VOLUME SIX

Second Edition

Handbook of Pharmaceutical Manufacturing Formulations

Sterile Products

SARFARAZ K. NIAZI

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Pharmaceutical Scientist, Inc.
Deerfield, Illinois, USA

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Handbook of Pharmaceutical Manufacturing Formulations Second Edition

Volume Series

Sarfaraz K. Niazi

Volume 1
Handbook of Pharmaceutical Manufacturing Formulations: Compressed Solid Products

Volume 2
Handbook of Pharmaceutical Manufacturing Formulations: Uncompressed Solid Products

Volume 3
Handbook of Pharmaceutical Manufacturing Formulations: Liquid Products

Volume 4
Handbook of Pharmaceutical Manufacturing Formulations: Semisolid Products

Volume 5
Handbook of Pharmaceutical Manufacturing Formulations: Over-the-Counter Products

Volume 6
Handbook of Pharmaceutical Manufacturing Formulations: Sterile Products

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To Professor Shamsuz Zoha

Preface to the Series—Second Edition

The science and the art of pharmaceutical formulation keeps evolving as new materials, methods, and machines become readily available to produce more reliable, stable, and release-controlled formulations. At the same time, globalization of sourcing of raw and finished pharmaceuticals brings challenges to regulatory authorities and results in more frequent revisions to the current good manufacturing practices, regulatory approval dossier requirements, and the growing need for cost optimization. Since the publication of the first edition of this book, a lot has changed in all of these areas of importance to pharmaceutical manufacturers. The second edition builds on the dynamic nature of the science and art of formulations and provides an evermore useful handbook that should be highly welcomed by the industry, the regulatory authorities, as well as the teaching institutions.

The first edition of this book was a great success as it brought under one umbrella the myriad of choices available to formulators. The readers were very responsive and communicated with me frequently pointing out to the weaknesses as well as the strengths of the book. The second edition totally revised attempts to achieve these by making major changes to the text, some of which include:

1. Complete, revised errors corrected and subject matter reorganized for easy reference. Whereas this series has six volumes differentiated on the basis of the type of dosage form and a separate inclusion of the U.S. OTC products, ideally the entire collection is needed to benefit from the myriad of topics relating to formulations, regulatory compliance, and dossier preparation.
2. Total number of pages is increased from 1684 to 2726.
3. Total number of formulations is expanded by about 30% with many newly approved formulations.
4. Novel formulations are now provided for a variety of drugs; these data are collected from the massive intellectual property data and suggest toward the future trend of formulations. While some of these formulations may not have been approved in the United States or Europe, these do provide additional choices, particularly for the NDA preparation. As always, it is the responsibility of the manufacturer to assure that the intellectual property rights are not violated.
5. A significant change in this edition is the inclusion of commercial products; while most of this information is culled out from the open source such as the FOIA (http://www.fda.gov/foi/default.htm), I have made attempts to reconstruct the critical portions of it based on what I call the generally acceptable standards. The drug companies are advised to assure that any intellectual property rights are not violated and this applies to all information contained in this book. The freedom of information act (FOIA) is an extremely useful conduit for reliable information and manufacturers are strongly urged to make use of this information. Whereas this information is provided free of charge, the process of obtaining the information may be cumbersome, in which case, commercial sources of these databases can prove useful, particularly for the non-U.S. companies.
6. Also included are the new Good Manufacturing Guidelines (2007) with amendments (2008) for the United States and similar updates for European Union and WHO; it is strongly urged that the companies discontinue using all old documents as there are significant changes in the revised form, many of them are likely to reduce the cost of GMP compliance.
7. Details on design of clean rooms is a new entry that will be of great use to sterile product manufacturers; whereas the design and flow of personnel and material flow is of critical nature, regulatory agencies view these differently and the manufacturer is advised always to comply with most stringent requirements.
8. Addition of a self-auditing template in each volume of the series. While the cGMP compliance is a complex issue and the requirements diversified across the globe, the basic compliance remains universal. I have chosen the European Union guidelines (as these are more in tune with the ICH) to prepare a self-audit module that I recommend that every manufacturer adopt as a routine to assure GMP compliance. In most instances reading the template by those responsible for compliance with keep them sensitive to the needs of GMP.
9. OTC products cross-referenced in other volumes where appropriate. This was necessary since the regulatory authorities worldwide define this class of drug differently. It is important to iterate that regardless of the prescription or the OTC status of a product, the requirements for compliance with the cGMP apply equally.
10. OTC monograph status is a new section added to the OTC volume and this should allow manufacturers to chose appropriate formulations that may not require a filing with the regulatory agencies; it is important to iterate that an approved OTC monograph includes details of formulation including the types and quantities of active drug and excipients, labeling, and presentation. To qualify the exemption, the manufacturer must comply with the monograph in its entirety. However, subtle modifications that are merely cosmetic in nature and where there is an evidence that the modification will not affect the safety and efficacy of the products can be made but require prior approval of the regulatory agencies and generally these approvals are granted.
11. Expanded discussion on critical factors in the manufacturing of formulations provided; from basic shortcuts to smart modifications now extend to all dosage forms. Pharmaceutical compounding is one of the oldest professions and whereas the art of formulations has been

relegated to more objective parameters, the art nevertheless remains. An experienced formulator, like an artist, would know what goes with what and why; he avoids the pitfalls and stays with conservative choices. These sections of the book present advice that is time tested, although it may appear random at times; this is intended for experienced formulators.

12. Expanded details on critical steps in the manufacturing processes provided but to keep the size of the book manageable, and these are included for prototype formulations. The reader is advised to browse through similar formulations to gain more insight. Where multiple formulations are provided for the same drug, it intended to show the variety of possibilities in formulating a drug and whereas it pertains to a single drug, the basic formulation practices can be extended to many drugs of same class or even of diversified classes. Readers have often requested that more details be provided in the Manufacturing Direction sections. Whereas sufficient details are provided, this is restricted to prototype formulations to keep the size of the book manageable and to reduce redundancy.
13. Addition of a listing of approved excipients and the level allowed by regulatory authorities. This new section allows formulators a clear choice on which excipients to choose; the excipients are reported in each volume pertaining to the formulation type covered. The listing is drawn from the FDA-approved entities. For the developers of an ANDA, it is critical that the level of excipients be kept within the range generally approved to avoid large expense in justifying any unapproved level. The only category for which the listing is not provided separately is the OTC volume since it contains many dosage forms and the reader is referred to dosage form–specific title of the series. The choice of excipients forms keeps increasing with many new choices that can provide many special release characteristics to the dosage forms. Choosing correct excipients is thus a tedious exercise and requires sophisticated multivariate statistical analysis. Whereas the formulator may choose any number of novel or classical components, it is important to know the levels of excipients that are generally allowed in various formulations to reduce the cost of redundant exercises; I have therefore included, as an appendix to each volume, a list of all excipients that are currently approved by the U.S. FDA along with their appropriate levels. I suggest that a formulator consult this table before deciding on which level of excipient to use; it does not mean that the excipient cannot be used outside this range but it obviates the need for a validation and lengthy justification studies in the submission of NDAs.
14. Expanded section on bioequivalence submission was required to highlight the recent changes in these requirements. New entries include a comprehensive listing of bioequivalence protocols in abbreviated form as approved by the U.S. FDA; these descriptions are provided in each volume where pertinent. To receive approval for an ANDA, an applicant must generally demonstrate, among other things, equivalence of the active ingredient, dosage form, strength, route of administration, and conditions of use as the listed drug, and that the proposed drug product is bioequivalent to the reference listed drug [21 USC 355(j)(2)(A); 21 CFR 314.94(a)]. Bioequivalent drug products show no significant difference in the rate and extent of absorption of the therapeutic ingredient [21 USC 355(j)(8); 21 CFR 320.1(e)]. BE studies are undertaken in support of ANDA submissions with the goal of demonstrating BE between a proposed generic drug product and its reference listed drug. The regulations governing BE are provided at 21 CFR in part 320. The U.S. FDA has recently begun to promulgate individual bioequivalence requirements. To streamline the process for making guidance available to the public on how to design product-specific BE studies, the U.S. FDA will be issuing product-specific BE recommendations (www.fda.gov/cder/ogd/index.htm). To make this vital information available, an appendix to each volume includes a summary of all currently approved products by the U.S. FDA where a recommendation on conducting bioequivalence studies is made available by the U.S. FDA. When filing an NDA or an ANDA, the filer is faced with the choice of defending the methods used to justify the bioavailability or bioequivalence data. The U.S. FDA now allows application for waiver of bioequivalence requirement; a new chapter on this topic has been added along with details of the dissolution tests, where applicable, approved for various dosage forms.
15. Dissolution testing requirements are included for all dosage forms where this testing is required by the FDA. Surrogate testing to prove efficacy and compliance is getting more acceptance at regulatory agencies; in my experience, a well-designed dissolution test is the best measure of continuous compliance. Coupled with chapters on waivers of bioequivalence testing, this information on dissolution testing should be great value to all manufacturers; it is recommended that manufacturers develop their own in-house specifications, more stringent than those allowed in these listings and the USP.
16. Best-selling products (top 200 prescription products) are identified with an asterisk and a brand name where applicable; in all instances, composition of these products is provided and formulation of generic equivalents. Despite the vast expansion of pharmaceutical sales and shifting of categories of blockbuster drugs, basic drugs affecting gastrointestinal tract, vascular system, and brain remain most widely prescribed.
17. Updated list of approved coloring agents in the United States, Canada, European Union, and Japan is included to allow manufactures to design products for worldwide distribution.
18. Tablet-coating formulations that meet worldwide requirements of color selection are included in the Volume 1 (compressed solids) and Volume 5 (OTC) because these represent the products often coated.
19. Guidelines on preparing regulatory filings are now dispersed throughout the series depending on where these guidelines are more crucial. However, the reader would, as before, need access to all volumes to benefit from the advice and guidelines provided.

As always, comments and criticism from the readers are welcomed and these can be sent to me at Niazi@pharmsci.com or Niazi@niazi.com. I would try to respond to any inquiries requiring clarification of the information enclosed in these volumes.

"I would like to express deep gratitude to Sherri R. Niziolek and Michelle Schmitt-DeBonis at Informa, the publisher of this work, for seeing an immediate value to the readers in publishing the second edition of this book and allowing me enough time to prepare this work. The diligent editing and composing staff at Informa, particularly Joseph Stubenrauch, Baljinder Kaur and others are highly appreciated. Regardless, all errors and omissions remain altogether mine."

In the first edition, I had dedicated each volume to one of my mentors; the second edition continues the dedication to these great teachers.

Sarfaraz K. Niazi, Ph.D.
Deerfield, Illinois, U.S.A.

Preface to the Series—First Edition

No industry in the world is more highly regulated than the pharmaceutical industry because of potential threat to a patient's life from the use of pharmaceutical products. The cost of taking a new chemical entity (amortized over the cost of all molecules racing) to final regulatory approval is a staggering $800 million, making the pharmaceutical industry one of the most research-intensive industries in the world. In the year 2004, it is anticipated that the industry will spend about $20 billion on research and development. The generic market of drugs as the new entities come off patent is one of the fastest growing segments of the pharmaceutical industry, with every major multinational company having a significant presence in this field.

Whereas many stages of new drug development are inherently constrained with time, the formulation of drugs into desirable dosage forms remains an area where expediency can be practiced with appropriate knowledge by those who have mastered the skills of pharmaceutical formulations. The *Handbook of Pharmaceutical Manufacturing Formulations* is the first major attempt to consolidate the available knowledge about formulations in a comprehensive, and by nature a rather voluminous, presentation.

The book is divided into six volumes, based strictly on the type of formulation science involved in the development of these dosage forms: sterile products, compressed solids, uncompressed solids, liquid products, semisolid products, and OTC products. The separation of OTC products even though they may easily fall into one of the other five categories is made to comply with the industry norms of separate research divisions for OTC products. Sterile products require skills related to sterilization of product, and of less importance is the bioavailability issue, which is an inherent problem of compressed dosage forms. These types of considerations have led to the classification of products into these six categories.

Each volume includes a description of regulatory filing techniques for the formulations described. Also included are the current regulatory guidelines on cGMP compliance specific to the dosage form. Advice is offered on how to scale up the production batches.

It is expected that formulation scientists will use this information to benchmark their internal development protocols and cut the race to file short by adopting formulae that have survived the test of time. Many of us who have worked in the pharmaceutical industry suffer from a close paradigm when it comes to selecting formulations—"not invented here" perhaps reigns in the mind of many seasoned formulations scientists subconsciously when they prefer to choose only a certain platform for development. It is expected that with the quick review of possibilities available to formulate made available in this book, scientists will benefit from the experience of others.

For the teachers of formulation sciences, this series offers a wealth of information. Whether it is a selection of a preservative system or the choice of a disintegrant, the series offers a wide choice to study and rationalize.

Many have assisted me in the development of this work that has taken years to compile, and I thank scores of my graduate students and colleagues for their help. A work of this size cannot be produced without errors, although I hope that these errors do not distract the reader from the utility of the book. I would sincerely appreciate if readers point out these mistakes for corrections in future editions.

Sarfaraz K. Niazi, Ph.D.
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Preface to the Volume—First Edition

The (HPMF/SP) is written for the pharmaceutical scientist and others involved in the regulatory filing and manufacturing of new sterile products. No other area of regulatory compliance receives more attention and scrutiny by regulatory authorities than the regulation of sterile products, for obvious reasons. With the increasing number of potent products, particularly the new line of small protein products, joining the long list of proven sterile products—mainly parenteral and ophthalmic products—the technology of manufacturing sterile products has evolved into a very sophisticated industry. The entry barrier to this technology is much higher compared with those for other dosage forms. Consequently, the cost of production remains high as well. In recent years, regulatory agencies around the world have taken very serious notice of the deficiencies in the manufacturing specifications of the active raw material intended for parenteral administration. New guidelines for the API and aseptic processing of sterile products are the main issues of concern today for manufacturers. This volume of *HPMF/SP* does not delve into details related to starting material issues. Of interest in this issue are formulations of sterile dosage forms, regulatory filing requirements of sterile preparations, and cGMP compliance, all of which are tied together in the final preparation of the chemistry, manufacturing, and control (CMC) sections of regulatory applications.

