreditation or certification" using vastly differing criteria. The National Cooperation for Laboratory Accreditation (NACLA) was developed to try to make some sense out of this confusion. NACLA recognizes ISO Guide 58 and ISO Guide 25 (17025) as the fundamental criteria to be met by laboratory accreditation bodies and laboratories respectively. NACLA has an operating structure, bylaws, policies, and procedures, and has completed the peer evaluation process for two U.S. based applicants to become NACLA MRA signatories.

The membership of each regional cooperation is open to accreditation bodies who are interested in supporting the cooperations' activities, want to gain experience and know-how about operating a system to international criteria, or are signatories to the MRA for that cooperation. Signatory status is only achieved after the peer evaluation process is completed. Geographic location of the accreditation body is not a barrier to joining a regional cooperation. For example, A2LA is an MRA signatory to both EA and APLAC, and also a member and active committee participant in IAAC. Each regional cooperation operates in accordance with set policies and procedures developed through consensus.

ILAC has established a plan for one ILAC MRA that would pull together the regional MRA efforts and provide a "loose umbrella" over the whole process. This would ensure that the operations between regions are harmonious, so promotion of the acceptance of test data can continue.

MRA Peer Evaluation Process

Each regional cooperation has policies and procedures in place to guide the application, peer evaluation, and decision-making processes inherent to an applicant accreditation body eventually becoming signatory to an MRA.

Application. The applicant must submit a series of documents to the secretariat of the regional cooperation with which they wish to sign an MRA. These documents must provide the written evidence that the applicant has addressed the ISO Guide 58 documentation requirements and described their measurement traceability policy and their laboratories' proficiency testing participation. If the applicant has any doubt about the adequacy of the documentation or the readiness of the system to be evaluated, a pre-evaluation can be requested.

Evaluators. Once a completed application is received, an evaluation team leader is recruited from a list of approved evaluators kept by each regional cooperation. Evaluators, for the most part, are recruited from the senior staff of accrediting bodies that are members of the regional cooperations. Additional evaluators sometimes come from the national metrology institutes (NMI) when specific expertise in the calibration area may be needed.

Accreditation body staff gain experience towards team leader status by first observing a number of MRA evaluations. Evaluators must then serve on at least two MRA teams before they qualify as team leaders. Periodically, training seminars for evaluators and team leaders are held at different locations internationally and each regional cooperation may send a number of attendees.

The assigned team leader chooses evaluation team members with technical background that coincide with the kinds of laboratories that the applicant body is accrediting. If the applicant body accredits calibration laboratories, one of the team members must have a strong background in calibration.

Pre-evaluation. If a pre-evaluation is requested or agreed upon, the team leader may take on this responsibility alone or include one of the team members. The pre-evaluation serves to point out any large omissions in the applicant's conformance to ISO Guide 58. Any issues from the pre-evaluation must be satisfactorily addressed by the applicant body before the full evaluation can move forward.

Full evaluation. Prior to the full evaluation, the team leader carries out the full document review and may delegate certain tasks to the team members. To better determine the applicant's conformance and implementation of the ISO Guide 58 requirements, one part of the evaluation takes place at the applicant's headquarters. Records are reviewed and staff is interviewed in order for the team to gather objective evidence of compliance.

The extent to which the applicant body's laboratories have successfully participated in proficiency testing and interlaboratory comparisons (ILCs) is also evaluated. This is one means by which the evaluators can gain a level of confidence that the laboratories have been properly assessed to ISO/IEC 17025 and are competent to perform tests or calibrations. If the applicant body wishes to include calibration laboratory accreditation as part of the MRA, the applicant must participate in a number of national or international ILCs, including different calibration disciplines. The required number of ILCs is dependent upon the number and disciplines of calibration accreditations that the applicant has granted.

To further the level of confidence that the applicant body is operating an accreditation program that is effective in determining the competence of the laboratories they accredit, the evaluation team must attend, where possible, a representative sample of assessments, reassessments, and surveillance visits. The task of the evaluation team is to appraise the compliance of the laboratory with ISO/IEC 17025, with any specific technical program requirements, and with any of the applicant body's requirements. The effectiveness of the applicant body's assessors as they perform the assessments is observed. The assessors are observed for their technical knowledge and assessment skills, their understanding and adherence to the applicant's procedures and requirements for performing assessments, and their abilities to perform assessments that thoroughly cover the ISO/IEC 17025 requirements and the test method requirements on the laboratory's scope of accreditation.

The team must also check the relationship between the accreditation body and the national or regional measurement system and the arrangement to ensure that traceability of measurement to appropriate primary standards of measurement is possible. The National Institute for Standards and Technology (NIST) is greatly respected internationally. Its affiliation with the National Voluntary Laboratory Accreditation Program (NVLAP), and A2LA and NVLAP recognition of each other through the APLAC MRA, affords each of these accrediting bodies a satisfactory link to NIST and its national standards of measurement.

When the national measurement institute is not as well known as NIST, the calibration expert on the evaluation team will often visit the NMI to gain a better understanding of their scope of work and their general capabilities. The level of their participation in ILCs sponsored by other NMIs or the International Bureau of Weights and Measures (BIPM) is also evaluated, again to achieve a satisfactory level of confidence that the NMI can provide support to the accrediting bodies and the testing and calibration laboratories in their efforts to establish traceability of their measurements.

The evaluation team must establish whether the requirements of ISO/IEC 17025 are being satisfied and that the measurements performed have an appropriate measurement uncertainty. Calibration measurements must also include the assignment of best measurement capability. The international accreditation community has determined that the requirement for traceable measurements can best be satisfied and verified by either using reference standards that are directly traceable to a national measurement institute, or by using calibration laboratories accredited by an MRA signatory to a recognized regional cooperation.

A significant challenge for both accrediting bodies and *testing* laboratories is the new requirement that these laboratories estimate the uncertainty of their test measurements, where appropriate. This is *not* a new requirement for calibration laboratories. Tutorials for estimating measurement uncertainty and guidance for determining the test methods for which it is appropriate to estimate uncertainty are needed to support the laboratories' implementation of this new ISO/IEC 17025 requirement. Accrediting bodies must also ensure that their staff and testing assessors are trained to understand and properly apply the estimation of measurement uncertainty.

For future MRA evaluations, when compliance with ISO/IEC 17025 has been fully implemented by the laboratories, the evaluators will have to appraise the effectiveness

of the applicant accrediting body's program to implement these new requirements. In a resolution agreed to by all of the member bodies of ILAC, the laboratory accreditors agreed to begin implementation of ISO/IEC 17025 within two years from the date of publication of ISO/IEC 17025. The laboratories' compliance with this standard will be checked during the normal surveillance schedule for the laboratory. ISO/IEC 17025 was officially published on December 15, 1999 and many of the accreditors intended to begin ISO/IEC 17025 assessments in the last half of 2000. Plans are to have all of their laboratories assessed for compliance to ISO/IEC 17025 by the last half of 2002, through a gradual phase-in program.

Decision on signatory acceptance. Any concerns resulting from the evaluation are written into a formal report by the evaluation team and provided to the applicant body. The applicant body responds in writing to the team leader with a corrective action. Once the team leader deems the corrective action adequate (with the team's concurrence), the team leader drafts a recommendation that is submitted to the MRA acceptance panel for the regional cooperation. The acceptance panel is made up of representatives from accrediting bodies that are already signatories to the MRA. The acceptance panel also receives the final report and any supporting documentation to help them in making a decision. The acceptance panel decides whether or not the applicant body can enter the MRA, or in the case of a re-evaluation, can remain as a signatory. Positive decisions can be accompanied by conditions, such as the need for a follow-up evaluation or a full re-evaluation prior to the normal schedule. In general, accrediting bodies are re-evaluated every four years. A negative decision can be appealed.

Maintenance of MRAs

In order to maintain the value and meaning of the agreements, the MRA signatories agree to notify each other about any significant changes in the status or operation of the body. Issues of significance include changes in name or legal/corporate status; new agreements negotiated with other accrediting bodies or the revision, suspension, or termination of any agreements; changes in key senior staff or the organizational structure; or significant changes in the operations of the body. Each signatory to an MRA must also designate a liaison officer to afford a consistent channel of communication between the accrediting bodies.

CONCLUSION

The mutual recognition arrangement (MRA) process has proven successful in building confidence between accrediting bodies and their ability to determine a laboratory's competence to perform testing or calibrations. ISO Guide 25, and now ISO/IEC 17025, play an integral role in building this confidence. Confidence facilitates the acceptance of testing and calibration results between countries when the results can be demonstrated to come from accredited laboratories. This ultimately helps to reduce the technical barriers to trade.

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ISO Guide 65, "General requirements for bodies operating product certification systems."

Part V

Additional Appendices

Appendix F

The OECD Principles of Good Laboratory Practice

Chemicals control laws passed in Organisation for Economic Co-operation and Development (OECD) Member countries in recent decades call for testing and assessing of chemicals to determine their potential hazards. A basic principle of this legislation is that assessments of hazards associated with chemicals should be based on test data of assured quality.

Good Laboratory Practice (GLP) is intended to promote the quality and validity of test data. It is a managerial concept covering the organizational process and the conditions under which laboratory studies are planned, performed, monitored, recorded, and reported.