Chapter 1 describes the specifications of a manufacturing facility to manufacture compliant sterile products. Chapter 2 outlines the new drug application (NDA) or abbreviated new drug application (ANDA) filing requirements of sterile products. Chapter 3 describes in detail the layout of formulations provided in the book. This chapter must be thoroughly examined to make the best use of this book. Because the intent of the information provided in this book is to help the formulator develop a product for regulatory filing, boilerplate details are left out. Chapter 3 provides these details and also makes strong recommendations on how the formulator can benefit from the information available from suppliers of components and chemicals used in the formulation.

These three chapters are followed by the body of the book, which provides an alphabetical presentation of formulations of pharmaceutical products based on their generic names. There are three types of formulation entries. In the first type, both the bill of materials and manufacturing directions are provided. This type is further composed of two types, wherein greater detail is provided for some products. This differentiation is intentional because the common details are often omitted in subsequent presentations. The second type of formulations is provided with bill of materials only. This may include products for which the manufacturing directions are obvious to a prospective manufacturer, particularly in light of the details already provided for similar products elsewhere in the book, and also those products for which such information is not readily available. The third category of formulations includes experimental formulations, which may not yet have been commercialized or received regulatory approvals. These formulations are included to show to the formulation scientist unique opportunities that exist for the chemical entity in question.

Formulations of biotechnology-derived drugs are provided with some additional details and remain restricted to declaration of composition, yet they provide a good overview of the complexities involved in such formulations.

In consolidating the details of formulations, efforts have been made to present them in as unified a form as possible; nevertheless, some nonuniformities exist because of the large variety of presentations possible for the wide diversity of formulations presented in the book. A limited number of products intended for veterinary use are also included. These products are subject to cGMP compliance similar to that for human products.

The formulations provided here meet the *4S* requirements:

1. *Safety.* This is an important issue for parenteral products; the choice of excipients is limited by this consideration. In most of the formulations, the ingredients are fully approved by the regulatory authorities; in some formulations, the active drug moiety may have been banned in some countries, for example, dipyrone.
2. *Sterility.* The compositions presented are fully sterilizable either by terminal treatment or by aseptic processing; where preservatives are added, these are in sufficient quantity to fulfill the dedicated function.
3. *Stability*. Besides the rigor of treatment in rendering a product sterile, incompatibility issues may render a sterile product prone to instability. The formulations included here have been fully validated to provide sufficient shelf life, depending on the product.
4. *Scalability.* Whereas the batch formulation is presented for a 1-l batch, these formulations are linearly scalable. Manufacturing losses have been included and these formulations can be readily scaled up to any size; of course, the requirements of size change in the validation protocol should be considered.

One of the best utilities of the database included in this book is to benchmark the products intended for development. A large number of formulation possibilities exist for any drug; though with the 4S limitations, the choice of ingredients (excipients) narrows rather rapidly. Multivitamin formulations are one such example wherein extreme instability and cost considerations have resulted in a variety of formulations. A study of many possibilities tells us about the problems we can anticipate while formulating these products. In some instances, only composition details are provided, along with raw material manufacturing details, because they are often an integral part of the formulation, such as in the case of biotechnology-derived products. Whereas this information may be at best cursory, it is useful to provide a study of these product formulations.

The information contained in this book has been obtained mainly from sources open to the public. It has taken years

to accumulate this database and no warranties are provided that these formulation compositions will not infringe on any proprietary product or intellectual property. The formulators must consider this before using the information. Also, as with all scientific experimental data, it should be understood that replication is subject to many factors, including type of equipment used, grade of material employed, and other processing techniques implemented. The road to converting these formulations to validated parts of a CMC package for submission to regulatory authorities is a long one; nevertheless, working with these formulations will reduce the risk of prolonged experimentation, and for generic formulation development, it will expedite entrance to the market. Some scientists may find this information useful in improving their products for any of the 4S considerations. More information is available on the Web site of Pharmaceutical Scientist, Inc. (http://www.pharmsci.com), wherein scientists can find updated information on regulatory compliance and additional tools for writing the CMC portions of the ANDA and NDA filings. The readers are encouraged to consult this Web site.

Although I have tried to sift through the large databases in both the formative and proofreading stages of the handbook, it is possible that errors remain. I would appreciate it if readers point these out to me by e-mailing me at niazi@pharmsci.com.

I am grateful to CRC Press for taking this lead in publishing what is possibly the largest such work in the field of pharmaceutical sciences. It has been a distinct privilege to know Mr. Stephen Zollo, senior editor at CRC Press. Stephen has done more than what any editor can do to encourage an author into conceiving, planning, drafting, and finally, despite many reasons why it could not be done, completing the work on a timely basis. I am greatly indebted to him. The editorial assistance provided by CRC Press staff was indeed exemplary, particularly the help given by Erika Dery, Gail Renard, Sara Kreisman, and others at CRC Press. Although the editors and proofreaders have pored over this book diligently, any mistakes remaining are altogether mine.

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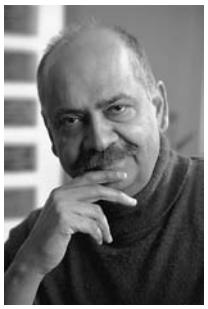

Sarfaraz K. Niazi has been teaching and conducting research in the pharmaceutical industry for over 35 years. He has authored hundreds of scientific papers, textbooks, and presentations on the topics of pharmaceutical formulation, biopharmaceutics, and pharmacokinetics of drugs. He is also an inventor with scores of patents in the field of drug and dosage form delivery systems; he is also licensed to practice law before the U.S. Patent and Trademark Office. Having formulated hundreds of products from the most popular consumer entries to complex biotechnology-derived products, he has accumulated a wealth of knowledge in the science and art of formulating and regulatory filings of Investigational New Drugs (INDs) and New Drug Applications (NDAs). Dr. Niazi advises the pharmaceutical industry internationally on issues related to formulations, cGMP compliance, pharmacokinetics and bioequivalence evaluation, and intellectual property issues (http://www.pharmsci.com). He can be contacted at Niazi@pharmsci.com.

Contents

Preface to the Series—Second Edition v
Preface to the Series—First Edition viii
Preface to the Volume—First Edition ix
About the Author xi

PART I REGULATORY AND MANUFACTURING

1. Sterile Manufacturing Formulations Template 2
I. Autoclaves 4
II. Aseptic Contract Manufacturers 4
A. Manufacturing Formulations Template 4
III. Clean-Room Design and Construction 4
IV. Clean-in-Place/Steam-in-Place (CIPISIP) 5
V. Closure Washing and Sterilization 5
VI. Consultants 5
VII. Disinfectants and Preservatives 5
VIII. Distillation equipment 5
IX. Engineering and Construction 5
X. Filling Machines 5
XI. Filter AIDS 6
XII. Flowmeters (Sanitary) 6
XIII. Freeze-Dryers (Sterilizable) 6
XIV. Microfiltration Equipment and Filters 6
A. Manufacturing Formulations Template 6
XV. Pumps (Sanitary) 6
XVI. Sterile Tanks and Related Stainless Equipment 6
XVII. Sterility Test Equipment 7
XVIII. Sterilizing and Drying Tunnels (Hot Air) 7
XIX. Stoppering Machines 7
XX. Vial and Bottle Washers 7

2. GMP Audit Template, EU Guidelines 8

Glossary 27

3. Inspection of Sterile Product Manufacturing Facilities 30
I. Introduction 30
II. cGMP Compliance Basics 30
A. Personnel 30
B. Buildings 30
C. Air 30
D. Environmental Controls 30
E. Equipment 30
F. Water for Injection 31
G. Containers and Closures 31
H. Sterilization 31
1. Methods 31
2. Indicators 31
3. Filled Containers 31
I. Personnel Practices 32
J. Laboratory Controls 32
1. Retesting for Sterility 32
2. Retesting for Pyrogens 32
3. Particulate Matter Testing 32
4. Production Records 32
III. Aseptic Processing 32
A. Introduction 32
B. Buildings and Facilities 32
1. Critical Area (Class 100) 33
2. Supporting Clean Areas 34
3. Clean Area Separation 34
4. Air Filtration 34
5. Design 35
C. Personnel Training, Qualification, and Monitoring 35
1. Manufacturing Personnel 36
2. Laboratory Personnel 36
3. Monitoring Program 37
D. Components and Containers/Closures 37
1. Components 37
2. Containers/Closures 37
E. Endotoxin Control 38
F. Time Limitations 38
G. Process Validation and Equipment Qualification 39
1. Process Simulations 39
2. Filtration Efficacy 41
3. Sterilization of Equipment and Containers/Closures 42
H. Laboratory Controls 43
1. Environmental Monitoring 43
2. Microbiological Media and Identification 44
I. Sterility Testing 44
1. Choice of Methods 45
2. Media 45
3. Personnel 45
4. Sampling and Incubation 45
5. Investigation of Sterility Positives 45
J. Batch Record Review: Process Control Documentation 46
IV. Processing Prior to Filling and Sealing Operations 47
A. Aseptic Processing from Early Manufacturing Steps 47

B. Aseptic Processing of Cell-Based Therapy Products (or of Products Intended for Use as Cell-Based Therapies) *47*
V. Aseptic Processing Isolators *47*
A. Maintenance *47*
1. General *47*
2. Glove Integrity *47*
B. Design *47*
1. Airflow *47*
2. Materials of Construction *48*
3. Pressure Differential *48*
4. Clean-Area Classifications *48*
C. Transfer of Materials and Supplies *48*
1. Introduction *48*
2. Discharge *48*
D. Decontamination *48*
1. Surface Exposure *48*
2. Efficacy *48*
3. Frequency *48*
E. Filling Line Sterilization *48*
F. Environmental Monitoring *49*
G. Personnel *49*
VI. Blow-fill-seal Technology *49*
A. Equipment Design and Air Quality *49*
B. Validation and Qualification *49*
C. Batch Monitoring and Control *49*
VII. Lyophilization of Parenterals *50*
A. Introduction *50*
B. Product Type and Formulation *50*
C. Filling *50*
D. Lyophilization Cycle and Controls *51*
E. Cycle Validation *52*
F. Lyophilizer Sterilization and Design *52*
G. Finished Product Testing *53*
1. Dose Uniformity *54*
2. Stability Testing *54*
3. Sterility Testing *54*
H. Finished Product Inspection—Meltback *54*
VIII. High-Purity Water Systems *54*
A. System Design *54*
B. System Validation *55*
C. Microbial Limits *55*
1. WFI Systems *55*
2. Purified Water Systems *56*
D. WFI Systems *56*
E. Still *56*
F. Heat Exchangers *56*
G. Holding Tank *56*
H. Pumps *57*
I. Piping *57*
J. Reverse Osmosis *57*
K. Purified Water Systems *57*
L. Process Water *58*
M. Evaluation Strategy *58*
Relevant Guidance Documents (FDA) *58*
Glossary *58*
References *61*

4. New Drug Application for Sterilized Products *62*
I. Introduction *62*
II. Terminal Heat Sterilization *62*
A. Description of the Process and Product *62*
B. Thermal Qualification of the Cycle *62*
C. Microbiological Efficacy of the Cycle *62*
D. Microbiological Monitoring of the Environment *63*
E. Container/Closure and Package Integrity *63*
F. Bacterial Endotoxins Test and Method *63*
G. Sterility Testing Methods and Release Criteria *63*
H. Evidence of Formal Written Procedures *63*
III. Other Terminal Sterilization Processes *63*
A. Ethylene Oxide *64*
B. Radiation *64*
IV. Aseptic Fill Manufacturing Processes *64*
A. Buildings and Facilities *64*
B. Overall Manufacturing Operation *64*
C. Containers and Closures *64*
D. Procedures and Specifications for Media Fills *65*
E. Actions Concerning Product When Media Fills Fail *65*
F. Microbiological Monitoring of the Environment *65*
G. Container/Closure and Package Integrity *65*
H. Sterility Testing Methods and Release Criteria *65*
I. Bacterial Endotoxins Test and Method *65*
J. Evidence of Formal Written Procedures *65*
V. Maintenance of Microbiological Control and Quality: Stability Considerations *66*
A. Container/Closure Integrity *66*
B. Preservative Effectiveness *66*
C. Pyrogen or Endotoxin Testing *66*

5. Validation of Cleaning Process *67*
I. Introduction *67*
II. Background *67*
III. General Requirements *67*
IV. Evaluation of Cleaning Validation *67*
A. Equipment Design *68*
B. Cleaning Process, Written Procedure, and Documentation *68*
C. Analytical Methods *68*
D. Sampling *68*
1. Direct Surface Sampling *69*
2. Rinse Samples *69*
3. Routine Production In-Process Control Monitoring *69*
V. Establishment of Limits *69*

VI. Other Issues *69*
A. Placebo Product *69*
B. Detergent *69*
C. Test Until Clean *69*

6. Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin *70*
I. Introduction *70*
II. Potential Sources of Virus Contamination *70*
A. Viruses That Could Occur in the Master Cell Bank *70*
B. Adventitious Viruses That Could Be Introduced during Production *71*
III. Cell Line Qualification: Testing for Viruses *71*
A. Suggested Virus Tests for MCB, Working Cell Bank, and Cells at the Limit of In Vitro Cell Age Used for Production *71*
1. Master Cell Bank *71*
2. Working Cell Bank *71*
3. Cells at the Limit of In Vitro Cell Age Used for Production *71*
B. Recommended Viral Detection and Identification Assays *71*
1. Tests for Retroviruses *72*
2. In Vitro Assays *72*
3. In Vivo Assays *72*
4. Antibody Production Tests *72*
C. Acceptability of Cell Lines *72*
IV. Testing for Viruses in Unprocessed Bulk *73*
V. Rationale and Action Plan for Viral Clearance Studies and Virus Tests on Purified Bulk *73*
VI. Evaluation and Characterization of Viral Clearance Procedures *75*
A. The Choice of Viruses for the Evaluation and Characterization of Viral Clearance *75*
1. "Relevant" Viruses and "Model" Viruses *75*
2. Other Considerations *75*
B. Design and Implications of Viral Clearance Evaluation and Characterization Studies *76*
1. Facility and Staff *76*
2. Scaled-Down Production System *76*
3. Analysis of StepWise Elimination of Virus *76*
4. Determining Physical Removal Vs. Inactivation *76*
5. Inactivation Assessment *76*
6. Function and Regeneration of Columns *76*
7. Specific Precautions *76*
C. Interpretation of Viral Clearance Studies *77*
1. Acceptability *77*
D. Limitations of Viral Clearance Studies *77*
E. Statistics *78*
F. Reevaluation of Viral Clearance *78*
VII. Summary *78*
Glossary *78*
Appendix 1: Products Derived from Characterized Cell Banks which were Subsequently Grown In Vivo *79*
Appendix 2: The Choice of Viruses for Viral Clearance Studies *79*
Appendix 3: Statistical Considerations for Assessing Virus Assays *80*
Probability of Detection of Viruses at Low Concentrations *80*
Appendix 4: Calculation of Reduction Factors in Studies to Determine Viral Clearance *80*
Appendix 5: Calculation of Estimated Particles per Dose *81*

7. Analysis of the Expression Construct in Cells Used for Production of rDNA-Derived Protein Products *82*
I. Introduction *82*
II. Rationale for Analysis of the Expression Construct *82*
III. Characterization of the Expression System *82*
A. Expression Construct and Cell Clone Used to Develop the Master Cell Bank *82*
B. Cell Bank System *83*
C. Limit for In Vitro Cell Age for Production *83*
IV. Conclusion *83*
Glossary *83*

8. Stability Testing of Biotechnological/Biological Products *84*
I. Preamble *84*
II. Scope of the Annex *84*
III. Terminology *84*
IV. Selection of Batches *84*
A. Drug Substance (Bulk Material) *84*
B. Intermediates *85*
C. Drug Product (Final Container Product) *85*
D. Sample Selection *85*
V. Stability-Indicating Profile *85*
A. Protocol *85*
B. Potency *85*
C. Purity and Molecular Characterization *86*
D. Other Product Characteristics *86*
VI. Storage Conditions *86*
A. Temperature *86*
B. Humidity *86*
C. Accelerated and Stress Conditions *86*
D. Light *87*
E. Container/Closure *87*
F. Stability After Reconstitution of Freeze-Dried Product *87*

VII. Testing Frequency *87*
VIII. Specifications *87*
IX. Labeling *87*
Glossary *87*

9. Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products *89*
I. Introduction *89*
A. Objective *89*
B. Rationale *89*
C. Scope *89*
II. Guidelines *89*
A. Source, History, and Generation of the Cell Substrate *89*
1. Introduction *89*
2. Origin, Source, and History of Cells *89*
3. Generation of the Cell Substrate *90*
B. Cell Banking *90*
1. Cell Banking System *90*
2. Cell Banking Procedures *91*
C. General Principles of Characterization and Testing of Cell Banks *91*
1. Tests of Identity *91*
2. Tests of Purity *92*
3. Cell Substrate Stability *92*
4. Tests for Karyology and Tumorigenicity *93*
Glossary *93*
Reference *94*
Appendix 1: Primary Cell Substrates *94*
Introduction *94*
Source Tissue and Other Raw Materials *94*
Preparation of Primary Cell Substrates *94*
Testing of Primary Cell Substrates *94*

10. Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process *95*
I. Introduction *95*
A. Objectives of the Guideline *95*
B. Background *95*
C. Scope *95*
D. General Principles *95*
II. Guidelines *96*
A. Considerations for the Comparability Exercise *96*
B. Quality Considerations *96*
1. Analytical Techniques *96*
2. Characterization *97*
3. Specifications *98*
4. Stability *98*
C. Manufacturing Process Considerations *98*
D. Demonstration of Comparability during Development *99*
E. Nonclinical and Clinical Considerations *99*
1. Factors to be Considered in Planning Nonclinical and Clinical Studies *99*
2. Type of Studies *100*
Glossary *100*
References *100*

11. Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products *101*
I. Introduction *101*
A. Objective *101*
B. Background *101*
C. Scope *101*
II. Principles for Consideration in Setting Specifications *101*
A. Characterization *101*
1. Physicochemical Properties *101*
2. Biological Activity *102*
3. Immunochemical Properties *102*
4. Purity, Impurities, and Contaminants *102*
5. Quantity *103*
B. Analytical Considerations *103*
1. Reference Standards and Reference Materials *103*
2. Validation of Analytical Procedures *103*
C. Process Controls *103*
1. Process-Related Considerations *103*
2. In-Process Acceptance Criteria and Action Limits *103*
3. Raw Materials and Excipient Specifications *104*
D. Pharmacopoeial Specifications *104*
E. Release Limits vs. Shelf life Limits *104*
F. Statistical Concepts *104*
III. Justification of the Specification *104*
IV. Specifications *104*
A. Drug Substance Specification *105*
1. Appearance and Description *105*
2. Identity *105*
3. Purity and Impurities *105*
4. Potency *105*
5. Quantity *105*
B. Drug Product Specification *105*
1. Appearance and Description *105*
2. Identity *105*
3. Purity and Impurities *105*
4. Potency *105*
5. Quantity *106*
6. General Tests *106*
7. Additional Testing for Unique Dosage Forms *106*
Glossary *106*
References *106*
Appendices *107*
6.1 Appendix for Physicochemical Characterization *107*

6.1.1. Structural Characterization and Confirmation *107*
6.1.2. Physicochemical Properties *107*
6.2 Appendix for Impurities *107*
6.2.1. Process-Related Impurities and Contaminants *108*
6.2.2. Product-Related Impurities Including Degradation Products *108*

12. Essential Clean-Room Design Elements *109*
I. Optimized Designs *111*
II. Turbulent Type Clean Rooms *114*
III. Vertical Flow Clean Rooms *114*
IV. Laminar Flow Clean Rooms *115*
V. Horizontal Laminar Flow Clean Rooms *115*
A. Design of Class 500K Rooms *116*
B. Design of Class 100K Rooms *117*
C. Design of Class 10,000 Clean Rooms *121*
VI. The USP <797> Guidelines *124*
A. Issues *124*
B. Definitions *124*
C. Recommendations *125*

13. Approved Excipients in Sterile Dosage Forms *129*

PART II MANUFACTURING FORMULATIONS

Sterile Products *172*
Abciximab Injection *172*
Acetazolamide Injection *172*
Acetylcholine Chloride Intraocular Solution *173*
Acyclovir Sodium Injection *173*
Adenosine 5′ Monophosphate Injection *173*
Adenosine Injection *173*
Adrenal Cortex Injection *174*
Adrenaline Tartarate Injection *174*
Alatrofloxacin Mesylate Injection *174*
Alatrofloxacin Mesylate Injection *174*
Alatrofloxacin Mesylate Injection *175*
Alatrofloxacin Mesylate Injection *175*
Albumin (Human) *175*
Albumin 5% Solution *175*
Albumin 20% Solution *176*
Albumin 25% Solution *176*
Albuterol Sulfate Inhalation Solution *176*
Aldesleukin for Injection *176*
Alemtuzumab Injection *177*
Alpha-Tocopherol (Vitamin E) Injection *177*
Alprostadil for Injection *177*
Alteplase Recombinant Injection *177*
Amikacin Sulfate Injection (50 mg/mL) *178*
Amikacin Sulfate Injection (250 mg/mL) *178*
Amikacin Sulfate Injection *179*
Amino Acid Parenteral Nutrition Solution *180*
Amino Acid Parenteral Nutrition Solution (8.5%) *181*
Amino Acid Parenteral Nutrition Solution: 10% *182*
Amino Acid Parenteral Injection *183*
Aminohippurate Sodium for Injection *183*
Aminophylline Injection *184*
Amiodarone Injection *184*
Amiodarone Injection *185*
Amoxicillin–Clavulanic Acid Injection *185*
Amoxicillin Powder for Injection *185*
Amphotericin B Cholesteryl Sulfate Complex for Injection *186*
Amphotericin B Injection *186*
Amphotericin B Lipid Complex Injection *187*
Amphotericin B Liposome for Injection *187*
Antazoline Sulfate and Xylometazoline Hydrochloride Ophthalmic Drops *187*
Antipyrine, Phenylephrine, and Pyrilamine Maleate Ophthalmic Drops *188*
Antipyrine, Phenylephrine, and Sodium Thiosulfate Ophthalmic Solution *189*
Antithymocyte Globulin (Rabbit) for Injection *190*
Aprotinin Injection *190*
Argatroban (Thrombin Inhibitor) Injection *190*
Arsenic Trioxide Injection *190*
Ascorbic Acid and B Complex Vitamins (Two Vials) *191*
Ascorbic Acid and B Complex Vitamins *192*
Ascorbic Acid and B Complex Vitamins Lyophilized in Covial *193*
Ascorbic Acid and B Complex Vitamins *194*
Ascorbic Acid and B Complex Vitamins Lyophilized with Diluent *194*
Ascorbic Acid and B Complex Vitamins *195*
Ascorbic Acid, B Complex Vitamin, with Beta-Carotene Injection *195*
Ascorbic Acid Injection *196*
Ascorbic Acid, USP, Injection With Disodium Edetate *196*
Ascorbic Acid, USP (250 mg/mL Injection) *196*
Asparaginase for Injection *197*
Atropine, Chlorpheniramine Maleate, and Phenylpropanolamine Injection *197*
Atropine Sulfate Injection *197*
Atropine Sulfate Injection *198*
Aztreonam for Injection *198*
Basiliximab for Injection *198*
B Complex Injection: Niacinamide, Pyridoxine, Riboflavin, and Thiamine Injection *199*
B Complex Injection *200*
Solution 1 *200*
Solution 2 *201*
B Complex Injection *202*
B Complex Injection *203*
Solution 1 *204*
Solution 2 *205*
B Complex Injection *205*
B Complex Vitamin Veterinary *206*
B Complex Vitamin Veterinary *206*
B Complex Vitamin Veterinary *207*
B Complex Vitamin Veterinary *207*
B Complex with Minerals Injection (Veterinary) *207*
B Complex Vitamins with Hormones *208*
B Complex Vitamins with Liver Extract Injection *208*
Benzodiazepine Injection *208*
Benztropine Mesylate Injection *209*

Beta-Carotene Injection *209*
Betamethasone Suspension Injection *209*
Bethanechol Chloride Injection *209*
Biotin Injection *210*
Biperiden Lactate Injection *210*
Bisantrene Emulsion Injection *210*
Bisantrene Emulsion Injection *210*
Borax Sodium Lubricating Ophthalmic Drops *211*
Botulinum Toxin: Type A Purified Neurotoxin Complex *211*
Botulinum Toxin (Type B Injectable Solution) *212*
Bretylium Tosylate in Dextrose Injection *212*
Buflomedil Injection *213*
Bupivacaine Hydrochloride Injection 1: 0.75% in Dextrose 8.25% Injection *213*
Bupivacaine Hydrochloride Injection *214*
Bupivacaine Hydrochloride Injection: Bupivacaine with Epinephrine Injection *214*
Buprenorphine Hydrochloride Injectable *215*
Caffeine Citrate Injection *215*
Calcitonin Injection *215*
Calcitonin Injection *215*
Calcitriol Injection *216*
Calcitriol Injection *217*
Calcium Glycerophosphate Injection with Lactate *217*
Calcium Glycerophosphate Injection: Calcium Glycerophosphate Injection (Human and Veterinary) *218*
Calcium Gluconate Injection *218*
Calcium Glycerophosphate Injection *218*
Camphor Injection *219*
Camptothecin Injection *219*
Carboplatin for Infusion *219*
Carboplatin Injection *219*
Carprofen Injection *220*
Cefamandole Nafate for Injection *220*
Cefazolin Injection *220*
Cefepime Hydrochloride for Injection *220*
Cefotaxime Injection *221*
Cefotetan Injection *221*
Cefoxitin Injection Premixed IV Solution *221*
Ceftazidime for Injection: L-Arginine Formulation *221*
Ceftazidime Injection Dry Powder *222*
Ceftazidime Injection Premix *222*
Ceftriaxone Injection: 500-mg Injection (IM and IV) *222*
Ceftriaxone Injection (250-mg Injection, IM and IV) *223*
Ceftriaxone Injection Premix *223*
Cefuroxime for Injection *223*
Cetrorelix Acetate for Injection *223*
Chloramphenicol and Phenylmercuric Nitrate Ophthalmic Drops *224*
Chloramphenicol for Injection *225*
Chloramphenicol Injection *226*
Chloramphenicol Sodium Succinate for Injection *226*
Chlordiazepoxide Hydrochloride Injection *227*
Chloroprocaine Hydrochloride Injection *227*
Chloroquine Phosphate Injection *227*
Chlorothiazide Sodium for Injection *228*
Chlorpheniramine Maleate Injection (25 mg/mL) *228*
Chlorpheniramine Maleate Injection (10 mg/mL) *228*
Chlorpromazine Hydrochloride Injection (10 mg/mL) *228*
Chlorpromazine Hydrochloride Injection (25 mg/mL) *229*
Choriogonadotropin-Alpha (Recombinant) for Injection *229*
Chorionic Gonadotropin for Injection (20,000 U/ 10 mL Covial) *229*
Chorionic Gonadotropin for Injection (10000 U// 10 mL) *230*
Chromium Chloride Additive Injection (5-mL Vial) *230*
Chromium Chloride Additive Injection (10-mL Vial) *230*
Chromium Chloride Additive Injection (30-mL Vial) *231*
Cidofovir Injection *231*
Cimetidine Injection *231*
Cimetidine Injection *232*
Ciprofloxacin Hydrochloride Ophthalmic Solution *232*
Ciprofloxacin Injection *232*
Cisplatin Diaminedichloride Injection *233*
Cisplatin with 2,2′-Dithio-*bis*-Ethane Sulfonate Injection *233*
Cladribine Injection Infusion *234*
Clarithromycin Injection *234*
Lactobionic Acid (12% w/v Solution) *234*
Clindamycin Injection in 5% Dextrose *235*
Clindamycin Phosphate Injection 150 mg/mL (4 mL in 5-mL Vial, 600 mg; 6-mL in 10-mL vial, 900 mg) *235*
Clonidine Hydrochloride Injection *236*
Coagulation Factor VIIa (Recombinant) for Injection *236*
Coagulation Factor IX (Recombinant) for Injection *236*
Colistin Sulfate, Neomycin Sulfate, Thonzonium Bromide, and Hydrocortisone Acetate Otic Suspension *237*
Conjugated Estrogens for Injection *237*
Copper Sulfate Additive Injection (5-mL Vial) *237*
Copper Sulfate Additive Injection (10-mL Vial) *237*
Copper Sulfate Additive Injection (30-mL Vial) *238*
Corticorelin Ovine Triflutate for Injection *238*
Cortisone Acetate Injectable Suspension *238*
Cosyntropin for Injection *238*
Cromolyn Sodium Ophthalmic Solution *239*
Crude Liver Extract Injection *239*
Cyanocobalamin and Thiamine Injection *239*
Cyanocobalamin, Choline, and Niacinamide Injection *239*
Cyanocobalamin Injection *240*
Cyanocobalamin Injection *240*
Cyanocobalamin Injection for Veterinary Use *241*
Cyanocobalamin Repository Injection (1000 mg/mL) *241*
Cyanocobalamin, Pyridoxine, and Thiamine Injection *242*