The application of GLP is of crucial importance to national authorities entrusted with the responsibility of assessing test data and evaluating chemical hazards. The issue of data quality also has an international dimension. If countries can rely on test data developed in other countries, duplicative testing can be avoided and costs to government and industry saved. Moreover, common principles and procedures for GLP facilitate the exchange of information and prevent the emergence of non-tariff barriers to trade while contributing to environmental and health protection.

The OECD Principles of Good Laboratory Practice were developed by an Expert Group on GLP established in 1978 under the Special Programme on the Control of Chemicals. The GLP regulations for non-clinical laboratory studies, published by the US Food and Drug Administration in 1976, provided the basis for the work of the Expert Group. The Group was chaired by Dr. Carl Morris, United States Environmental Protection Agency. The following countries and organizations participated in the Expert Group: Australia, Austria, Belgium, Canada, Denmark, France, the Federal Republic of Germany, Greece, Italy, Japan, the Netherlands, New Zealand, Norway, Sweden, Switzerland, the United Kingdom, the United States, the Commission of the European

Communities, the World Health Organization, and the International Organization for Standardization (ISO/ CERTICO).

The OECD Principles of GLP as set out in Part One of this publication were reviewed in the relevant policy bodies of the Organisation and were formally recommended for use in Member countries by the OECD Council in 1981. They are an integral part of the Council Decision on Mutual Acceptance of Data, which states "that data generated in the testing of chemicals in an OECD Member country in accordance with OECD Test Guidelines* and OECD Principles of Good Laboratory Practice shall be accepted in other Member countries for purposes of assessment and other uses relating to the protection of man and the environment" [C(81)30(Final)].

The OECD Principles of GLP were first published in 1982 in Good *Laboratory Practice in the Testing of Chemicals.*** This publication also contained guidance provided in the final report of the Expert Group. Since the early 1980's OECD has continued to elaborate and refine this guidance, and has undertaken further work on national and international aspects of compliance with the GLP Principles and monitoring of such compliance. The results of that work are being published (or reprinted) in this OECD Series on Good Laboratory Practice and Compliance Monitoring, beginning in 1991. It is therefore appropriate that the OECD Principles of GLP and the Council Acts concerning GLP be the subject of this first number of the series.

PART ONE: THE OECD PRINCIPLES OF GLP***

Section 1: Introduction

Preface

A number of OECD Member countries have recently passed legislation to control chemical substances and others are about to do so. This legislation usually requires the manufacturer to perform laboratory studies and to submit the results of these studies to a governmental authority for assessment of the potential hazard to human health and the environment.

Government and industry are increasingly concerned with the quality of studies upon which hazard assessments are based. As a consequence, several OECD Member countries have, or plan to establish, criteria for the performance of these studies.

To avoid different schemes of implementation that could impede international trade in chemicals, OECD Member countries have recognised the unique opportunity for international harmonization of test methods and good laboratory practices.

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* *OECD Guidelines for the Testing of Chemicals* (1981 and continuing series).

** OECD, 1982, out of print.

*** The OECD Principles of Good Laboratory Practice are contained in Annex 11 of the Decision of the Council concerning the Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30(Final)].

During 1979–80, an international group of experts established under the Special Programme on the Control of Chemicals developed this document concerning the "Principles of Good Laboratory Practice (GLP)" utilising common managerial and scientific practices and experience from various national and international sources.

The purpose of these Principles of Good Laboratory Practice is to promote the development of quality test data. Comparable quality of test data forms the basis for the mutual acceptance of test data among countries.

If individual countries can confidently rely on test data developed in other countries, duplicative testing can be avoided, thereby introducing economies in test costs and time. The application of these Principles should help avoid the creation of technical barriers to trade, and further improve the protection of human health and the environment.

1. Scope

These Principles of Good Laboratory Practice should be applied to testing of chemicals to obtain data on their properties and/or their safety with respect to human health or the environment.

Studies covered by Good Laboratory Practice also include work conducted in field studies.

These data would be developed for the purpose of meeting regulatory requirements.

2. Definitions of Terms

2.1 *Good Laboratory Practice*

1. Good Laboratory Practice (GLP) is concerned with the organisational process and the conditions under which laboratory studies are planned, performed, monitored, recorded, and reported.

2.2 *Terms Concerning the Organisation of a Test Facility*

1. *Test facility* means the persons, premises, and operational unit(s) that are necessary for conducting the study.
2. *Study Director* means the individual responsible for the overall conduct of the study.
3. *Quality Assurance Programme* means an internal control system designed to ascertain that the study is in compliance with these Principles of Good Laboratory Practice.
4. *Standard Operating Procedures (SOPs)* means written procedures which describe how to perform certain routine laboratory tests or activities normally not specified in detail in study plans or test guidelines.
5. *Sponsor* means a person(s) or entity who commissions and/or supports a study.

2.3 *Terms Concerning the Study*

1. *Study* means an experiment or set of experiments in which a test substance is examined to obtain data on its properties and/or its safety with respect to human health and environment.
2. *Study plan* means a document which defines the entire scope of the study.
3. *OECD Test Guideline* means a test guideline which the OECD has recommended for use in its Member countries.
4. *Test system* means any animal, plant, microbial, as well as other cellular, sub-cellular, chemical, or physical system or a combination thereof used in a study.
5. *Raw data* means all original laboratory records and documentation, or verified copies thereof, which are the result of the original observations and activities in a study.
6. *Specimen* means any material derived from a test system for examination, analysis, or storage.

2.4 *Terms Concerning the Test Substance*

1. *Test substance* means a chemical substance or a mixture which is under investigation.
2. *Reference substance (control substance)* means any well defined chemical substance or any mixture other than the test substance used to provide a basis for comparison with the test substance.
3. *Batch* means a specific quantity or lot of a test or reference substance produced during a defined cycle of manufacture in such a way that it could be expected to be of a uniform character and should be designed as such.
4. *Vehicle (carrier)* means any agent which serves as a carrier used to mix, disperse, or solubilise the test or reference substance to facilitate the administration to the test system.
5. *Sample* means any quantity of the test or reference substance.

Section II: Good Laboratory Practice Principles

1. Test Facility Organisation and Personnel

1.1 *Management's Responsibilities*

1. Test facility management should ensure that the Principles of Good Laboratory Practice are complied with in the test facility.

2. At a minimum it should:

   a. ensure that qualified personnel, appropriate facilities, equipment, and materials are available;

   b. maintain a record of the qualifications, training, experience, and job description for each professional and technical individual;

   c. ensure that personnel clearly understand the functions they are to perform and, where necessary, provide training for these functions;

   d. ensure that health and safety precautions are applied according to national and/or international regulations;

   e. ensure that appropriate Standard Operating Procedures are established and followed;

   f. ensure that there is a Quality Assurance Programme with designated personnel;

   g. where appropriate, agree to the study plan in conjunction with the sponsor;

   h. ensure that amendments to the study plan are agreed upon and documented;

   i. maintain copies of all study plans;

   j. maintain a historical file of all Standard Operating Procedures;

   k. for each study ensure that a sufficient number of personnel is available for its timely and proper conduct;

   l. for each study designate an individual with the appropriate qualifications, training, and experience as the Study Director before the study is initiated. If it is necessary to replace a Study Director during a study, this should be documented;

   m. ensure that an individual is identified as responsible for the management of the archives.

1.2 *Study Director's Responsibilities*

1. The Study Director has the responsibility for the overall conduct of the study and for its report.

2. These responsibilities should include, but not be limited to, the following functions:

   a. should agree to the study plan;

   b. ensure that the procedures specified in the study plan are followed, and that authorisation for any modification is obtained and documented together with the reasons for them;

c. ensure that all data generated are fully documented and recorded;

d. sign and date the final report to indicate acceptance of responsibility for the validity of the data and to confirm compliance with these Principles of Good Laboratory Practice;

e. ensure that after termination of the study, the study plan, the final report, raw data, and supporting material are transferred to the archives.

1.3 *Personnel Responsibilities*

1. Personnel should exercise safe working practice. Chemicals should be handled with suitable caution until their hazard(s) has been established.
2. Personnel should exercise health precautions to minimise risk to themselves and to ensure the integrity of the study.
3. Personnel known to have a health or medical condition that is likely to have an adverse effect on the study should be excluded from operations that may affect the study.

2. Quality Assurance Programme

2.1 *General*

1. The test facility should have a documented quality assurance programme to ensure that studies performed are in compliance with these Principles of Good Laboratory Practice.
2. The quality assurance programme should be carried out by an individual or by individuals designated by and directly responsible to management and who are familiar with the test procedures.
3. This individual(s) should not be involved in the conduct of study being assured.
4. This individual(s) should report any findings in writing directly to management and to the Study Director.