Cyanocobalamin, Pyridoxine, and Thiamine Injection *243*
Cyanocobalamin, Pyridoxine, and Thiamine Injection *243*
Cyanocobalamin, Pyridoxine, and Thiamine Injection *244*
Cyclosporine Ampoules for Infusion *244*
Cytarabine Liposome Injection for Intrathecal Use (50 mg/5 mL Vial) *245*
Cytomegalovirus Immune Globulin IV (Human) *245*
Dacarbazine Injection *246*
Daclizumab for Injection *246*
Dactinomycin for Injection *246*
Dalteparin Sodium Injection *247*
Danaparoid Sodium Injection *247*
Dantrolene Sodium for Injection *247*
Dapiprazole Hydrochloride Ophthalmic Solution (0.5%) *248*
Daunorubicin HCl Injection *248*
Daunorubicin Citrate Liposome Injection *248*
Desmopressin Acetate Injection (Intranasal) *249*
Dexamethasone Acetate Suspension Injection: Dexamethasone Acetate (8 mg/mL) *249*
Dexamethasone Acetate/Sodium Phosphate Suspension (8/2 mg/mL) *249*
Dexamethasone Sodium Phosphate Injection *250*
Dexamethasone Sodium Phosphate Injection *250*
Dexamethasone Injection, Veterinary *251*
Dexamethasone Sodium Phosphate Injection *251*
Dexpanthenol, Niacinamide, Pyridoxine, Riboflavin, and Thiamine Injection *252*
Dexrazoxane for Injection *253*
Dextrose 25% Injection (Flexible Container) *253*
Dextrose Injection (5% and 10% LVP) *253*
Dextrose with Sodium Chloride Injection LVP *254*
Diazepam Emulsion Injection *254*
Diazepam Emulsion Injection *255*
Diazepam Injection *255*
Diazepam Rectal Solution *256*
Dibenzazepine Carboxamide Injection *256*
Diclofenac Sodium Injection *257*
Diclofenac-Lecithin Injection *258*
Diclofenac with Acetylcysteine Injection *258*
Diclofenac Lyophilized Injection *258*
Diclofenac Lyophilized Injection *259*
Dicyclomine Hydrochloride Injection *259*
Digoxin Injection *259*
Dihydroergotamine Mesylate Drops *260*
Dihydroergotamine Mesylate Injection *261*
Dihydroergotamine Mesylate Nasal Spray *261*
Diisopropylphenol Injection *261*
Diltiazem Hydrochloride Injection *262*
Dimenhydrinate Injection *262*
Dimethyl Sulfoxide Injection *262*
Dinoprostone Cervical Gel *263*
Diphenhydramine Hydrochloride Injection *263*
Diphenylmethyl Piperazine Injection *263*
Dipyrone Injection *264*
Dipyrone, Papaverine HCl, and Atropine Sulfate Injection *264*
Disodium Edetate Injection (150 mg/mL) *265*
Disulfonic Acids Injection *265*
Dobutamine Injection *265*
Dopamine Hydrochloride Injection *266*
Doxapram Hydrochloride Injection, USP *266*
Doxercalciferol Injection *267*
Doxorubicin for Injection *267*
Doxycycline Hyclate Injection *268*
Doxycycline Hyclate Injection *268*
Doxycycline Hydrochloride Injection *268*
Ebselen Liposomal Injection *269*
Edetate Sodium, Polyvinyl Alcohol, Sodium Sulfacetamide, Sodium Thiosulfate Ophthalmic Drops with Thimerosal *269*
Edetate Sodium, Polyvinyl Alcohol, Sodium Sulfacetamide, Sodium Thiosulfate Ophthalmic Drops With Benzalkonium Chloride *271*
Edrophonium Injectable *272*
Electrolyte Maintenance Fluid (For Maintenance) *272*
Electrolyte Maintenance Fluid (For Rehydration) *273*
Electrolyte Maintenance Fluid (Maintenance, Pediatric) *273*
Electrolyte Maintenance Fluid *274*
5 Electrolyte Maintenance Fluid Rehydration (75 mEq) *274*
Electrolyte Maintenance Fluid Rehydration (90 mEq) *274*
Electrolytes, TPN Injection *275*
Emetine Hydrochloride Injection *275*
Enalaprilat Injection *275*
Ephedrine and Pyrilamine Maleate Injection Veterinary *275*
Ephedrine Sulfate Injection *276*
Epinephrine Auto Injector Injection *276*
Epinephrine Injection *277*
Epoetin-Alpha for Injection *277*
Epoprostenol Sodium for Injection *277*
Ergocalciferol Injection (Vitamin D) *278*
Ergonovine Maleate Injection *278*
Ergonovine Maleate Injection Veterinary *278*
Erythromycin Injection *279*
Esmolol Hydrochloride Injection Infusion Concentrate *280*
Estradiol Cypionate Injection *280*
Estradiol Suspension Injection *281*
Estradiol Valerate Injection *281*
Estrogenic Substances in Oil Injection *281*
Estrone, Estradiol, and Cyanocobalamin Injection *281*
Estrone Sterile Suspension Veterinary Injection *282*
Etanercept Injection *282*
Etorphine Hydrochloride Veterinary *282*
Exemestane Aqueous Suspension Injection *283*
Famotidine Injection *283*
Fenoldopam Mesylate Injection *284*
Fentanyl Citrate Injection *284*
Filgrastim Injection *284*
Flosulide Injection *285*
Fluconazole Injection *285*
Flumazenil Injection *285*
Folic Acid and Niacinamide Injection *286*
Follitropin-Beta for Injection *286*
Furosemide Injection *287*
Gentamicin and Prednisolone Ophthalmic Drops *288*
Gentamicin Injection (20 mg/2 mL) *289*
Gentamicin Injection (80 mg/2 mL) *290*

Gentamicin Ophthalmic Drops *291*
Glycine Antagonist Injection Infusion *292*
Glycopyrrolate Injection *292*
Granisetron Hydrochloride Injection Single Dose *293*
Granisetron Hydrochloride Injection Multiple Dose *293*
Guaiacol–Iodide Solution Veterinary *293*
Haloperidol Injection *293*
Hemin for Injection *293*
Heparin Injection *294*
Hexamethylmelamine Injection *295*
Hydrochloric Acid *295*
Hydrocortisone Sodium Phosphate Injection *295*
Hydrocortisone Sodium Succinate for Injection (Single-Unit System Lyophilized) *296*
Hydrocortisone Sodium Succinate for Injection (Nonlyophilized) *297*
Solution 1 *297*
Solution 2 *298*
Hydromorphone Hydrochloride Injection Single Dose *299*
Hydromorphone Hydrochloride Injection Multiple Dose *299*
Hydroxycobalamin Injection *299*
Hydroxyprogesterone Caproate Injection *300*
Hydroxypropylmethylcellulose Ophthalmic Solution *300*
Hyoscine Butylbromide Injection *301*
Ibuprofen Lysinate Injection *301*
Ibutilide Fumarate Injection *302*
Idarubicin Hydrochloride Injections *302*
Imiglucerase for Injection *302*
Immune Globulin (Human) for Injection *303*
Infliximab Recombinant for Injection *303*
Insulin Aspart Injection *303*
Insulin Glargine Injection *304*
Insulin Human 70/30 *304*
Insulin Human Isophane Suspension (NPH) *306*
Insulin Lispro Injection *307*
Insulin Regular *307*
Interferon Injection 1: Interferon Alpha-2a *308*
Interferon Injection 1: Interferon Alpha-2a (Prefilled Syringe) *308*
Interferon Beta-1b Injection *308*
Interferon Beta-1a Injection *308*
Interferon Alpha-n3 Injection *309*
5: Interferon Alphacon-1 Injection *309*
Interferon Gamma-1b Injection *309*
Interleukin for Injection (IL-2) *310*
Iodine IV Additive *310*
Iron Copper Solution Veterinary *310*
Iron Dextran Injection *310*
Iron Sucrose Injection *311*
Isometheptene Hydrochloride Veterinary Injection *311*
Itraconazole Injection *311*
Ketoprofen Lysine Injection *311*
Ketorolac Tromethamine Injection *312*
Ketorolac Tromethamine Ophthalmic Solution *312*
Labetalol Hydrochloride Injection *312*
Lactobionic Acid Injection *313*
Lamotrigine Injection *313*
Lazaroid Injection *314*
Lepirudin for Injection *314*
Leucovorin Calcium Injection (50 mg/5 mL, 10-mL Vial Lyophilized) *314*
Leucovorin Calcium Injection (3 mg/mL, 2-mL Vial) *315*
Leuprolide Acetate Injection (5 mg/mL Injection) *315*
Leuprolide Acetate Injection: Depot Preparation (3.75 and 7.50 mg for Injecting Every Month) *316*
Leuprolide Acetate Injection (11.25 and 22.50 mg for Injecting Every 3 Months) *316*
Leuprolide Acetate Injection (30 mg for Injecting Every 4 Months) *317*
Levorphanol Tartarate Injection *317*
Levothyroxine Sodium for Injection *317*
Lidocaine Hydrochloride and Epinephrine Injection *318*
Lidocaine Hydrochloride and Epinephrine Injection *318*
Lidocaine Hydrochloride and Epinephrine Injection *318*
Lidocaine Hydrochloride Injection (1% or 1.5% 20 mL) *319*
Lincomycin Hydrochloride Injection *319*
Liothyronine Sodium Injection (T_3) *320*
Lipid Emulsion 20% for Parenteral Nutrition *320*
Liver, Iron, and Cyanocobalamin with Procaine Injection *320*
Liver, Iron, and Vitamin B_{12} Injection Veterinary *321*
Liver, Iron, and Vitamin B_{12} Injection Veterinary *321*
Lorazepam Injection *321*
Magnesium Sulfate 50% Injection *321*
Manganese Sulfate Injection (5-mL Vial) *322*
Manganese Sulfate Injection (10-mL Vial) *322*
Manganese Sulfate Injection (30-mL Vial) *322*
Mechlorethamine Hydrochloride for Injection Trituration *322*
Medroxyprogesterone Acetate Sterile Aqueous Suspension *323*
Medroxyprogesterone Acetate Sterile Aqueous Suspension *323*
Medroxyprogesterone Acetate Sterile Aqueous Suspension *324*
Medroxyprogesterone and Estradiol Sterile Suspension *324*
Melphalan Hydrochloride for Injection *325*
Menadione Injection *325*
Menadione Sodium Bisulfite Injection Veterinary (50 mg/mL) *325*
Menadione Sodium Bisulfite Injection Veterinary (5 mg/mL) *326*
Menotropins for Injection *326*
Meperidine Hydrochloride Injection *326*
Meperidine Hydrochloride and Promethazine Hydrochloride Injection *327*
Mepivacaine Hydrochloride Injection Single-Dose Vials *327*
Mepivacaine Hydrochloride Injection Multidose Vials *327*
Meropenem for Injection *328*
Mesoridazine Besylate Injection *328*

Metaraminol Bitartrate Injection *328*
Methandriol Dipropionate Injection *328*
Methocarbamol Injection *329*
Methohexital Sodium for Injection *329*
Methylprednisolone Acetate Suspension Injection *329*
Methylprednisolone Acetate Suspension Injection *329*
Metoclopramide Injection: Preservative Formula *330*
Metoclopramide Injection: Preservative-Free Formula *331*
Metolazone Injection *331*
Metronidazole Infusion *331*
Metronidazole Injection *332*
Metronidazole and Dextrose Infusion *332*
Midazolam Hydrochloride Injection *333*
Milrinone Lactate Injection *333*
Mineral Complex Injection *333*
Mitoxantrone for Injection *334*
Morphine Sulfate Infusion *334*
Morphine Sulfate Injection *334*
Moxidectin Injection *335*
Multiple Electrolytes and Dextrose Injection (Elliott's B Solution) *335*
Muromonab-CD3 Injection *336*
Nalbuphine Hydrochloride *336*
Naloxone Hydrochloride Injection (1 mg/mL) *336*
Naloxone Hydrochloride Injection (0.04 mg/mL) *337*
Naloxone Hydrochloride Injection (0.02 mg/mL) *337*
Nandrolone Decanoate Injection *337*
Nandrolone Phenylpropionate Injection *338*
Naphazoline Ophthalmic Drops *338*
Natamycin Ophthalmic Suspension *339*
Natural Estrogenic Substances Suspension *339*
Nedocromil Sodium Ophthalmic Solution *339*
Neomycin and Prednisolone Acetate Ophthalmic Suspension *340*
Neomycin Sulfate–Polymyxin B Sulfate for Irrigation *342*
Neostigmine Methylsulfate Injection Single-Dose Vial *342*
Neostigmine Methylsulfate Injection Multidose Vial *342*
Nesiritide for Injection *342*
Netilmicin Injection *343*
Niacinamide Injection *343*
Nicardipine Hydrochloride for Infusion *344*
Nicardipine Hydrochloride Injection *344*
Nikethamide Injection *344*
Nimesulide Injection *344*
Nimodipine Injection *345*
Nystatin for Injection *345*
Octreotide Acetate Injection Single-Dose Ampoule *345*
Octreotide Acetate Injection Multidose Vial *345*
Octreotide Acetate Injection Depot *346*
Ofloxacin Otic Solution *346*
Ondansetron Hydrochloride Injection Single-Dose Vial *346*
Ondansetron Hydrochloride Injection Multidose Vial *346*
Ondansetron Hydrochloride Injection Premixed for Infusion *347*
Oprelvekin for Injection *347*
Orphenadrine Citrate Injection *347*
Oxacarbazepine-10 Injection *347*
Oxazepine Injection *348*
Oxendolone Injection *348*
Oxymorphone Hydrochloride Injection *349*
Oxytetracycline Injection *349*
Oxytocin Injection *350*
Oxytocin Injection, USP (20 U/mL) *351*
Paclitaxel Injection *351*
Palivizumab for Injection *351*
Pancuronium Bromide Injection *351*
Parenteral Nutrition Fat Emulsion *352*
Paricalcitol Injection *352*
Pegademase Bovine Injection *353*
Pegaspargase Injection *353*
Peginterferon Alpha-2b for Injection *353*
Penicillin G Benzathine and Penicillin G Procaine Injection *353*
Penicillin G Benzathine Injectable Suspension *354*
Pentobarbital Sodium Solution Injection *354*
Pentostatin for Injection *354*
Pentylenetetrazol Injection *354*
Pheniramine Maleate Injection *355*
Phenol Saline Diluent *355*
Phenylbutazone and Dipyrone Injection *355*
Phenylbutazone Injection Veterinary *356*
Phenylephrine and Zinc Sulfate Ophthalmic Drops *356*
Phenylpropanolamine Hydrochloride Injection *357*
Phenytoin Sodium Injection *357*
Phytonadione (Vitamin K_1) Injection *357*
Phytonadione (Vitamin K_1) Injection *358*
Phytonadione Injection—Aqueous Colloidal Solution of Vitamin K_1 *358*
Piperacillin Sodium and Tazobactam Sodium Injection *358*
Plicamycin for Injection *359*
Polyvinyl Alcohol Ophthalmic Solution *359*
Potassium Estrone Sulfate Injection Veterinary *360*
Potassium Estrone Sulfate Suspension Injection *360*
Potassium Phosphate Injection *360*
Prednisolone and Neomycin Ophthalmic Suspension *361*
Prednisolone Injection: Acetate/Phosphate Injection *362*
Acetate Suspension Injection (50 mg/mL) *363*
Acetate Suspension Injection (10 mg/mL) *363*
Prednisolone Acetate Suspension with Niacinamide Injection (20 mg/mL) *363*
Prednisolone Ophthalmic Drops *364*
Procaine Hydrochloride Injection *366*
Prochlorperazine Injection *366*
Progesterone and Tocopheryl Acetate Injection *366*
Progesterone Injection Repository Veterinary *367*
Promazine Hydrochloride Injection *367*
Promethazine Hydrochloride Injection Vial *368*
Promethazine Hydrochloride Injection Cartridge Unit *368*
Propofol Emulsion Injection *369*
Pyridoxine and Thiamine Injection *369*
Pyridoxine Hydrochloride Injection (100 mg/mL, 30-mL vial) *369*