2.2 *Responsibilities of the Quality Assurance Personnel*

1. The responsibilities of the quality assurance personnel should include, but not be limited to, the following functions:

a. ascertain that the study plan and Standard Operating Procedures are available to personnel conducting the study;

b. ensure that the study plan and Standard Operating Procedures are followed by periodic inspections of the test facility and/or by auditing the study in progress. Records of such procedures should be retained;

c. promptly report to management and the Study Director unauthorised deviations from the study plan and from Standard Operating Procedures;

d. review the final reports to confirm that the methods, procedures, and observations are accurately described, and that the reported results accurately reflect the raw data of the study;

e. prepare and sign a statement, to be included with the final report, which specifies the dates inspections were made and the dates any findings were reported to management and to the Study Director.

3. Facilities

3.1 *General*

1. The test facility should be of suitable size, construction, and location to meet the requirements of the study and minimise disturbances that would interfere with the validity of the study.

2. The design of the test facility should provide an adequate degree of separation of the different activities to assure the proper conduct of each study.

3.2 *Test System Facilities*

1. The test facility should have a sufficient number of rooms or areas to assure the isolation of test systems and the isolation of individual projects, involving substances known or suspected of being biohazardous.

2. Suitable facilities should be available for the diagnosis, treatment and control of diseases, in order to ensure that there is no unacceptable degree of deterioration of test systems.

3. There should be storage areas as needed for supplies and equipment. Storage areas should be separated from areas housing the test systems and should be adequately protected against infestation and contamination. Refrigeration should be provided for perishable commodities.

3.3 *Facilities for Handling Test and Reference Substances*

1. To prevent contamination or mix-ups, there should be separate areas for receipt and storage of the test and reference substances, and mixing of the test substances with a vehicle.

2. Storage areas for the test substances should be separate from areas housing the test systems and should be adequate to preserve identity, concentration, purity, and stability, and ensure safe storage for hazardous substances.

3.4 *Archive Facilities*

1. Space should be provided for archives for the storage and retrieval of raw data, reports, samples, and specimens.

3.5 *Waste Disposal*

1. Handling and disposal of wastes should be carried out in such a way as not to jeopardise the integrity of studies in progress.
2. The handling and disposal of wastes generated during the performance of a study should be carried out in a manner which is consistent with pertinent regulatory requirements. This would include provision for appropriate collection, storage and disposal facilities, decontamination and transportation procedures, and the maintenance of records related to the preceding activities.

4. Apparatus, Material, and Reagents

4.1 *Apparatus*

1. Apparatus used for the generation of data, and for controlling environmental factors relevant to the study should be suitably located and of appropriate design and adequate capacity.
2. Apparatus used in a study should be periodically inspected, cleaned, maintained, and calibrated according to Standard Operating Procedures. Records of procedures should be maintained.

4.2 *Material*

1. Apparatus and materials used in studies should not interfere with the test systems.

4.3 *Reagents*

1. Reagents should be labelled, as appropriate, to indicate source, identity, concentration, and stability information and should include the preparation date, earliest expiration date, specific storage instructions.

5. Test Systems

5.1 *Physical/Chemical*

1. Apparatus used for the generation of physical/chemical data should be suitably located and of appropriate design and adequate capacity.
2. Reference substances should be used to assist in ensuring the integrity of the physical/chemical test systems.

5.2 *Biological*

1. Proper conditions should be established and maintained for the housing, handling, and care of animals, plants, microbial as well as other cellular and sub-cellular systems, in order to ensure the quality of the data.

2. In addition, conditions should comply with appropriate national regulatory requirements for the import, collection, care and use of animals, plants, microbial as well as other cellular and sub-cellular systems.
3. Newly received animal and plant test systems should be isolated until their health status has been evaluated. If any unusual mortality or morbidity occurs, this lot should not be used in studies and, when appropriate, humanely destroyed.
4. Records of source, date of arrival, and arrival condition should be maintained.
5. Animal, plant, microbial, and cellular test systems should be acclimatised to the test environment for an adequate period before a study is initiated.
6. All information needed to properly identify the test systems should appear on their housing or containers.
7. The diagnosis and treatment of any disease before or during a study should be recorded.

6. Test and Reference Substances

6.1 *Receipt, Handling, Sampling, and Storage*

1. Records including substance characterisation, date of receipt, quantities received and used in studies should be maintained.
2. Handling, sampling, and storage procedures should be identified in order that the homogeneity and stability is assured to the degree possible and contamination or mix-up are precluded.
3. Storage container(s) should carry identification information, earliest expiration date, and specific storage instructions.

6.2 *Characterization*

1. Each test and reference substance should be appropriately identified (e.g. code, chemical abstract number (CAS), name).
2. For each study, the identity, including batch number, purity, composition, concentrations, or other characterisations to appropriately define each batch of the test or reference substances should be known.
3. The stability of test and reference substances under conditions of storage should be known for all studies.
4. The stability of test and reference substances under the test conditions should be known for all studies.

5. If the test substance is administered in a vehicle, Standard Operating Procedures should be established for testing the homogeneity and stability of the test substance in that vehicle.
6. A sample for analytical purposes from each batch of test substance should be retained for studies in which the test substance is tested longer than four weeks.

7. Standard Operating Procedures

7.1 *General*

1. A test facility should have written Standard Operating Procedures approved by management that are intended to ensure the quality and integrity of the data generated in the course of the study.
2. Each separate laboratory unit should have immediately available Standard Operating Procedures relevant to the activities being performed therein. Published text books, articles and manuals may be used as supplements to these Standard Operating Procedures.

7.2 *Application*

1. Standard Operating Procedures should be available for, but not limited to, the following catagories of laboratory activities. The details given under each heading are to be considered as illustrative examples.
   a. *Test and Reference Substance:* Receipt, identification, labelling, handling, sampling, and storage.
   b. *Apparatus and Reagents:* Use, maintenance, cleaning, calibration of measuring apparatus and environmental control equipment; preparation of reagents.
   c. *Record Keeping, Reporting, Storage, and Retrieval:* Coding of studies, data collection, preparation of reports, indexing systems, handling of data, including the use of computerised data systems.
   d. *Test system (where appropriate):*
      i. Room preparation and environmental room conditions for the test system.
      ii. Procedures for receipt, transfer, proper placement, characterisation, identification, and care of test system.
      iii. Test system preparation, observations, examinations, before, during, and at termination of the study.

iv. Handling of test system individuals found moribund or dead during the study.

v. Collection, identification, and handling of specimens including necropsy and histopathology.

e. *Quality Assurance Procedures:* Operation of quality assurance personnel in performing and reporting study audits, inspections, and final study report reviews.

f. *Health and Safety Precautions:* As required by national and/or international legislation or guidelines.

8. Performance of the Study

8.1 *Study Plan*

1. For each study, a plan should exist in a written form prior to initiation of the study.
2. The study plan should be retained as raw data.
3. All changes, modifications, or revisions of the study plan, as agreed to by the Study Director, including justification(s), should be documented, signed and dated by the Study Director, and maintained with the study plan.

8.2 *Content of the Study Plan*

The study plan should contain, but not be limited to the following information:

1. *Identification of the Study, the Test and Reference Substance*
   a. A descriptive title;
   b. A statement which reveals the nature and purpose of the study;
   c. Identification of the test substance by code or name (IUPAC; CAS number, etc.);
   d. The reference substance to be used.
2. *Information Concerning the Sponsor and the Test Facility*
   a. Name and address of the Sponsor;
   b. Name and address of the Test Facility;
   c. Name and address of the Study Director.

3. *Dates*
    a. The date of agreement to the study plan by signature of the Study Director, and when appropriate, of the sponsor and/or the test facility management;
    b. The proposed starting and completion dates.
4. *Test Methods*
    a. Reference to OECD Test Guideline or other test guideline to be used.
5. *Issues (where applicable)*
    a. The justification for selection of the test system;
    b. Characterisation of the test system, such as the species, strain, substrain, source of supply, number, body weight range, sex, age, and other pertinent information;
    c. The method of administration and the reasons for its choice;
    d. The dose levels and/or concentrations (s), frequency, duration of administration;
    e. Detailed information on the experimental design, including a description of the chronological procedure of the study, all methods, materials and conditions, type and frequency of analysis, measurements, observations and examinations to be performed.
6. *Records*
    a. A list of records to be retained.

8.3 *Conduct of the Study*

1. A unique identification should be given to each study. All items concerning this study should carry this identification.
2. The study should be conducted in accordance with the study plan.
3. All data generated during the conduct of the study should be recorded directly, promptly, accurately, and legibly by the individual entering the data. These entries should be signed or initialled and dated.
4. Any change in the raw data should be made so as not to obscure the previous entry, and should indicate the reason, if necessary, for change and should be identified by date and signed by the individual making the change.
5. Data generated as a direct computer input should be identified at the time of data input by the individual(s) responsible for direct data entries. Corrections should be entered separately by the reason for change, with the date and the identity of the individual making the change.

9. Reporting of Study Results

9.1 *General*

1. A final report should be prepared for the study.
2. The use of the International System of Units (SI) is recommended.
3. The final report should be signed and dated by the Study Director.
4. If reports of principal scientists from co-operating disciplines are included in the final report, they should sign and date them.
5. Corrections and additions to a final report should be in the form of an amendment. The amendment should clearly specify the reason for the corrections or additions and should be signed and dated by the Study Director and by the principal scientist from each discipline involved.

9.2 *Content of the Final Report*
The final report should include, but not be limited to, the following information:

1. *Identification of the Study, the Test and Reference Substance*
   a. A descriptive title;
   b. Identification of the test substance by code or name (IUPAC; CAS number, etc.);
   c. Identification of the reference substance by chemical name;
   d. Characterisation of the test substance including purity, stability, and homogeneity.
2. *Information Concerning the Test Facility*
   a. Name and address;
   b. Name of the Study Director;
   c. Name of other principal personnel having contributed reports to the final report.
3. *Dates*
   a. Dates on which the study was initiated and completed.
4. *Statement*
   a. A Quality Assurance statement certifying the dates inspections were made and the dates any findings were reported to management and to the Study Director.

5. *Description of Materials and Test Methods*
    a. Description of methods and materials used;
    b. Reference to OECD Test Guidelines or other test guidelines.
6. *Results*
    a. A summary of results;
    b. All information and data required in the study plan;
    c. A presentation of the results, including calculations and statistical methods;
    d. An evaluation and discussion of the results and, where appropriate, conclusions.
7. *Storage*
    a. The location where all samples, specimens, raw data, and the final report are to be stored.

10. Storage and Retention of Records and Material

10.1 *Storage and Retrieval*

1. Archives should be designed and equipped for the accommodation and the secure storage of:
    a. The study plans;
    b. The raw data;
    c. The final reports;
    d. The reports of laboratory inspections and study audits performed according to the Quality Assurance Programme;
    e. Samples and specimens.
2. Material retained in the archives should be indexed so as to facilitate orderly storage and rapid retrieval.
3. Only personnel authorised by management should have access to the archives. Movement of material in and out of the archives should be properly recorded.

10.2 *Retention*

1. The following should be retained for the period specified by the appropriate authorities:
   a. The study plan, raw data, samples, specimens, and the final report of each study;
   b. Records of all inspections and audits performed by the Quality Assurance Programme;
   c. Summary of qualifications, training, experience, and job descriptions of personnel;
   d. Records and reports of the maintenance and calibration of equipment;
   e. The historical file of Standard Operating Procedures.
2. Samples and specimens should be retained only as long as the quality of the preparation permits evaluation.
3. If a test facility or an archive contracting facility goes out of business and has no legal successor, the archive should be transferred to the archives of the sponsor(s) of the study(s).

PART TWO: OECD COUNCIL ACTS ON GLP PRINCIPLES AND COMPLIANCE MONITORING

DECISION OF THE COUNCIL concerning the Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30(Final)]

(Adopted by the Council at its 535th Meeting on 12th May, 1981)

The Council,
Having regard to Articles 2(a), 2(d), 5(a), and 5(b) of the Convention on the Organisation for Economic Co-operation and Development of 14th December, 1960;

Having regard to the Recommendation of the Council of 26th May, 1972, on Guiding Principles concerning International Economic Aspects of Environmental Policies [C(72)128];

Having regard to the Recommendation of the Council of 14th November, 1974, on the Assessment of the Potential Environmental Effects of Chemicals [C(74)215];

Having regard to the Recommendation of the Council of 26th August, 1976, concerning Safety Controls over Cosmetics and Household Products [C(76)144 (Final)];

Having regard to the Recommendation of the Council of 7th July, 1977, establishing Guidelines in respect of Procedure and Requirements for Anticipating the Effects of Chemicals on Man and in the Environment [C(77)97 (Final)];

Having regard to the Decision of the Council of 21st September, 1978, concerning a Special Programme on the Control of Chemicals and the Programme of Work established therein [C(78)127 (Final)];

Having regard to the Conclusions of the First High Level Meeting of the Chemicals Group of 19th May, 1980, dealing with the control of health and environmental effects of chemicals [ENV/CHEM/HLM/80.M/1];

Considering the need for concerted action amongst OECD Member countries to protect man and his environment from exposure to hazardous chemicals;

Considering the importance of international production and trade in chemicals and the mutual economic and trade advantages which accrue to OECD Member countries from harmonization of policies for chemicals control;

Considering the need to minimise the cost burden associated with testing chemicals and the need to utilise more effectively scarce test facilities and specialist manpower in Member countries;

Considering the need to encourage the generation of valid and high quality test data and noting the significant actions taken in this regard by OECD Member countries through provisional application of OECD Test Guidelines and OECD Principles of Good Laboratory Practice;

Considering the need for and benefits of mutual acceptance in OECD countries of test data used in the assessment of chemicals and other uses relating to protection of man and the environment;

On the proposal of the High Level Meeting of the Chemicals Group, endorsed by the Environment Committee;

PART I

1. DECIDES that data generated in the testing of chemicals in an OECD Member country in accordance with OECD Test Guidelines and OECD Principles of Good Laboratory Practice shall be accepted in other Member countries for purposes of assessment and other uses relating to the protection of man and the environment.

2. DECIDES that for the purposes of this decision and other Council actions the terms OECD Test Guidelines and OECD Principles of Good Laboratory Practice shall mean guidelines and principles adopted by the Council.

3. INSTRUCTS the Environment Committee to review action taken by Member countries in pursuance of this Decision and to report periodically thereon to the Council.

4. INSTRUCTS the Environment Committee to pursue a programme of work designed to facilitate implementation of this Decision with a view to establishing further agreement on assessment and control of chemicals within Member countries.

PART II

To implement the Decision set forth in Part 1:

1. RECOMMENDS that Member countries, in the testing of chemicals, apply the OECD Test Guidelines and the OECD Principles of Good Laboratory Practice, set forth respectively in Annexes I and II* which are integral parts of this text.
2. INSTRUCTS the Management Committee of the Special Programme on the Control of Chemicals in conjunction with the Chemicals Group of the Environment Committee to establish an updating mechanism to ensure that the aforementioned test guidelines are modified from time to time as required through the revision of existing Guidelines or the development of new Guidelines.
3. INSTRUCTS the Management Committee of the Special Programme on the Control of Chemicals to pursue its programme of work in such a manner as to facilitate internationally-harmonized approaches to assuring compliance with the OECD Principles of Good Laboratory Practice and to report periodically thereon to the Council.

COUNCIL DECISION-RECOMMENDATION
on Compliance with Principles of Good Laboratory Practice
[C(89)87(Final)]

(Adopted by the Council as its 717th Meeting on 2nd October 1989)

The Council,
Having regard to Articles 5 a) and 5 b) of the Convention on the Organisation for Economic Co-operation and Development of 14th December 1960;

Having regard to the Recommendation of the Council of 7th July 1977 Establishing Guidelines in Respect of Procedure and Requirements for Anticipating the Effects of Chemicals on Man and in the Environment [C(77)97 (Final)];

Having regard to the Decision of the Council of 12th May 1981 concerning the Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30(Final)] and, in particular, the Recommendation that Member countries, in the testing of chemicals, apply the OECD Principles of Good Laboratory Practice, set forth in Annex 2 of that Decision;

Having regard to the Recommendation of the Council of 26th July 1983 concerning the Mutual Recognition of Compliance with Good Laboratory Practice [C(83)95 (Final)];

*Annex I to the Council Decision (the OECD Test Guidelines) was published separately. Annex II (the OECD Principles of Good Laboratory Practice) will be found on pages 71–85 (Part One).

Having regard to the conclusions of the Third High Level Meeting of the Chemicals Group (OECD, Paris, 1988);

Considering the need to ensure that test data on chemicals provided to regulatory authorities for purposes of assessment and other uses related to the protection of human health and the environment are of high quality, valid and reliable;

Considering the need to minimise duplicative testing of chemicals, and thereby to utilise more effectively scarce test facilities and specialist manpower, and to reduce the number of animals used in testing;

Considering that recognition of procedures for monitoring compliance with good laboratory practice will facilitate mutual acceptance of data and thereby reduce duplicative testing of chemicals;

Considering that a basis for recognition of compliance monitoring procedures is an understanding of, and confidence in, the procedures in the Member country where the data are generated;

Considering that harmonized approaches to procedures for monitoring compliance with good laboratory practice would greatly facilitate the development of the necessary confidence in other countries' procedures;

On the proposal of the Joint Meeting of the Management Committee of the Special Programme on the Control of Chemicals and the Chemicals Group, endorsed by the Environment Committee;

PART I

GLP Principles and Compliance Monitoring

1. DECIDES that Member countries in which testing of chemicals for purposes of assessment related to the protection of health and the environment is being carried out pursuant to principles of good laboratory practice that are consistent with the OECD Principles of Good Laboratory Practice as set out in Annex 2 of the Council Decision C(81)30(Final) (hereinafter called "GLP Principles) shall:

   i. establish national procedures for monitoring compliance with GLP Principles, based on laboratory inspections and study audits;

   ii. designate an authority or authorities to discharge the functions required by the procedures for monitoring compliance; and

   iii. require that the management of test facilities issue a declaration, where applicable, that a study was carried out in accordance with GLP Principles and pursuant to any other provisions established by national legislation or administrative procedures dealing with good laboratory practice.