Pyridoxine Hydrochloride Injection (100 mg/mL, 1-mL Ampoule) *370*
Pyrilamine Maleate and Ephedrine Injection Veterinary *370*
Quinidine Sulfate Injection *370*
Quinolone–Calcium Lactate Complex for Injection *371*
Ranitidine Injection Ampoule *371*
Ranitidine Injection Ampoule (50-mL Flexible Plastic Container) *372*
Reteplase Recombinant for Injection *372*
Retinol (Vitamin A) Injection *372*
Rh_o (D) Immune Globulin (Human) Injection *373*
Ringer Lactate Solution Injection *373*
Rituximab Injection *374*
Rubella Virus Vaccine Live *374*
Salbutamol Aerosol for Inhalation *375*
Sisomicin Injection *376*
Sodium Bicarbonate and Disodium Edetate Injection *377*
Sodium Bicarbonate Injection *378*
Sodium Chloride Bacteriostatic Injection *379*
Sodium Chloride Injection *379*
Sodium Ferric Gluconate Complex in Sucrose Injection *379*
Sodium Hyaluronate Injection *379*
Sodium Lactate Compound (Hartmann's) Injection *380*
Sodium Thiosulfate Injection *380*
Somatropin (rDNA Origin) Injection (4- or 8-mg Vials, ca. 12 or 24 IU) *380*
Somatropin (rDNA Origin) Injection (5 mg/1.5 mL, 10 mg/1.5 mL, or 15 mg/1.5 mL Cartridge) *381*
Sterile Water for Injection *381*
Streptomycin Sulfate Injection *381*
Succinylcholine Chloride Injection: Lyophilized *382*
Succinylcholine Chloride Injection: Ampoule *383*
Succinylcholine Chloride Injection: Veterinary Nonsterile *383*
Sulfadimethoxine Veterinary Injectable Solution (2.5% = 250 mg/10 mL) *383*
Sulfadoxine + Trimethoprim Veterinary Injectable Solution (1000 mg + 200 mg/10 mL) *383*
Sulfadoxine solution (2% = 20 mg/mL) *383*
Sulfamoxole + Trimethoprim Veterinary Injectable Solution (400 mg + 80 mg/10 mL) *383*
Sulfathiazole veterinary injectable and oral solutions (0.8% = 8 mg/mL) *383*
Sumatriptan Succinate Injection *384*
Tenecteplase for Injection *384*
Testosterone Suspension Injection *384*
Testosterone Cypionate Injection *384*
Testosterone Enanthate–Estradiol Valerate Injection *385*
Testosterone Enanthate Injection *385*
Testosterone Repository Veterinary Injection *385*
Testosterone Propionate Injection *385*
Testosterone Propionate Injection *386*
Tetrahydrozoline Ophthalmic Drops *386*
Theophylline and Dextrose Injection *387*
Thiamine Hydrochloride Injection: Unbuffered *387*
Thiamine Hydrochloride Injection: with Citric Acid and Gelatin *388*
Thiamine Hydrochloride Injection: Buffered *388*
Thiamine Hydrochloride Injection: with Sodium Formaldehyde Sulfoxylate *388*
Thiamine Hydrochloride Injection: Buffered and Gelatin *388*
Thiopental Sodium for Injection *389*
Thiotepa for Injection *389*
Thiothixene Hydrochloride Injection *389*
Thyrotropin-Alpha for Injection *389*
Timolol Ophthalmic Solution *390*
Tinzaparin Sodium Injection *390*
Tirofiban Hydrochloride Injection *390*
Tobramycin Solution for Inhalation *390*
Tobramycin Sulfate Injection *391*
Tobramycin Sulfate Injection *392*
Topotecan Hydrochloride for Injection *392*
Trace Element Concentrate Injection: (1- or 10-mL Vial) *392*
Trace Element Concentrate Injection (3- or 10-mL Vial) *393*
Tranexamic Acid Injection *393*
Trastuzumab for Injection *393*
Triamcinolone Acetonide Suspension Injection *394*
Trifluprazine Hydrochloride Injection *394*
Trifluprazine Hydrochloride Injection *395*
Trifluprazine Hydrochloride Injection *395*
Tripelennamine Hydrochloride Injection Veterinary *395*
Tubocurarine Chloride Injection *396*
Typhoid Vi Polysaccharide Vaccine *396*
Urokinase for Injection *397*
Valproate Sodium Injection *397*
Valrubicin for Intravesical Instillation *397*
Vancomycin for Injection *398*
Varicella Virus Vaccine Live *399*
Vasopressin (8-Arginine Vasopressin) Injection *399*
Vecuronium Bromide for Injection *399*
Verapamil Hydrochloride Injection *400*
Vinblastine Sulfate for Injection *400*
Vincristine Sulfate Injection *401*
Vincristine Sulfate Injection *401*
Water for Injection *402*
Water for Injection, Bacteriostatic *403*
Zinc Sulfate Additive Injection (5-mL Vial) *403*
Zinc Sulfate Additive Injection (10-mL Vial) *403*
Zinc Sulfate Additive Injection (30-mL Vial) *403*
Zoledronic Acid for Injection *404*
Commercial Pharmaceutical Formulations *404*

Index 427

Part I

Regulatory and Manufacturing

1

Sterile Manufacturing Formulations Template

This chapter lists the sections and specific details of the template used for compiling the formulations:

1. Generic name (as it appears in the *Physician's Desk Reference* or United States Pharmacopoeia) is used in the following:
   - Where there is more than one active component in the formulation, the ingredients appear in alphabetical order.
   - Where there are large number of active ingredients, such as in vitamin B-complex formulations, the ingredients are listed under the generic category, for example, B-complex vitamin.
   - Individual vitamins are listed with their name first; for example, Vitamin C appears as ascorbic acid, Vitamin E as α-tocopherol, and Vitamin D as retinol.
   - Veterinary formulations are identified and listed separately from human formulations. For example, *B-Complex Vitamin, Veterinary* is a different listing from *B-Complex Vitamin*, in which no indication is made for its intended use.
   - Where a special packaging is described, such as "covial or diluent included," it is also specified in the title description because it often requires special techniques, and diluent may contain other drugs, such as lidocaine.
   - Where a specific and unique packaging is involved, such as a flexible bottle, it is listed as well.
   - Compendial references are not indicated, such as a USP or BP product; however, where there are monographs available, it is assumed that the material will comply with these monographs.
   - Where a popular alternative name is available, such as Elliott's solution, it is provided in parentheses.
   - Strength of formulation is not specified in the title.
   - The USP provides strict definitions for providing the title of a product; for example, Drug for Injection means a product that must be reconstituted or diluted before use; Suspension for Injection indicates the nature of the product. While these titles are maintained, often they are not clearly indicated.
2. Bill of Materials is a tabular presentation of the scale and quantities of materials used in the following:
   - The scale is generally presented as a per-milliliter quantity (however, watch for different scales; lyophilized products may have a per-vial specification, and in the case of premixed pharmacy packs, a 50-mL specification, for example).
   - The quantities for a 1-L batch are presented with appropriate UOM (units of measurement) and include any excesses (overages), equivalent quantities due to differences in the chemical forms, or the potency of the ingredient. In some instances, the label includes the quantity of base and the ingredient used in a salt; the quantity of salt may have to be calculated if it is an equivalent quantity so marked.
   - The term QS, or sufficient quantity, is often used for the medium such as Water for Injection, for chemicals used to adjust pH, or for those used to purge the formulations, such as nitrogen gas.
   - The raw material specifications are all of pharmacopoeia grade where available; however, a listing of a raw material without requiring compendial specification should be ignored.
   - Where an "injectable grade" material is available, it is the preferred form, although it may not be so stated, particularly in the formulation of vitamin products.
   - Purity grade of the active pharmaceutical ingredient (API) is not always defined; even the pharmacopoeia-grade starting material may be subject to different impurity profiles. The formulator should remember that the regulatory agencies place a very high degree of importance on the impurity profile of the API; the supplier must be able to provide a drug master file (DMF) description assuring that the raw material is manufactured under cGMP requirements. It is possible that a manufacturer might have a DMF on some of its products but not all; therefore, the formulator should inquire specifically about the DMF of the API (with its appropriate grade clearly spelled out).
   - Multiple bills of material (BOMs) are often listed for the same product; they may appear similar or may differ only in strength; however, often there are different excipients or methods of manufacture involved. Often there are different formulations, all very useful; a sampling of these is presented as well.
3. Manufacturing Directions include a step-by-step methodology for manufacturing the product on a commercial scale in the following:
   - To avoid redundancy and to conserve space, detailed instructions are provided for each of the types of products, such as an ampoule, vial, infusion, large volume, drops, nasal preparations, or ophthalmic drops, in some formulations only; obviously, many steps involved in the preparation of commodities, sterilization procedures such as the use of 0.22-mm membrane filter, procedures for transferring to a staging vessel, presterilization of filters, testing of filters by a bubble method, autoclaving, or heat sterilization, are common to many. The reader is advised to review the detailed formulations of the specific type to obtain additional information.
   - Where unusual precautions are necessary, such as when handling a hazardous substance, a highly sensitive substance (sensitive to light or air), or a substance requiring special handling, a warning is written as the first paragraph before the manufacturing steps.
   - It is assumed that the formulator is well versed in cGMP compliance, but the reader is referred to chapter 1 to review the most recent qualification requirements.

- Manufacturing environment, documentation, personnel, and material handling issues are addressed only when peculiarities are involved.
- It is customary and, in most cases, required that the preparation vessel be of at least 316 L resistance stainless steel or higher, and thus this step is often omitted but assumed by default.
- Where there is a need to use a glass-lined vessel, it is clearly indicated. In some instances, an option is provided wherein the preference remains toward the glass-lined vessel. In some instances, glass-lined vessels should not be used, and this too is clearly indicated.
- The order and manner of mixing, the timing of mixing, the temperature of mixing, etc., when given, form essential parts of the formulation. These should be strictly followed. With in-house validation for other methods, these can be modified. The reasons for specific directions are to assure complete mixing, avoid foam formation, and reduce physical and compatibility issues. Where no specific mention is made, these details are generally inconsequential and the formulator may use conditions convenient to the manufacturing equipment and environment.
- The formulation medium in most instances is water for injection, USP grade. While in some instances other grades of water may be used, it is advisable to keep this standard wherever possible. Experience tells us that water is often the most significant source of contamination in sterile products; this can also be a source of heavy-metal contamination coming from the pitting of the pipelines (of stainless steel that contains highly reactive metal). It should be remembered that distilled water is highly corrosive and while it does not generally promote growth of bacteria, it is capable of carrying them. A closed loop running at high temperature offers the best opportunity of assuring compliance. In some instances, a formulation may specify "freshly boiled distilled water," or a similar specification, and it is intended to assure that there were no residues or endotoxin developed during storage.
- A good practice is to qualify the quality of water at the beginning of the manufacturing operation. A typical qualification process would measure pH and conductivity of water prior to use. However, note that conductivity is *not* an indicator of sterility.
- In many instances, it is recommended to bubble nitrogen gas for a sufficient length of time; the length of time depends on the capacity of the vessel, but generally should be at least 20 min; where a cover of nitrogen gas is recommended, the preparation vessel should provide a good seal to keep the nitrogen gas contained.
- When the temperature of the preparation vessel is stated as room temperature, the definition of USP is intended here.
- Where heating or cooling is recommended, this is provided by a jacketed vessel with hot- or cold-water recirculation facility.
- The cGMP compliance considerations require a detailed record of all of these steps; in listing the formulations in this book, no effort is made to illustrate this aspect of manufacturing record keeping. A fully compliant manufacturing document will have provisions for signing off on all of these observations, including the name of the operator, the time a process was begun and finished, and the observations made; often the record will be cosigned by a supervisor.
- Sampling of products during manufacturing is required and, in some instances, recommendations are made concerning where to take the sample. Samples will be sent either to in-process quality checks or to the quality control laboratory.
- In all instances, before the product is filled, it must be cleared by the quality control laboratory.
- Where extra precautions are called for, conditions are prescribed for holding the preparation pending release from the quality control laboratory before filling ampoules, vials, or bottles. Where such conditions are not prescribed, it is assumed that the preparations will be stored at the lowest temperature compatible with the product and under cover of nitrogen gas where prescribed.
- Adjustment of pH using hydrochloric acid, sodium hydroxide, acetic acid, etc. is one of the common steps in the compliance process to assure that the product meets final specifications. Although the concentrations of these acids and bases are specified, generally a 10% concentration is acceptable (higher where volume restrictions arise). The addition of these acids and bases should be gradual and in small portions, with continuous stirring to avoid drastic changes in the localized pH at the point of addition. Experienced operators should be able to determine these conditions (such as stirring speed and time to add a portion of component) and make them a part of the manufacturing document.
- In many instances, more than one manufacturing vessel is required to make separate preparations for mixing later in the process of manufacturing. It is important to assure that these vessels are held in close proximity or have a closed system for transferring liquids between vessels. Because the starting stage of manufacturing is done in less-than-sterile conditions, the exchange between vessels can be an important source of contamination and must be carefully monitored.
- Once the preparation has been properly mixed (it is likely a clear solution), it is filtered before the filling step. In all instances, there is also a step involving transferring the product into a staging vessel that will feed the filling machine, either a mobile tank or a tank in the filling room.
- The filtration step is critical, and great care should be exercised not only in selecting a proper filter (based on the dielectric property of the preparation) but also in validating the use of a filter, especially if it is not changed in each operation cycle.
- A bubble point test before and after filling is assumed in all instances. (See chap. 1 on the requirements of aseptic processing of products.)
- The retentive power of the filter is also critical and is determined partly by the nature of product (its viscosity, polarity, etc.), but generally a 0.45-mm prefilter is recommended, followed by a 0.22-mm filter.
- Whether a product is terminally sterilized or not, the goal during processing is to reduce bioburden and thus the endotoxin levels later in the product.
- The formulator has several good options in selecting the filtration equipment. While it is not the author's intent to endorse a product or a particular brand, it is important to point to ready sources of information on critical steps. One of the best sources for information on selecting and validating the filtration system is the Pall Corporation Web site (http://www.pall.com). With its broad worldwide resources, it should help one select an