2. RECOMMENDS that, in developing and implementing national procedures for monitoring compliance with GLP Principles, Member countries apply the "Guidelines for Compliance Monitoring Procedures for Good Laboratory

Practice and the "Guidance for the Conduct of Laboratory Inspections and Study Audits, set out respectively in Annexes I and II which are integral part of this Decision-Recommendation.*

PART II

Recognition of GLP Compliance among Member countries

1. DECIDES that Member countries shall recognise the assurance by another Member country that test data have been generated in accordance with GLP Principles if such other Member country complies with Part I above and Part II paragraph 2 below.

2. DECIDES that, for purposes of the recognition of the assurance in paragraph 1 above, Member countries shall:

   i. designate an authority or authorities for international liaison and for discharging other functions relevant to the recognition as set out in this Part and in the Annexes to this Decision-Recommendation;

   ii. exchange with other Member countries relevant information concerning their procedures for monitoring compliance, in accordance with the guidance set out in Annex III which is an integral part of this Decision-Recommendation;** and

   iii. implement procedures whereby, where good reason exists, information concerning GLP compliance of a test facility (including information focussing on a particular study) within their jurisdiction can be sought by another Member country.

3. DECIDES that the Council Recommendation concerning the Mutual Recognition of Compliance with Good Laboratory Practice [C(83)95 (Final)] shall be repealed.

PART III

Future OECD Activities

1. INSTRUCTS the Environment Committee and the Management Committee of the Special Programme on the Control of Chemicals to ensure that the "Guidelines for Compliance Monitoring Procedures for Good Laboratory Practice" and the "Guidance for the Conduct of Laboratory Inspections and

* Annexes I and II of the Council Act will be found in Numbers 2 and 3, respectively, of this OECD series on Principles of GLP and Compliance Monitoring.

** Annex III of the Council Act will be found in Number 2 of this OECD series on Principles of GLP and Compliance Monitoring.

Study Audits set out in Annexes I and II are updated and expanded, as necessary, in light of developments and experience of Member countries and relevant work in other international organisations.

2. INSTRUCTS the Environment Committee and the Management Committee of the Special Programme on the Control of Chemicals to pursue a programme of work designed to facilitate the implementation of this Decision-Recommendation, and to ensure continuing exchange of information and experience on technical and administrative matters related to the application of GLP Principles and the implementation of procedures for monitoring compliance with good laboratory practice.

3. INSTRUCTS the Environment Committee and the Management Committee of the Special Programme on the Control of Chemicals to review actions taken by Member countries in pursuance of this Decision-Recommendation.

Appendix G

FDA Good Laboratory Practices for Nonclinical Lab Studies

AUTHORITY : 21 U.S.C. 342, 346, 346a, 348, 351, 352, 353, 355, 360, 360b–360f, 360h–360j, 371, 379e, 381; 42 U.S.C. 216, 262, 263b–263n.

SOURCE: 43 FR 60013, Dec. 22, 1978, unless otherwise noted.

Subpart A–General Provisions

§ 58.1 Scope.

(a) This part prescribes good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, animal food additives, human and animal drugs, medical devices for human use, biological products, and electronic products. Compliance with this part is intended to assure the quality and integrity of the safety data filed pursuant to sections 406, 408, 409, 502, 503, 505, 506, 510, 512–516, 518–520, 721, and 801 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354–360F of the Public Health Service Act.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33779, Sept. 4, 1987; 64 FR 399, Jan. 5, 1999]

§ 58.3 Definitions.

As used in this part, the following terms shall have the meanings specified:

(a) Act means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201–902, 52 Stat. 1040 *et seq.,* as amended (21 U.S.C. 321–392)).

(b) *Test article* means any food additive, color additive, drug, biological product, electronic product, medical device for human use, or any other article subject to regulation under the act or under sections 351 and 354–360F of the Public Health Service Act.

(c) *Control article* means any food additive, color additive, drug, biological product, electronic product, medical device for human use, or any article other than a test article, feed, or water that is administered to the test system in the course of a nonclinical laboratory study for the purpose of establishing a basis for comparison with the test article.

(d) *Nonclinical laboratory study* means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article.

(e) *Application for research or marketing permit* includes:

(1) A color additive petition, described in part 71.

(2) A food additive petition, described in parts 171 and 571.

(3) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for use, which use results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in §§170.35 and 570.35.

(4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in §180.1.

(5) An *investigational new drug application,* described in part 312 of this chapter.

(6) A *new drug application,* described in part 314.

(7) Data and information regarding an over-the-counter drug for human use, submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(8) Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in parts 109 and 509.

(9) Data and information regarding an antibiotic drug submitted as part of the procedures for issuing, amending,

or repealing regulations for such drugs, described in § 314.300 of this chapter.

(10) *A Notice of Claimed Investigational Exemption for a New Animal Drug,* described in part 511.

(11) A *new animal drug application,* described in part 514.

(12) [Reserved]

(13) An *application for a biologics license*, described in part 601 of this chapter.

(14) An *application for an investigational device exemption,* described in part 812.

(15) An *Application for Premarket Approval of a Medical Device,* described in section 515 of the act.

(16) A Product Development Protocol for a Medical Device, described in section 515 of the act.

(17) Data and information regarding a medical device submitted as part of the procedures for classifying such devices, described in part 860.

(18) Data and information regarding a medical device submitted as part of the procedures for establishing, amending, or repealing a performance standard for such devices, described in part 861.

(19) Data and information regarding an electronic product submitted as part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation safety performance standard, described in subpart D of part 1003.

(20) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such product, described in section 358 of the Public Health Service Act.

(21) Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard as described in §1010.4.

(22) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from any electronic product performance standard, as described in §1010.5.

(f) *Sponsor* means:

(1) A person who initiates and supports, by provision of financial or other resources, a nonclinical laboratory study;

(2) A person who submits a nonclinical study to the Food and Drug Administration in support of an application for a research or marketing permit; or

(3) A testing facility, if it both initiates and actually conducts the study.

(g) *Testing facility* means a person who actually conducts a nonclinical laboratory study, i.e., actually uses the test article in a test system. *Testing facility* includes any establishment required to register under section 510 of the act that conducts nonclinical laboratory studies and any consulting laboratory described in section 704 of the act that conducts such studies. *Testing facility* encompasses only those operational units that are being or have been used to conduct nonclinical laboratory studies.

(h) *Person* includes an individual, partnership, corporation, association, scientific or academic establishment, government agency, or organizational unit thereof, and any other legal entity.

(i) *Test system* means any animal, plant, microorganism, or subparts thereof to which the test or control article is administered or added for study. *Test system* also includes appropriate groups or components of the system not treated with the test or control articles.

(j) *Specimen* means any material derived from a test system for examination or analysis.

(k) *Raw data* means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature), the exact copy or exact transcript may be substituted for the original source as raw data. *Raw data* may include photographs,

microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments.

(l) *Quality assurance unit* means any person or organizational element, except the study director, designated by testing facility management to perform the duties relating to quality assurance of nonclinical laboratory studies.

(m) *Study director* means the individual responsible for the overall conduct of a nonclinical laboratory study.

(n) *Batch* means a specific quantity or lot of a test or control article that has been characterized according to §58.105(a).

(o) *Study initiation date* means the date the protocol is signed by the study director.

(p) *Study completion date* means the date the final report is signed by the study director.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33779, Sept. 4, 1987; 54 FR 9039, Mar. 3, 1989; 64 FR 56448, Oct. 20, 1999]

§58.10 Applicability to studies performed under grants and contracts.

When a sponsor conducting a nonclinical laboratory study intended to be submitted to or reviewed by the Food and Drug Administration utilizes the services of a consulting laboratory, contractor, or grantee to perform an analysis or other service, it shall notify the consulting laboratory, contractor, or grantee that the service is part of a nonclinical laboratory study that must be conducted in compliance with the provisions of this part.

§58.15 Inspection of a testing facility.

(a) A testing facility shall permit an authorized employee of the Food and Drug Administration, at reasonable times and in a reasonable manner, to inspect the facility and to inspect (and in the case of records also to copy) all records and specimens required to be maintained regarding studies within the scope of this part. The records inspection and copying requirements shall not apply to quality assurance unit records of findings and problems, or to actions recommended and taken.

(b) The Food and Drug Administration will not consider a nonclinical laboratory study in support of an application for a research or marketing permit if the testing facility refuses to permit inspection. The determination that a nonclinical laboratory study will not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any applicable statute or regulation to submit the results of the study to the Food and Drug Administration.

Subpart B–Organization and Personnel

§58.29 Personnel.

(a) Each individual engaged in the conduct of or responsible for the supervision of a nonclinical laboratory study shall have education, training, and experience, or combination thereof, to enable that individual to perform the assigned functions.

(b) Each testing facility shall maintain a current summary of training and experience and job description for each individual engaged in or supervising the conduct of a nonclinical laboratory study.

(c) There shall be a sufficient number of personnel for the timely and proper conduct of the study according to the protocol.

(d) Personnel shall take necessary personal sanitation and health precautions designed to avoid contamination of test and control articles and test systems.

(e) Personnel engaged in a nonclinical laboratory study shall wear clothing appropriate for the duties they perform. Such clothing shall be changed as often as necessary to prevent microbiological, radiological, or chemical contamination of test systems and test and control articles.

(f) Any individual found at any time to have an illness that may adversely affect the quality and integrity of the nonclinical laboratory study shall be excluded from direct contact with test systems, test and control articles and any other operation or function that may adversely affect the study until

the condition is corrected. All personnel shall be instructed to report to their immediate supervisors any health or medical conditions that may reasonably be considered to have an adverse effect on a nonclinical laboratory study.

§58.31 Testing facility management.

For each nonclinical laboratory study, testing facility management shall:

(a) Designate a study director as described in §58.33, before the study is initiated.

(b) Replace the study director promptly if it becomes necessary to do so during the conduct of a study.

(c) Assure that there is a quality assurance unit as described in §58.35.

(d) Assure that test and control articles or mixtures have been appropriately tested for identity, strength, purity, stability, and uniformity, as applicable.

(e) Assure that personnel, resources, facilities, equipment, materials, and methodologies are available as scheduled.

(f) Assure that personnel clearly understand the functions they are to perform.

(g) Assure that any deviations from these regulations reported by the quality assurance unit are communicated to the study director and corrective actions are taken and documented.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]

§58.33 Study director.

For each nonclinical laboratory study, a scientist or other professional of appropriate education, training, and experience, or combination thereof, shall be identified as the study director. The study director has overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting of results, and represents the single point of study control. The study director shall assure that:

(a) The protocol, including any change, is approved as provided by §58.120 and is followed.

(b) All experimental data, including observations of unanticipated responses of the test system are accurately recorded and verified.

(c) Unforeseen circumstances that may affect the quality and integrity of the nonclinical laboratory study are noted when they occur, and corrective action is taken and documented.

(d) Test systems are as specified in the protocol.

(e) All applicable good laboratory practice regulations are followed.

(f) All raw data, documentation, protocols, specimens, and final reports are transferred to the archives during or at the close of the study.

[43 FR 60013, Dec. 22, 1978; 44 FR 17657, Mar. 23, 1979]

§58.35 Quality assurance unit.

(a) A testing facility shall have a quality assurance unit which shall be responsible for monitoring each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the regulations in this part. For any given study, the quality assurance unit shall be entirely separate from and independent of the personnel engaged in the direction and conduct of that study.

(b) The quality assurance unit shall:

(1) Maintain a copy of a master schedule sheet of all nonclinical laboratory studies conducted at the testing facility indexed by test article and containing the test system, nature of study, date study was initiated, current status of each study, identity of the sponsor, and name of the study director.

(2) Maintain copies of all protocols pertaining to all nonclinical laboratory studies for which the unit is responsible.

(3) Inspect each nonclinical laboratory study at intervals adequate to assure the integrity of the study and maintain written and properly signed records of each periodic inspection showing the date of the inspection, the study inspected, the phase or segment of the study inspected, the person performing the inspection, findings and problems, action recommended and taken to resolve existing problems, and any scheduled date for reinspection. Any problems found during the course

of an inspection which are likely to affect study integrity shall be brought to the attention of the study director and management immediately.

(4) Periodically submit to management and the study director written status reports on each study, noting any problems and the corrective actions taken.

(5) Determine that no deviations from approved protocols or standard operating procedures were made without proper authorization and documentation.

(6) Review the final study report to assure that such report accurately describes the methods and standard operating procedures, and that the reported results accurately reflect the raw data of the nonclinical laboratory study.

(7) Prepare and sign a statement to be included with the final study report which shall specify the dates inspections were made and findings reported to management and to the study director.

(c) The responsibilities and procedures applicable to the quality assurance unit, the records maintained by the quality assurance unit, and the method of indexing such records shall be in writing and shall be maintained. These items including inspection dates, the study inspected, the phase or segment of the study inspected, and the name of the individual performing the inspection shall be made available for inspection to authorized employees of the Food and Drug Administration.

(d) A designated representative of the Food and Drug Administration shall have access to the written procedures established for the inspection and may request testing facility management to certify that inspections are being implemented, performed, documented, and followed-up in accordance with this paragraph.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0203)

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]

Subpart C–Facilities

§ 58.41 General.

Each testing facility shall be of suitable size and construction to facilitate the proper conduct of nonclinical laboratory studies. It shall be designed so that there is a degree of separation that will prevent any function or activity from having an adverse effect on the study.

[52 FR 33780, Sept. 4, 1987]

§ 58.43 Animal care facilities.

(a) A testing facility shall have a sufficient number of animal rooms or areas, as needed, to assure proper: (1) Separation of species or test systems, (2) isolation of individual projects, (3) quarantine of animals, and (4) routine or specialized housing of animals.

(b) A testing facility shall have a number of animal rooms or areas separate from those described in paragraph (a) of this section to ensure isolation of studies being done with test systems or test and control articles known to be biohazardous, including volatile substances, aerosols, radioactive materials, and infectious agents.

(c) Separate areas shall be provided, as appropriate, for the diagnosis, treatment, and control of laboratory animal diseases. These areas shall provide effective isolation for the housing of animals either known or suspected of being diseased, or of being carriers of disease, from other animals.

(d) When animals are housed, facilities shall exist for the collection and disposal of all animal waste and refuse or for safe sanitary storage of waste before removal from the testing facility. Disposal facilities shall be so provided and operated as to minimize vermin infestation, odors, disease hazards, and environmental contamination.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]

§ 58.45 Animal supply facilities.

There shall be storage areas, as needed, for feed, bedding, supplies, and equipment. Storage areas for feed and bedding shall be separated from areas

housing the test systems and shall be protected against infestation or contamination. Perishable supplies shall be preserved by appropriate means.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]

§58.47 Facilities for handling test and control articles.

(a) As necessary to prevent contamination or mixups, there shall be separate areas for:

(1) Receipt and storage of the test and control articles.

(2) Mixing of the test and control articles with a carrier, e.g., feed.

(3) Storage of the test and control article mixtures.

(b) Storage areas for the test and/or control article and test and control mixtures shall be separate from areas housing the test systems and shall be adequate to preserve the identity, strength, purity, and stability of the articles and mixtures.

§58.49 Laboratory operation areas.

Separate laboratory space shall be provided, as needed, for the performance of the routine and specialized procedures required by nonclinical laboratory studies.

[52 FR 33780, Sept. 4, 1987]

§58.51 Specimen and data storage facilities.

Space shall be provided for archives, limited to access by authorized personnel only, for the storage and retrieval of all raw data and specimens from completed studies.

Subpart D–Equipment

§58.61 Equipment design.

Equipment used in the generation, measurement, or assessment of data and equipment used for facility environmental control shall be of appropriate design and adequate capacity to function according to the protocol and shall be suitably located for operation, inspection, cleaning, and maintenance.

[52 FR 33780, Sept. 4, 1987]

§58.63 Maintenance and calibration of equipment.

(a) Equipment shall be adequately inspected, cleaned, and maintained. Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated and/or standardized.

(b) The written standard operating procedures required under §58.81(b)(11) shall set forth in sufficient detail the methods, materials, and schedules to be used in the routine inspection, cleaning, maintenance, testing, calibration, and/or standardization of equipment, and shall specify, when appropriate, remedial action to be taken in the event of failure or malfunction of equipment. The written standard operating procedures shall designate the person responsible for the performance of each operation.

(c) Written records shall be maintained of all inspection, maintenance, testing, calibrating and/or standardizing operations. These records, containing the date of the operation, shall describe whether the maintenance operations were routine and followed the written standard operating procedures. Written records shall be kept of nonroutine repairs performed on equipment as a result of failure and malfunction. Such records shall document the nature of the defect, how and when the defect was discovered, and any remedial action taken in response to the defect.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0203)

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]

Subpart E–Testing Facilities Operation

§58.81 Standard operating procedures.

(a) A testing facility shall have standard operating procedures in writing setting forth nonclinical laboratory study methods that management is satisfied are adequate to insure the quality and integrity of the data generated in the course of a study. All deviations in a study from standard operating procedures shall be authorized by

the study director and shall be documented in the raw data. Significant changes in established standard operating procedures shall be properly authorized in writing by management.

(b) Standard operating procedures shall be established for, but not limited to, the following:

(1) Animal room preparation.

(2) Animal care.

(3) Receipt, identification, storage, handling, mixing, and method of sampling of the test and control articles.

(4) Test system observations.

(5) Laboratory tests.

(6) Handling of animals found moribund or dead during study.

(7) Necropsy of animals or postmortem examination of animals.

(8) Collection and identification of specimens.

(9) Histopathology.

(10) Data handling, storage, and retrieval.

(11) Maintenance and calibration of equipment.

(12) Transfer, proper placement, and identification of animals.

(c) Each laboratory area shall have immediately available laboratory manuals and standard operating procedures relative to the laboratory procedures being performed. Published literature may be used as a supplement to standard operating procedures.

(d) A historical file of standard operating procedures, and all revisions thereof, including the dates of such revisions, shall be maintained.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]

§ 58.83 Reagents and solutions.

All reagents and solutions in the laboratory areas shall be labeled to indicate identity, titer or concentration, storage requirements, and expiration date. Deteriorated or outdated reagents and solutions shall not be used.

§ 58.90 Animal care.

(a) There shall be standard operating procedures for the housing, feeding, handling, and care of animals.