appropriate filtration system and provide methods of validating the filter. The new guidelines proposed for products that are aseptically filled require special enforcement of filter validation, and the need to develop a validation system cannot be overemphasized. The filtration assembly is sterilized in an autoclave prior to use and there must be no breach prior to the use of the filtration assembly. Compatibility between the product and the hoses used to transfer it is often critical, and in some instances a specific grade of tubing is specified, such as Tygon®. The formulation scientist is referred to http://www.tygon.com for assuring that compatibility data are available before selecting a tubing grade. These suppliers are in a better position to advise because of their experience with similar products.

- The packaging commodities, such as vials, ampoules, rubber stoppers, and aluminum seals, form an integral part of the product because their integrity is required to assure that there is no contamination from external sources and no leaching of chemicals from the packaging commodities into the product. The selection of these commodities is a critical step.
- Whereas USP requires type I glass, there may be a more detailed specification, such as using a low-alkali-type as in the case of LVPs; where flexible containers are used, the possibility of chemicals leaching into the product should be considered, and attention should also be paid to the leaching of chemical components from the rubber stoppers.
- A good source of information on selecting appropriate rubber stoppers is the West Pharmaceutical Services, Inc. (http://www.west-pharma.com). From the most common butyl rubber to highly customized compositions for stoppers, the site is a good source because West Pharmaceutical Services knows who is using what type of closures for which product. Often the formulations details provided indicate coated rubber stoppers, such as siliconized, or a Teflon® product. However, where no recommendations are made, it is not assumed that any type of product is adequate.
- The choice of vials must be made concurrently with the choice of stoppers, as vials must be compatible in size (particularly the neck) to allow proper fitting of stoppers. Most companies that manufacture glass vials offer them in dimensions that allow use of off-the-shelf rubber stoppers; nevertheless, when requirements arise, customized glass vials can be fitted to an appropriate rubber stopper and vice versa. A good source of information on selection of glass vials is Wheaton Scientific (http://www.wheaton-sci.com); ampoules are also supplied by Wheaton (http://www.alcanpackaging.com/pharma/eng/html/tubularam-poules.php).
- Treatment of stoppers, vials, and ampoules prior to their use is also an integral part of manufacturing, and details of these processes are described in the master documents. Rubber stoppers are routinely washed with surfactants, rinsed with water for injection, and then heat sterilized; open ampoules and vials are washed and sterilized. Sterilization cycles of commodities must be properly validated. Suppliers of these commodities should be able to provide optimal validated cycles.
- In-process testing of products is most rigorous for sterile products, partly because it is not possible to salvage a batch once it is packaged. All products undergo a 100% visual testing (now conducted with automated systems) and proper validation of the testing procedures is required even though it is not so stated in the formulations listed in the book.

I. AUTOCLAVES

AMSCO (American Sterilizer Co.), 2425 West 23rd Street, Erie, PA 16514, USA; Telephone: (814) 452-3100
Castle Co., 1777 E. Henrietta Road, Rochester, NY 14623, USA; Telephone: (716) 475-1400
Getinge International, Inc., 1100 Towbin Avenue, Lakewood, NJ 08701, USA; Telephone: (732) 370-8800
Gruenberg, Inc., 2121 Reach Road, Williamsport, PA 17701, USA; Telephone: (717) 326-1755
STERIS Corporation, 5960 Heisley Road, Mentor, OH 44060, Phone: 440.354.2600

II. ASEPTIC CONTRACT MANUFACTURERS

American Pharmaceutical Partners, 1101 Perimeter Drive, Schaumburg, IL 60173, USA; Telephone: (847) 330-1357

A. Manufacturing Formulations Template

Connaught Laboratories, Route 411, Swiftwater, PA 18370, USA; Telephone: (717) 839-7187
Elkins-Sinn, 2 Esterbrook Lane, Cherry Hill, NJ 08003-4099, USA; Telephone: (800) 257-8349 TWX: 710-896-0804
Pharma-Hameln, Langes Feld 30-38 D-3250 Hameln 1, Germany; Telephone: (05151) 581-255
Pharmacia, 7000 Portage Road, Kalamazoo, MI 49001, USA; Telephone: 616-833-5844, Fax: 616-833-3604
Schering-Plough, U.S. Pharmaceutical Products Division, Kenilworth, NJ 07033, USA; Telephone: (201) 558-4811/4809, Telex: 138316/138280
Smith-Kline and French Call Box SKF Cidra, PR 00639, USA; Telephone: (809) 766-4000
Steris Laboratories, Inc., 620 N. 51st Avenue, Phoenix, AZ 85043, USA; Telephone: (602) 939-7565
Summa Manufacturing Sciences, 4272 Balloon Park Road, NE, Albuquerque, NM 87109, USA; Telephone: (800) 843-4339
Survival Technology, 8101 Glenbrook Road, Bethesda, MD 20814, USA; Telephone: (301) 656-5600
Taylor Pharmacal, P. O. Box 1230 Decatur, IL 62525, USA; Telephone: (217) 428-1100
Vitamed, P. O. Box 16085 IL-61160 Tel Aviv, Israel; Telephone: (03) 551-8042

III. CLEAN-ROOM DESIGN AND CONSTRUCTION

Cambridge Filter Corp., P. O. Box 4906, Syracuse, NY 13221-4906, USA; Telephone: (315) 457-1000
Clean Room Technology, Inc., 4003 Eastbourne Drive, Syracuse, NY 13206, USA; Telephone: (315) 437-2152
Comp-Aire Systems, Inc., 4185 44th SE, Grand Rapids, MI 49508, USA; Telephone: (616) 698-9660
Flanders, P. O. Box 1708, Washington, NC 27889, USA; Telephone: (919) 946-8081
Liberty Industries, Inc., 133 Commerce Street, East Berlin, CT 06023, USA; Telephone: (203) 828-6361

IV. CLEAN-IN-PLACE/STEAM-IN-PLACE (CIPISIP)

BLH Electronics, 42 Fourth Avenue, Waltham, MA 02254, USA
Clenesco, P. O. Box 2918, Cincinnati, OH 45201, USA
Degussa Corporation, P. O. Box 2004, Teterborough, NJ 07608, USA
Diversey Wyandotte Corporation, 1532 Biddle Avenue, Wyandotte, MI 48192, USA
Electrol Specialties Company, 441 Clark Street, South Beloit, IL 61080, USA
Endress & Hauser, Inc., 2350 Endress Place, Greenwood, IN 46142, USA
Foxboro Company, 38 Neponsett Avenue, Foxboro, MA 02035, USA
Klenzade, Osborn Building, St. Paul, MN 55102, USA
Ladish-Triclover, 9201 Wilmot Road, Kenosha, WI 53141, USA
National Sonies, 250 Marcus Boulevard, Hauppauge, NY 11787, USA
Pyromation, 5211 Industrial Road Fort, Wayne, IN 46895, USA
Sarco Company, 1951 26th S. W. Allentown, PA 18105, USA
Viatran Corporation, 300 Industrial Drive Grand Island, NY 14072, USA

V. CLOSURE WASHING AND STERILIZATION

Huber Maschinenfabrik Angerstrasse 16, P O. Box 1544 D-8050 Freising, Germany; Telephone: 49-81-611-3063
Huber Seidenader Equipment, Inc., 35 Airport Park, Morristown, NJ 07960, USA; Telephone: (201) 267-8730
Paxall Schubert Division, P. O. Box 836, Pine Brook, NJ 07058, USA; Telephone: (201) 227-4677
Pharma-Technik-Smeja, Postfach 2029, D-4172 Straelen-Herongen, Germany; Telephone: 609-921-1220

VI. CONSULTANTS

Bio-Separation Consultants, 3935 Falcon Avenue, Long Beach, CA 90807, USA; Attn: Fred Rothstein, Telephone: (213) 427-2844
Filtration Specialists Ltd., Pump Green House, Evenlode (Associate offices in England, Israel, Italy, and Japan)
International Consultants Association, 199 N. El Camino Real #F-318, Encinitas, CA 92024, USA; Telephone: (619) 753-0790
Interpharm International Ltd., P. O. Box 530, Prairie View, IL 60069, USA; Telephone: (312) 459-8480, Fax: (312) 459-4536
Lachman Consultant Services, 591 Stewart Avenue, Garden City, NY 11530, USA; Telephone: (516) 222-6222
Magid-Haffher Associates, 4400 Kerrybrooke Drive, Alexandria, VA 22310, USA; Telephone: (703) 971-3988
Niazi Consultants, Inc., 20 Riverside Drive, Deerfield, IL 60015, USA; Telephone: 847-267-8038
Planning Masters, 3343 William Drive, Newbury Park, CA 91320, USA; Telephone: (805) 499-7526
RI&D Engineering Associates, 22 Foxwood Drive, Somerset, NJ 08873, USA; Telephone: (201) 545-2002
Skyland Scientific Services, Gallatin Field, P. O. Box 34, Belgrade, MT 59714, USA; Telephone: (406) 388-4051
Swift Technical Services Ltd., 7 Manor Close, Oadby Leicester LE 2 4FE, England; Telephone: (0533) 712500

VII. DISINFECTANTS AND PRESERVATIVES

Alcide, Inc., One Willard Road, Norwalk, CT 06851, USA; Telephone: (203) 847-2555, Telex: 510-1003-219
Lonza, Inc., 22-10 Route 208, Fairlawn, NJ 07410, USA; Telephone: (201) 794-2400
Mallinckrodt, Inc., P. O. Box 5439, St. Louis, MO 63147, USA; Telephone: (314) 895-2000
Spectrum Chemical Co., 14422 South San Pedro Street, Gardena, CA 90248, USA; Telephone: (800) 543-0652
Sporicidin International, 4000 Massachusetts Avenue NW, Washington, D.C. 20016, USA; Telephone: (800) 424-3733
Vestal Laboratories, Inc., 5035 Manchester Avenue, St. Louis, MO 63110, USA; Telephone: (800) 325-8690

VIII. DISTILLATION EQUIPMENT

Aqua-Chem, Inc., P. O. Box 421, Milwaukee, WI 53201, USA; Telephone: (414) 961-2829
Consolidated Stills/Sterilizers, 76 Ashford Street, P. O. Box 297, Boston, MA 02134, USA; Telephone: 617-782-6072
Finn-Aqua America, Inc., 11105 Main Street, Bellevue, WA 98004, USA; Telephone: (206) 451-1900
MECO, 861 Carondelet Street, New Orleans, LA 70130, USA; Telephone: (504) 523-7271
Pennwalt Corp., Stokes Vacuum Components Dept., 5500 Tabor Road, Philadelphia, PA 19120, USA
Santasalo-Sohlberg Oy, Hankasuontie, 4-6 SF-00390 Helsinki 39, Finland
Stilmas S.p.a., Viale delle Industrie I-20090 Settala, Milano, Italy
Vaponies, Inc., Cordage Park, Plymouth, MA 02360, USA; Telephone: (617) 746-7555

IX. ENGINEERING AND CONSTRUCTION

CRS Sirrine, Inc., P. O. Box 5456, Greenville, SC 29606, USA; Telephone: (803) 281-8518
Daniel Engineering Services, Daniel Building, Greenville, SC 29602, USA; Telephone: (803) 298-3262
Davy McKee Engineers, 300 S. Riverside Plaza, Chicago, IL 60606, USA; Telephone: (312) 902-1218
Kling Lindquist, Inc., 2301 Chestnut Street, Philadelphia, PA 19103, USA; Telephone: (215) 665-9930 Telex: 244423 KLIN UR

X. FILLING MACHINES

Adtech, Inc., 1170 Church Road, Lansdale, PA 19446, USA; Telephone: (215) 368-7040
Bausch und Strobel, P. O. Box 20, D-7174 llshoven, Germany; Telephone: (07904) 701-256
Cozzoli Machine Co., 401 East 3rd Street, Plainfield, NJ 07060, USA; Telephone: (201) 757-2040
Perry Industries, 1163 Glory Road, P. O. Box 19043, Green Bay, WI 54307-9043, USA; Telephone: (414) 336-4343
TL Systems, 5617 Corvallis Avenue, North Minneapolis, MN 35429, USA; Telephone: (612) 535-51232
Vetter Pharma Fertigung, P. O. Box 2380, D-7980 Ravensburg, Germany; Telephone: (0751) 3700-0

XI. FILTER AIDS

Cuno, Inc., 400 Research Parkway, Meriden, CT 06450, USA Telephone: (800) 243-6894
Eagle-Picher Industries, 580 A Walnut Street, Cincinnati, OH 45202, USA; Telephone: (1513) 721-7010
Filter Media Co., 3603 Westcenter Drive, Houston, TX 77042, USA; Telephone: (713) 780-9000
Manville Corp., Ken-Caryl Ranch, Denver, CO 80217, USA; Telephone: (303) 979-1000, Telex: 454404

XII. FLOWMETERS (SANITARY)

Foxboro Co., 120 Norfolk Street, Foxboro, MA 02035, USA; Telephone: (617) 543-8750
Leeds & Northrup, Sumneytown Park, North Wales, PA 19454, USA; Telephone: (215) 643-2000
Micro Motion, Inc. 7070 Winchester Circle, Boulder, CO 80301, USA; Telephone: (800) 522-6277

XIII. FREEZE-DRYERS (STERILIZABLE)

Edwards High Vacuum Manor Royal, Crawley West Sussex BH10 2LW, England; Telephone: (0293) 28844
Hull Corp., Davisville Road, Hatboro, PA 19040, USA; Telephone: (215) 672-7800
Leybold-Heraeus GmbH, Postfach 1555, D-6450 Hanau 1, Germany; Telephone: (06181) 34-0
Pennwalt (Stokes Division), 5500 Tabor Road, Philadelphia, PA 19120, USA; Telephone: (215) 831-5400
Usifroid Rue Claude Bernard Z. A. de Coignieres-Maurepas, 78310 Maurepas, France; Telephone: (33-3) 051-21-27
VirTis Route, 208 Gardiner, NY 12525, USA; Telephone: (800) 431-8232

XIV. MICROFILTRATION EQUIPMENT AND FILTERS

Alsop Engineering Co., Route 10, Milldale, CT 06467, USA; Telephone: (203) 628-9661
Ametek, Plymouth Products Div., 502 Indiana Avenue, Sheboygan, WI 53081, USA; Telephone: (414) 457-9435
Ballston, Inc., P. O. Box C, Lexington, MA 02173, USA; Telephone: (617) 861-7240
Brunswick GmbH, Mergenthalerallee 45-47, D-6236 Eschborn, Germany; Telephone: (06196) 427-0
Cumo, Inc., 400 Research Parkway Meriden, CT 06450, USA; Telephone: (800) 243-6894
Domnick Hunter Filters, 1Ad Durham Road D-3400 Birtley, County Durham DH3 2SF, UK; Telephone: (091) 4105121
Ertel Engineering, 20 Front Street Kingston, NY 12401, USA; Telephone: (914) 331-4552

A. Manufacturing Formulations Template

Filterite Corp., 4116 Sorrento Valley Building, San Diego, CA 92121, USA; Telephone: (800) 854-1571
Filtrox Werk AG, CH-9001 Street, Gallen, Switzerland
FPI (Filter Products, Inc.), 8314 Tiogawoods Drive, Sacramento, CA 95828, USA; Telephone: (916) 689-2328
Fuji Filter Mfg. Co. Ltd., Shiu-Muromachi Building, 4 Nihombahi-Huroshi 2-Chome Cuo-Ku, Tokyo 103, Japan; Telephone: (03) 241-4201
Gelman Sciences, 600 S. Wagner Road, Ann Arbor, MI 48106, USA; Telephone: (800) 521-1520
Gusmer-Cellulo Co., 27 North Avenue, East, Cranford, NJ 07016, USA; Telex: 96113
Kurita Machinery, Mfg. Co., 1-44 2-Chome, Sakaigawa, Nishiku, Osaka 550, Japan; Telephone: (06) 582-3001
Membrana (USA) See Gelman Sciences
Millipore Corp., Ashby Road, Bedford, MA 01730, USA; Telephone: (800) 225-1380
Nuclepore Corp., 2036 Commerce Circle, Pleasanton, CA 94566, USA; Telephone: (415) 462-2230
Pall Corp., 30 Sea Cliff Avenue, Glen Cove, NY 11542, USA; Telephone: (800) 645-6262
PTI (Purolator Technologies), 2323 Teller Road, Newbury Park, CA 91320, USA; Telephone: (800) 235-3518
Sartorius GmbH, Postfach 19, Gottingen, Germany; Telephone: (0551) 308219
Sartorius Filters, Inc., 30940 San Clemente Street, Hayward, CA 94544, USA; Telephone: (800) 227-2842
Schenk Filterbau GmbH, Postfach 95, D-7070 Schwabisch, Gmund, Germany; Telephone: (07171) 82091
Schleicher u. Schull GmbH, Postfach D-3354 Dassel, Germany; Telephone: (05564) 8995
Seitz-Filter-Werke GmbH, Planiger Street, 137 D-6550, Bad Kreuznach, Germany; Telephone: (0671) 66026
Sperry Filter Presses, 112 North Grant Street, North Aurora, IL 60542, USA; Telephone: (312) 892-4361
Star Systems, P. O. Box 518, Timmonsville, SC 29161, USA; Telephone: (803) 346-3101
Toyo Roshi Kaisha, 7, Nihonbacki Honcho 3-Chome, Chuo-Ku, Tokyo, Japan; Telephone: (03) 270-7441
Whatman Filter, Springfield Mill, Maidstone Kent ME14 2LE, UK; Telephone: (0622) 62692

XV. PUMPS (SANITARY)

Abex Corp., Waukesha Foundry 5510 Lincoln Avenue, Waukesha, WI 53186, USA; Telephone: (414) 542-0741
Alfa-Laval, P. O. Box 1008 S-221 03, Lund, Sweden; Telephone: (046) 105000
American Lewa, 132 Hopping Brook Road, Holliston, MA 01746, USA; Telephone: (617) 429-7403
Randolph Corp., 1112 Rosine Street, Houston, TX 77019, USA; Telephone: (713) 461-3400
Warren Rupp-Houdaille Co., P. O. Box 1568 TR, Mansfield, OH 44901, USA; Telephone: (419) 524-8388
Wilden Pump & Engineering, 22069 Van Buren Street, Colton, CA 92324, USA; Telephone: (714) 783-0621
The Ladish Co., 9201 Wilmot Road, Kenosha, WI 53141, USA; Telephone: (414) 694-5511, Fax: (414) 694-7104

XVI. STERILE TANKS AND RELATED STAINLESS EQUIPMENT

Bioengineering AG, Tannerstrasse 1 CH-8630, Rueti, Switzerland; Telephone: (055) 95 35 81
Cherryl Burrell, P. O. Box 1028, Little Falls, NY 13365, USA; Telephone: (315) 823-2000, Fax: (315) 823-2666
Paul Mueller Co., P. O. Box 828, Springfield, MO 65801, USA; Telephone: (800) 641-2830
Pfaudler Co., P. O. Box 1600, Rochester, NY 14692, USA; Telephone: (716) 235-1000

Stainless Metals, Inc., 43-49 10th Street, Long Island City, NY 11101, USA; Telephone: (718) 784-1454
Valex, 6080 Leland Street, Ventura, CA 93003, USA; Telephone: (805) 658-0944, Fax: (805) 658-1376
Walker Stainless Equipment, New Lisbon, WI 53950, USA; Telephone: (608) 562-3151

XVII. STERILITY TEST EQUIPMENT

Gelman Sciences, 600 Wagner Road, Ann Arbor, MI 48106, USA; Telephone: (800) 521-1520
MFS Division-Toyo Roshi, 6800 Sierra Court, Dublin, CA 94566, USA; Telephone: (415) 828-6010
Millipore Corp., Ashby Road, Bedford, MA 01730, USA; Telephone: (800) 225-1380
Sartorius GmbH, Postfach 19, D-3400 Göttingen, Germany; Telephone: (0551) 308219
Toyo Roshi Kaisha, 7, Nihonbacki Honcho 3-Chome, Chuo-Ku, Tokyo, Japan; Telephone: (03) 270-7441

XVIII. STERILIZING AND DRYING TUNNELS (HOT AIR)

Calumatic BV, 3 Steenstraat NE-5107, Dongen, The Netherlands; Telephone: (031) 1623-13454
Hans Gilowy Maschinefabrik "Meteorwerk" GmbH & Co., Schmalenbachstrasse 12-16 D-1000, Berlin 44, Germany; Telephone: (030) 684-6071
H. Strunck Maschinenfabrik, 7 Postfach 301269 D-5000 Köln 30, Germany

XIX. STOPPERING MACHINES

Adtech Inc., 1170 Church Road, Lansdale, PA 19446, USA; Telephone: (215) 368-7040
Calumatic BV, 3 Steenstraat 7, NE-5107 Dongen, The Netherlands; Telephone: (031) 1623-13454
Perry Industries, 1163 Glory Road, P. O. Box 19043, Green Bay, WI 54307-9043, USA; Telephone: (414) 336-4343
TL Systems, 5617 Corvallis Avenue, North Minneapolis, MN 55429-3594, USA; Telephone: (612) 535-5123

XX. VIAL AND BOTTLE WASHERS

Bausch und Strobel, P. O. Box 20, D-7174 llshofen, Germany; Telephone: (07904) 701-256
Calumatic BV, 3 Steenstraat 7, NE-5107 Dongen, The Netherlands; Telephone: (031) 1623-13454
Cozzoli Machine Co., 401 East 3rd Street, Plainfield, NJ 07060, USA; Telephone: (201) 757-2040
Dawson Bros. Ltd., 406 Roding Lane, South Woodford Green, Essex, UK
Hans Gilowy Maschinenfabrik "Meteorwerk" GmbH & Co., Schmalenbachstrasse 12-1, 6 D-1000 Berlin 44, Germany; Telephone: (030) 684-6071
Schubert & Co., Vallenbaksvej 24, DK-2600 Glostrup, Denmark
H. Strunck Maschinenfabrik, Postfach 301269, D-5000 Köln 30, Germany

GMP Audit Template, EU Guidelines (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol4_en.htm)

		Compliance 1 2 3[a]	Remarks	EU-Guide
1	**PERSONNEL**			
1.1	Qualified personnel available?	☐ ☐ ☐		2.1
1.2	Organization charts available?	☐ ☐ ☐		2.2
1.3	Job descriptions available?	☐ ☐ ☐		2.2
1.4	Responsibilities clearly defined?	☐ ☐ ☐		2.2
	Key personnel			
	Responsible persons designated for			
1.5	• production?	☐ ☐ ☐		2.5
1.6	• quality control?	☐ ☐ ☐		2.6
1.7	Are they independent from each other?	☐ ☐ ☐		2.3
1.8	Are joint functions clearly defined?	☐ ☐ ☐		2.7
1.9	Are the responsible persons working full time?	☐ ☐ ☐		2.3
1.10	Do the responsible persons have the appropriate formation, knowledge, and experience?	☐ ☐ ☐		2.1/2.2
1.11	Do the relevant departments have enough personnel?	☐ ☐ ☐		2.1
	Training			
1.12	Continuous training programs for the production and QC staff?	☐ ☐ ☐		2.8
1.13	Initial job training for all employees?	☐ ☐ ☐		2.9
1.14	Teaching aids (videos, slides, brochures) available?	☐ ☐ ☐		2.9
1.15	External training courses for the staff?	☐ ☐ ☐		2.9
1.16	Training records?	☐ ☐ ☐		2.9
1.17	Special training in sensitive areas? (sterile prod. and toxic subs.)	☐ ☐ ☐		2.10
1.18	Information for visitors to the manufacturing area?	☐ ☐ ☐		2.11
2	**HYGIENE**			
	Personnel hygiene			
	Detailed written hygiene programs for			
2.1	• clothing?	☐ ☐ ☐		2.13
2.2	• use of washrooms?	☐ ☐ ☐		2.13
2.3	• behaviour in production areas?	☐ ☐ ☐		2.13
2.4	Precautions against sick or personnel with open wounds in production?	☐ ☐ ☐		2.14
	Medical examination			
2.5	• on recruitment?	☐ ☐ ☐		2.15
2.6	• regular reexaminations?	☐ ☐ ☐		2.15

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Duty of notification after			
2.7	• trips to tropical countries?	☐ ☐ ☐		2.15
2.8	• cases of contagious illness in the family?	☐ ☐ ☐		2.15
2.9	Instructions for appropriate working clothes?	☐ ☐ ☐		2.16
2.10	Absence of food and drinks (chewing gum) in the working area?	☐ ☐ ☐		2.17
2.11	Measures against contact with open product (gloves etc.)?	☐ ☐ ☐		2.18
2.12	Instructions for hand washing in production?	☐ ☐ ☐		2.19
2.13	Change of clothes when entering and leaving the production area?	☐ ☐ ☐		5.19
2.14	Change rooms and toilets easily within reach?	☐ ☐ ☐		3.31
2.15	Toilets and restrooms sufficiently separated from production areas?	☐ ☐ ☐		3.30/3.31
2.16	Workshops separate from production areas?	☐ ☐ ☐		3.32
2.17	Laboratory animal rooms totally segregated from production rooms?	☐ ☐ ☐		3.33
3	**WAREHOUSE**			
	Rooms, general			
3.1	Suitable for the intended use?	☐ ☐ ☐		3
3.2	• Adequate size?	☐ ☐ ☐		3
3.3	• Clean?	☐ ☐ ☐		3
3.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
3.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
3.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
3.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
3.8	Recording of temperature and humidity?	☐ ☐ ☐		
3.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
3.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
	Type of warehousing:			
3.11	Separation of goods sufficient?	☐ ☐ ☐		3.18
3.12	Provision for different storage temperatures?	☐ ☐ ☐		3.19
3.13	Goods receiving zone weather protected?	☐ ☐ ☐		3.20
3.14	Cleaning zone for incoming goods?	☐ ☐ ☐		3.20
3.15	Separate quarantine area with controlled access?	☐ ☐ ☐		3.21
3.16	Separate, protected sampling area?	☐ ☐ ☐		3.22
	Separate and safe storage of			
3.17	• returned goods?	☐ ☐ ☐		3.23
3.18	• rejected goods?	☐ ☐ ☐		3.23
3.19	Separate and safe storage of highly active, toxic, or dangerous substances?	☐ ☐ ☐		3.24
3.20	Safe storage of narcotics?	☐ ☐ ☐		3.24
3.21	Safe storage of printed packaging materials?	☐ ☐ ☐		3.25
3.22	Security measurements against theft?	☐ ☐ ☐		3.25