(b) All newly received animals from outside sources shall be isolated and their health status shall be evaluated in accordance with acceptable veterinary medical practice.

(c) At the initiation of a nonclinical laboratory study, animals shall be free of any disease or condition that might interfere with the purpose or conduct of the study. If, during the course of the study, the animals contract such a disease or condition, the diseased animals shall be isolated, if necessary. These animals may be treated for disease or signs of disease provided that such treatment does not interfere with the study. The diagnosis, authorizations of treatment, description of treatment, and each date of treatment shall be documented and shall be retained.

(d) Warm-blooded animals, excluding suckling rodents, used in laboratory procedures that require manipulations and observations over an extended period of time or in studies that require the animals to be removed from and returned to their home cages for any reason (e.g., cage cleaning, treatment, etc.), shall receive appropriate identification. All information needed to specifically identify each animal within an animal-housing unit shall appear on the outside of that unit.

(e) Animals of different species shall be housed in separate rooms when necessary. Animals of the same species, but used in different studies, should not ordinarily be housed in the same room when inadvertent exposure to control or test articles or animal mixup could affect the outcome of either study. If such mixed housing is necessary, adequate differentiation by space and identification shall be made.

(f) Animal cages, racks and accessory equipment shall be cleaned and sanitized at appropriate intervals.

(g) Feed and water used for the animals shall be analyzed periodically to ensure that contaminants known to be capable of interfering with the study and reasonably expected to be present in such feed or water are not present at levels above those specified in the protocol. Documentation of such analyses shall be maintained as raw data.

(h) Bedding used in animal cages or pens shall not interfere with the purpose or conduct of the study and shall be changed as often as necessary to keep the animals dry and clean.

(i) If any pest control materials are used, the use shall be documented.

Cleaning and pest control materials that interfere with the study shall not be used.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0203)

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987; 54 FR 15924, Apr. 20, 1989; 56 FR 32088, July 15, 1991]

Subpart F–Test and Control Articles

§58.105 Test and control article characterization.

(a) The identity, strength, purity, and composition or other characteristics which will appropriately define the test or control article shall be determined for each batch and shall be documented. Methods of synthesis, fabrication, or derivation of the test and control articles shall be documented by the sponsor or the testing facility. In those cases where marketed products are used as control articles, such products will be characterized by their labeling.

(b) The stability of each test or control article shall be determined by the testing facility or by the sponsor either: (1) Before study initiation, or (2) concomitantly according to written standard operating procedures, which provide for periodic analysis of each batch.

(c) Each storage container for a test or control article shall be labeled by name, chemical abstract number or code number, batch number, expiration date, if any, and, where appropriate, storage conditions necessary to maintain the identity, strength, purity, and composition of the test or control article. Storage containers shall be assigned to a particular test article for the duration of the study.

(d) For studies of more than 4 weeks' duration, reserve samples from each batch of test and control articles shall be retained for the period of time provided by §58.195.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0203)

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987]

§58.107 Test and control article handling.

Procedures shall be established for a system for the handling of the test and control articles to ensure that:

(a) There is proper storage.

(b) Distribution is made in a manner designed to preclude the possibility of contamination, deterioration, or damage.

(c) Proper identification is maintained throughout the distribution process.

(d) The receipt and distribution of each batch is documented. Such documentation shall include the date and quantity of each batch distributed or returned.

§58.113 Mixtures of articles with carriers.

(a) For each test or control article that is mixed with a carrier, tests by appropriate analytical methods shall be conducted:

(1) To determine the uniformity of the mixture and to determine, periodically, the concentration of the test or control article in the mixture.

(2) To determine the stability of the test and control articles in the mixture as required by the conditions of the study either:

(i) Before study initiation, or

(ii) Concomitantly according to written standard operating procedures which provide for periodic analysis of the test and control articles in the mixture.

(b) [Reserved]

(c) Where any of the components of the test or control article carrier mixture has an expiration date, that date shall be clearly shown on the container. If more than one component has

an expiration date, the earliest date shall be shown.

[43 FR 60013, Dec. 22, 1978, as amended at 45 FR 24865, Apr. 11, 1980; 52 FR 33781, Sept. 4, 1987]

Subpart G–Protocol for and Conduct of a Nonclinical Laboratory Study

§ 58.120

(a) Each study shall have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study. The protocol shall contain, as applicable, the following information:

(1) A descriptive title and statement of the purpose of the study.

(2) Identification of the test and control articles by name, chemical abstract number, or code number.

(3) The name of the sponsor and the name and address of the testing facility at which the study is being conducted.

(4) The number, body weight range, sex, source of supply, species, strain, substrain, and age of the test system.

(5) The procedure for identification of the test system.

(6) A description of the experimental design, including the methods for the control of bias.

(7) A description and/or identification of the diet used in the study as well as solvents, emulsifiers, and/or other materials used to solubilize or suspend the test or control articles before mixing with the carrier. The description shall include specifications for acceptable levels of contaminants that are reasonably expected to be present in the dietary materials and are known to be capable of interfering with the purpose or conduct of the study if present at levels greater than established by the specifications.

(8) Each dosage level, expressed in milligrams per kilogram of body weight or other appropriate units, of the test or control article to be administered and the method and frequency of administration.

(9) The type and frequency of tests, analyses, and measurements to be made.

(10) The records to be maintained.

(11) The date of approval of the protocol by the sponsor and the dated signature of the study director.

(12) A statement of the proposed statistical methods to be used.

(b) All changes in or revisions of an approved protocol and the reasons therefor shall be documented, signed by the study director, dated, and maintained with the protocol.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0203)

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987]

§ 58.130 Conduct of a nonclinical laboratory study.

(a) The nonclinical laboratory study shall be conducted in accordance with the protocol.

(b) The test systems shall be monitored in conformity with the protocol.

(c) Specimens shall be identified by test system, study, nature, and date of collection. This information shall be located on the specimen container or shall accompany the specimen in a manner that precludes error in the recording and storage of data.

(d) Records of gross findings for a specimen from postmortem observations should be available to a pathologist when examining that specimen histopathologically.

(e) All data generated during the conduct of a nonclinical laboratory study, except those that are generated by automated data collection systems, shall be recorded directly, promptly, and legibly in ink. All data entries shall be dated on the date of entry and signed or initialed by the person entering the data. Any change in entries shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of the change. In automated data collection systems, the individual responsible for direct data input shall be identified at the time of data input. Any change in automated data entries shall be made so as not to obscure the original entry, shall indicate the reason for

change, shall be dated, and the responsible individual shall be identified.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0203)

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987]

Subparts H–I [Reserved]

Subpart J–Records and Reports

§58.185 Reporting of nonclinical laboratory study results.

(a) A final report shall be prepared for each nonclinical laboratory study and shall include, but not necessarily be limited to, the following:

(1) Name and address of the facility performing the study and the dates on which the study was initiated and completed.

(2) Objectives and procedures stated in the approved protocol, including any changes in the original protocol.

(3) Statistical methods employed for analyzing the data.

(4) The test and control articles identified by name, chemical abstracts number or code number, strength, purity, and composition or other appropriate characteristics.

(5) Stability of the test and control articles under the conditions of administration.

(6) A description of the methods used.

(7) A description of the test system used. Where applicable, the final report shall include the number of animals used, sex, body weight range, source of supply, species, strain and substrain, age, and procedure used for identification.

(8) A description of the dosage, dosage regimen, route of administration, and duration.

(9) A description of all cirmcumstances that may have affected the quality or integrity of the data.

(10) The name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study.

(11) A description of the transformations, calculations, or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis.

(12) The signed and dated reports of each of the individual scientists or other professionals involved in the study.

(13) The locations where all specimens, raw data, and the final report are to be stored.

(14) The statement prepared and signed by the quality assurance unit as described in §58.35(b)(7).

(b) The final report shall be signed and dated by the study director.

(c) Corrections or additions to a final report shall be in the form of an amendment by the study director. The amendment shall clearly identify that part of the final report that is being added to or corrected and the reasons for the correction or addition, and shall be signed and dated by the person responsible.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987]

§58.190 Storage and retrieval of records and data.

(a) All raw data, documentation, protocols, final reports, and specimens (except those specimens obtained from mutagenicity tests and wet specimens of blood, urine, feces, and biological fluids) generated as a result of a nonclinical laboratory study shall be retained.

(b) There shall be archives for orderly storage and expedient retrieval of all raw data, documentation, protocols, specimens, and interim and final reports. Conditions of storage shall minimize deterioration of the documents or specimens in accordance with the requirements for the time period of their retention and the nature of the documents or specimens. A testing facility may contract with commercial archives to provide a repository for all material to be retained. Raw data and specimens may be retained elsewhere provided that the archives have specific reference to those other locations.

(c) An individual shall be identified as responsible for the archives.

(d) Only authorized personnel shall enter the archives.

(e) Material retained or referred to in the archives shall be indexed to permit expedient retrieval.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0203)

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987]

§ 58.195 Retention of records.

(a) Record retention requirements set forth in this section do not supersede the record retention requirements of any other regulations in this chapter.

(b) Except as provided in paragraph (c) of this section, documentation records, raw data and specimens pertaining to a nonclinical laboratory study and required to be made by this part shall be retained in the archive(s) for whichever of the following periods is shortest:

(1) A period of at least 2 years following the date on which an application for a research or marketing permit, in support of which the results of the nonclinical laboratory study were submitted, is approved by the Food and Drug Administration. This requirement does not apply to studies supporting investigational new drug applications (IND's) or applications for investigational device exemptions (IDE's), records of which shall be governed by the provisions of paragraph (b)(2) of this section.

(2) A period of at least 5 years following the date on which the results of the nonclinical laboratory study are submitted to the Food and Drug Administration in support of an application for a research or marketing permit.

(3) In other situations (e.g., where the nonclinical laboratory study does not result in the submission of the study in support of an application for a research or marketing permit), a period of at least 2 years following the date on which the study is completed, terminated, or discontinued.

(c) Wet specimens (except those specimens obtained from mutagenicity tests and wet specimens of blood, urine, feces, and biological fluids), samples of test or control articles, and specially prepared material, which are relatively fragile and differ markedly in stability and quality during storage, shall be retained only as long as the quality of the preparation affords evaluation. In no case shall retention be required for longer periods than those set forth in paragraphs (a) and (b) of this section.

(d) The master schedule sheet, copies of protocols, and records of quality assurance inspections, as required by §58.35(c) shall be maintained by the quality assurance unit as an easily accessible system of records for the period of time specified in paragraphs (a) and (b) of this section.

(e) Summaries of training and experience and job descriptions required to be maintained by § 58.29(b) may be retained along with all other testing facility employment records for the length of time specified in paragraphs (a) and (b) of this section.

(f) Records and reports of the maintenance and calibration and inspection of equipment, as required by § 58.63(b) and (c), shall be retained for the length of time specified in paragraph (b) of this section.

(g) Records required by this part may be retained either as original records or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records.

(h) If a facility conducting nonclinical testing goes out of business, all raw data, documentation, and other material specified in this section shall be transferred to the archives of the sponsor of the study. The Food and Drug Administration shall be notified in writing of such a transfer.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987; 54 FR 9039, Mar. 3, 1989]

Subpart K–Disqualification of Testing Facilities

§ 58.200 Purpose.

(a) The purposes of disqualification are:

(1) To permit the exclusion from consideration of completed studies that were conducted by a testing facility which has failed to comply with the requirements of the good laboratory practice regulations until it can be adequately demonstrated that such noncompliance did not occur during, or

did not affect the validity or acceptability of data generated by, a particular study; and

(2) To exclude from consideration all studies completed after the date of disqualification until the facility can satisfy the Commissioner that it will conduct studies in compliance with such regulations.

(b) The determination that a nonclinical laboratory study may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulation to submit the results of the study to the Food and Drug Administration.

§58.202 Grounds for disqualification.

The Commissioner may disqualify a testing facility upon finding all of the following:

(a) The testing facility failed to comply with one or more of the regulations set forth in this part (or any other regulations regarding such facilities in this chapter);

(b) The noncompliance adversely affected the validity of the nonclinical laboratory studies; and

(c) Other lesser regulatory actions (e.g., warnings or rejection of individual studies) have not been or will probably not be adequate to achieve compliance with the good laboratory practice regulations.

§58.204 Notice of and opportunity for hearing on proposed disqualification.

(a) Whenever the Commissioner has information indicating that grounds exist under §58.202 which in his opinion justify disqualification of a testing facility, he may issue to the testing facility a written notice proposing that the facility be disqualified.

(b) A hearing on the disqualification shall be conducted in accordance with the requirements for a regulatory hearing set forth in part 16 of this chapter.

§58.206 Final order on disqualification.

(a) If the Commissioner, after the regulatory hearing, or after the time for requesting a hearing expires without a request being made, upon an evaulation of the administrative record of the disqualification proceeding, makes the findings required in §58.202, he shall issue a final order disqualifying the facility. Such order shall include a statement of the basis for that determination. Upon issuing a final order, the Commissioner shall notify (with a copy of the order) the testing facility of the action.

(b) If the Commissioner, after a regulatory hearing or after the time for requesting a hearing expires without a request being made, upon an evaluation of the administrative record of the disqualification proceeding, does not make the findings required in §58.202, he shall issue a final order terminating the disqualification proceeding. Such order shall include a statement of the basis for that determination. Upon issuing a final order the Commissioner shall notify the testing facility and provide a copy of the order.

§58.210 Actions upon disqualification.

(a) Once a testing facility has been disqualified, each application for a research or marketing permit, whether approved or not, containing or relying upon any nonclinical laboratory study conducted by the disqualified testing facility may be examined to determine whether such study was or would be essential to a decision. If it is determined that a study was or would be essential, the Food and Drug Administration shall also determine whether the study is acceptable, notwithstanding the disqualification of the facility. Any study done by a testing facility before or after disqualification may be presumed to be unacceptable, and the person relying on the study may be required to establish that the study was not affected by the circumstances that led to the disqualification, e.g., by submitting validating information. If the study is then determined to be unacceptable, such data will be eliminated from consideration in support of the application; and such elimination may serve as new information justifying the termination or withdrawal of approval of the application.

(b) No nonclinical laboratory study begun by a testing facility after the date of the facility's disqualification shall be considered in support of any

application for a research or marketing permit, unless the facility has been reinstated under § 58.219. The determination that a study may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulation to submit the results of the study to the Food and Drug Administration.

[43 FR 60013, Dec. 22, 1978, as amended at 59 FR 13200, Mar. 21, 1994]

§ 58.213 Public disclosure of information regarding disqualification.

(a) Upon issuance of a final order disqualifying a testing facility under § 58.206(a), the Commissioner may notify all or any interested persons. Such notice may be given at the discretion of the Commissioner whenever he believes that such disclosure would further the public interest or would promote compliance with the good laboratory practice regulations set forth in this part. Such notice, if given, shall include a copy of the final order issued under § 58.206(a) and shall state that the disqualification constitutes a determination by the Food and Drug Administration that nonclinical laboratory studies performed by the facility will not be considered by the Food and Drug Administration in support of any application for a research or marketing permit. If such notice is sent to another Federal Government agency, the Food and Drug Administration will recommend that the agency also consider whether or not it should accept nonclinical laboratory studies performed by the testing facility. If such notice is sent to any other person, it shall state that it is given because of the relationship between the testing facility and the person being notified and that the Food and Drug Administration is not advising or recommending that any action be taken by the person notified.

(b) A determination that a testing facility has been disqualified and the administrative record regarding such determination are disclosable to the public under part 20 of this chapter.

§ 58.215 Alternative or additional actions to disqualification.

(a) Disqualification of a testing facility under this subpart is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the act. The Food and Drug Administration may, at any time, institute against a testing facility and/or against the sponsor of a nonclinical laboratory study that has been submitted to the Food and Drug Administration any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and prior to, simultaneously with, or subsequent to, disqualification. The Food and Drug Administration may also refer the matter to another Federal, State, or local government law enforcement or regulatory agency for such action as that agency deems appropriate.

(b) The Food and Drug Administration may refuse to consider any particular nonclinical laboratory study in support of an application for a research or marketing permit, if it finds that the study was not conducted in accordance with the good laboratory practice regulations set forth in this part, without disqualifying the testing facility that conducted the study or undertaking other regulatory action.

§ 58.217 Suspension or termination of a testing facility by a sponsor.

Termination of a testing facility by a sponsor is independent of, and neither in lieu of nor a precondition to, proceedings or actions authorized by this subpart. If a sponsor terminates or suspends a testing facility from further participation in a nonclinical laboratory study that is being conducted as part of any application for a research or marketing permit that has been submitted to any Center of the Food and Drug Administration (whether approved or not), it shall notify that Center in writing within 15 working days of the action; the notice shall include a statement of the reasons for such action. Suspension or termination of a testing facility by a sponsor does not relieve it of any obligation under any other applicable regulation to submit

the results of the study to the Food and Drug Administration.

[43 FR FR 60013, Dec. 22, 1978, as amended at 50 FR 8995, Mar. 6, 1985]

§ 58.219 Reinstatement of a disqualified testing facility.

A testing facility that has been disqualified may be reinstated as an acceptable source of nonclinical laboratory studies to be submitted to the Food and Drug Administration if the Commissioner determines, upon an evaluation of the submission of the testing facility, that the facility can adequately assure that it will conduct future nonclinical laboratory studies in compliance with the good laboratory practice regulations set forth in this part and, if any studies are currently being conducted, that the quality and integrity of such studies have not been seriously compromised. A disqualified testing facility that wishes to be so reinstated shall present in writing to the Commissioner reasons why it believes it should be reinstated and a detailed description of the corrective actions it has taken or intends to take to assure that the acts or omissions which led to its disqualification will not recur. The Commissioner may condition reinstatement upon the testing facility being found in compliance with the good laboratory practice regulations upon an inspection. If a testing facility is reinstated, the Commissioner shall so notify the testing facility and all organizations and persons who were notified, under § 58.213 of the disqualification of the testing facility. A determination that a testing facility has been reinstated is disclosable to the public under part 20 of this chapter.

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