		Compliance 1 2 3[a]	Remarks	EU-Guide
3.23	Smoke detectors?	☐ ☐ ☐		3.25
3.24	Fire extinguishing system?	☐ ☐ ☐		3.25
	Operations			
3.25	Reception, sampling, and labeling according to written procedures?	☐ ☐ ☐		5.2
3.26	Is a sampling plan available?	☐ ☐ ☐		suppl. 4
3.27	Cleaning of incoming containers?	☐ ☐ ☐		5.3
3.28	Investigation and recording of damaged deliveries?	☐ ☐ ☐		5.4
3.29	FIFO principle?	☐ ☐ ☐		5.7
3.30	Inventory system?	☐ ☐ ☐		5.8
3.31	The location of materials can be detected at all times?	☐ ☐ ☐		
3.32	Incoming goods: containers and seals intact?	☐ ☐ ☐		5.27
3.33	Incoming goods: conformity with bill of delivery?	☐ ☐ ☐		5.27
	Labeling of incoming containers with			
3.34	• internal name and code?	☐ ☐ ☐		5.29
3.35	• allocated batch number?	☐ ☐ ☐		5.29
3.36	• quarantine status?	☐ ☐ ☐		5.29
3.37	• expiry date or reanalysis date?	☐ ☐ ☐		5.29
3.38	Identity test for each incoming container?	☐ ☐ ☐		5.29
3.39	Are the sampled containers marked?	☐ ☐ ☐		5.30
3.40	Are reference samples taken?	☐ ☐ ☐		5.30
3.41	Safe storage of printed packaging materials?	☐ ☐ ☐		5.41
3.42	Lot tracing of all packaging materials possible?	☐ ☐ ☐		5.42
3.43	Are excessive packaging materials destroyed?	☐ ☐ ☐		5.43
	Release of starting materials by physical/inventory checks on raw materials, packaging materials, and finished goods:			
	Item: / Stocks: Physical:	Stocks: Inventory:	Storage conditions:	
4	**DISPENSING/ASSEMBLING**			
	Rooms, general			
4.1	Suitable for the intended use?	☐ ☐ ☐		3
4.2	• Adequate size?	☐ ☐ ☐		3
4.3	• Clean?	☐ ☐ ☐		3
4.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
4.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2

		Compliance 1 2 3[a]	Remarks	EU-Guide
4.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
4.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
4.8	Recording of temperature and humidity?	☐ ☐ ☐		
4.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
4.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
4.11	Segregated from production and warehouse?	☐ ☐ ☐		3.13
4.12	Separate weighing cabins?	☐ ☐ ☐		3.13
4.13	Separate AHU for each cabin?	☐ ☐ ☐		3.12
	Air pressure gradient from weighing cabin → corridor:			3.3
4.14	Dust extraction systems available?	☐ ☐ ☐		5.11
	Operations			
4.15	Balances regularly calibrated?	☐ ☐ ☐		3.41
4.16	Only pharmaceutical raw materials in this area?	☐ ☐ ☐		5.17
4.17	Check on remains from previous materials before entering of new materials into a weighing cabin?	☐ ☐ ☐		5.9/5.35
4.18	Only one material in one cabin?	☐ ☐ ☐		5.9
4.19	Are dispensed materials correct labeled?	☐ ☐ ☐		5.29
4.20	Only released products in the dispensing?	☐ ☐ ☐		5.31
4.21	Cleaning SOPs for the dispensing?	☐ ☐ ☐		4.28
4.22	Previously dispensed material recorded on weighing protocol?	☐ ☐ ☐		4.8
4.23	Safety measures against mix-up's during assembling (e.g., cage pallets)?	☐ ☐ ☐		5.32/5.34
5	**SOLIDS MANUFACTURING**			
	Field of activity:			
	• Granulation	☐		
	• Compression	☐		
	• Encapsulation	☐		
	• Film and sugar coating	☐		
	• Visual inspection (capsules, tablets, etc.)	☐		
	• Premix (human)	☐		
	Rooms, general			
5.1	Suitable for the intended use?	☐ ☐ ☐		3
5.2	• adequate size?	☐ ☐ ☐		3
5.3	• clean?	☐ ☐ ☐		3
5.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
5.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
5.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
5.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
5.8	Recording of temperature and humidity?	☐ ☐ ☐		
5.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
5.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Rooms, special requirements			
5.11	Separate manufacturing area for penicillins/cephalosporins or highly sensitizing substances?	☐ ☐ ☐		3.6
5.12	Only for processing of pharmaceuticals?	☐ ☐ ☐		3.6
5.13	Logical flow of materials?	☐ ☐ ☐		3.7
5.14	Walls, floors, and ceilings: smooth surface and free of cracks?	☐ ☐ ☐		3.8
5.15	Easy cleaning possible?	☐ ☐ ☐		3.10
5.16	Adequate drains with traps and grilles?	☐ ☐ ☐		3.11
5.17	Appropriate air-handling system?	☐ ☐ ☐		3.12
	Air pressure gradient from working bay → corridor:			
	Classification according to EC guide?			
5.18	Appropriate dust extraction system?	☐ ☐ ☐		3.14
5.19	Appropriate lighting?	☐ ☐ ☐		3.16
5.20	Separate rest rooms?	☐ ☐ ☐		3.30
5.21	Changing rooms designed to avoid contamination?	☐ ☐ ☐		3.31
5.22	Toilets segregated from manufacturing areas?	☐ ☐ ☐		3.31
	Equipment			
5.23	Suitable for the intended use?	☐ ☐ ☐		3.34
5.24	Well maintained?	☐ ☐ ☐		3.34
5.25	Written & validated cleaning procedures?	☐ ☐ ☐		3.36
5.26	Maintenance without contamination risk (sep. area)?	☐ ☐ ☐		3.35
5.27	Equipment in contact with product: suitable materials quality?	☐ ☐ ☐		3.39
5.28	Machinery equipped with measuring and control devices?	☐ ☐ ☐		3.40
5.29	Calibration in fixed intervals acc. to written procedures?	☐ ☐ ☐		3.41
5.30	Calibration records available?	☐ ☐ ☐		3.41
5.31	Contents and flow direction marked on pipes?	☐ ☐ ☐		3.42
5.32	Pipes for distilled and demineralized water regularly monitored and sanitized?	☐ ☐ ☐		3.43
5.33	Not functioning equipment in the production area (if yes: clearly marked)?	**Y N** ☐ ☐ ☐		3.44
5.34	Status of cleanliness indicated?	☐ ☐ ☐		5.13
5.35	Previous product indicated?	☐ ☐ ☐		5.13
	Operations			
5.36	Are written and validated procedures for all manufacturing steps available?	☐ ☐ ☐		5.2
5.37	Are all manufacturing steps recorded with actual parameters?	☐ ☐ ☐		5.2
5.38	Check of each single container of the starting materials (contents, weight, and identity)?	☐ ☐ ☐		5.3
5.39	Limits for yields?	☐ ☐ ☐		5.8
5.40	Only one batch of one product processed?	☐ ☐ ☐		5.9
5.41	Protection against microbial contamination?	☐ ☐ ☐		5.10
5.42	Appropriate measures against generation of dust (e.g., closed systems)?	☐ ☐ ☐		5.11

		Compliance 1 2 3[a]	Remarks		EU-Guide
	Correct labeling of containers, materials, equipment, and rooms with				5.12
5.43	• product name and batch no.	☐ ☐ ☐			5.12
5.44	• quarantine status?	☐ ☐ ☐			5.12
5.45	Deviations from standard procedures recorded and signed by the supervisor?	☐ ☐ ☐			5.14
5.46	Special procedures for the production of antibiotics, hormones etc.?	☐ ☐ ☐			5.19
5.47	• Campaign production?	☐ ☐ ☐			5.19
5.48	• Special monitoring?	☐ ☐ ☐			5.19
5.49	• Validated decontamination procedure?	☐ ☐ ☐			5.19
5.50	Double check on weight?	☐ ☐ ☐			5.34
5.51	Line clearance before start of production?	☐ ☐ ☐			5.35
5.52	Investigation of deviations in yields?	☐ ☐ ☐			5.39
5.53	Validated procedures for reworking of rejected batches?	☐ ☐ ☐			5.62
5.54	Detailed procedures for the addition of previous batches?	☐ ☐ ☐			5.63
5.55	Special release procedure (QA) for those batches?	☐ ☐ ☐			5.64
5.56	Use of protective clothing (hair cover, shoes, masks, gloves)?	☐ ☐ ☐			2.16
5.57	Clothing regulation for visitors?	☐ ☐ ☐			2.11
	IPC				5.38
	Who performs IPC?				
5.58	Are IPC methods approved by QC?	☐ ☐ ☐			6.18
	Performance of IPCs:	*During Start-up?* **Yes/No**	*Frequency*	*Automatic* data *recording?* **Yes/No**	
	Tablets/Kernels				
5.59	Individual weights	☐ ☐		☐ ☐	
5.60	Disintegration	☐ ☐		☐ ☐	
5.61	Thickness	☐ ☐		☐ ☐	
5.62	Hardness	☐ ☐		☐ ☐	
5.63	Friability/Abrasion	☐ ☐		☐ ☐	
	Sugar-/Film-coated tablets				
5.64	Weights	☐ ☐		☐ ☐	
5.65	Disintegration	☐ ☐		☐ ☐	
5.66	Residual absolute humidity (IR or)	☐ ☐		☐ ☐	
	Capsules				
5.67	Individual weights	☐ ☐		☐ ☐	
5.68	Disintegration	☐ ☐		☐ ☐	
	Validation				
5.69	Validation according to fixed procedures?	☐ ☐ ☐			5.21
5.70	New procedures released only after validation?	☐ ☐ ☐			5.22
	Validation of changes of				
5.71	• processes?	☐ ☐ ☐			5.23
5.72	• starting materials?	☐ ☐ ☐			5.23
5.73	• equipment?	☐ ☐ ☐			5.23

		Compliance 1 2 3[a]	Remarks	EU-Guide
5.74	Revalidation in fixed intervals?	☐ ☐ ☐		5.24
5.75	Procedures for the retrospective validation of old procedures?	☐ ☐ ☐		
6	**LIQUIDS MANUFACTURING**			
	Operations carried out:			
	• Dispensing (if different from solid)	☐ ☐ ☐		
	• Syrups and suspensions	☐ ☐ ☐		
	• Drops	☐ ☐ ☐		
	• Ointment manufacture	☐ ☐ ☐		
	• Ointment filling	☐ ☐ ☐		
	• Ampoule solution manufacture	☐ ☐ ☐		
	• Sterile or aseptic ampoule filling	☐ ☐ ☐		
	• Sterile freeze drying	☐ ☐ ☐		
	• Sterile powder filling	☐ ☐ ☐		
	Rooms, general			
6.1	Suitable for the intended use?	☐ ☐ ☐		3
6.2	• adequate size?	☐ ☐ ☐		3
6.3	• clean?	☐ ☐ ☐		3
6.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
6.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
6.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
6.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
6.8	Recording of temperature and humidity?	☐ ☐ ☐		
6.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
6.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
6.11	Separate manufacturing area for penicillins/cephalosporins or highly sensitizing substances?	☐ ☐ ☐		3.6
6.12	Only for processing of pharmaceuticals?	☐ ☐ ☐		3.6
6.13	Logical flow of materials?	☐ ☐ ☐		3.7
6.14	Walls, floors, and ceilings: smooth surface and free of cracks?	☐ ☐ ☐		3.8
6.15	Easy cleaning possible?	☐ ☐ ☐		3.10
6.16	Adequate drains with traps and grilles?	☐ ☐ ☐		3.11
6.17	Appropriate air-handling system with filtered air where open products are exposed to the environment?	☐ ☐ ☐		3.12
	Air pressure gradient from working bay → corridor:			
	Classification according to EC guide?			
6.18	Appropriate lighting?	☐ ☐ ☐		3.16
6.19	Separate rest rooms?	☐ ☐ ☐		3.30
6.20	Changing rooms designed to avoid contamination?	☐ ☐ ☐		3.31
6.21	Toilets segregated from manufacturing areas?	☐ ☐ ☐		3.31
	Equipment			
6.22	Suitable for the intended use?	☐ ☐ ☐		3.34
6.23	Well maintained?	☐ ☐ ☐		3.34

		Compliance 1 2 3[a]	Remarks	EU-Guide
6.24	Tanks, containers, pipework, and pumps designed for easy cleaning and sanitation (dead legs!)?	☐ ☐ ☐		Suppl. 2
6.25	Written & validated cleaning procedures?	☐ ☐ ☐		3.36
6.26	Maintenance without contamination risk (sep. area)?	☐ ☐ ☐		3.35
6.27	Equipment in contact with product: suitable materials quality?	☐ ☐ ☐		3.39
6.28	Machinery equipped with measuring and control devices?	☐ ☐ ☐		3.40
6.29	Calibration in fixed intervals acc. to written procedures?	☐ ☐ ☐		3.41
6.30	Calibration records available?	☐ ☐ ☐		3.41
6.31	Contents and flow direction marked on pipes?	☐ ☐ ☐		3.42
6.32	Pipes for distilled and demineralized water regularly monitored and sanitized?	☐ ☐ ☐		3.43
6.33	Not functioning equipment in the production area (if yes: clearly marked)?	Y/N ☐ ☐ ☐		3.44
6.34	Status of cleanliness indicated?	☐ ☐ ☐		5.13
6.35	Previous product indicated?	☐ ☐ ☐		5.13
	Operations			
6.36	Are written and validated procedures for all manufacturing steps available?	☐ ☐ ☐		5.2
6.37	Are all manufacturing steps recorded with actual parameters?	☐ ☐ ☐		5.2
6.38	Check of each single container of the starting materials (contents, weight, identity)?	☐ ☐ ☐		5.3
6.39	Limits for yields?	☐ ☐ ☐		5.8
6.40	Only one batch of one product processed?	☐ ☐ ☐		5.9
6.41	Protection against microbial contamination?	☐ ☐ ☐		5.10
	Correct labeling of containers, materials, equipment, and rooms with			5.12
6.42	• product name and batch no.	☐ ☐ ☐		5.12
6.43	• quarantine status?	☐ ☐ ☐		5.12
6.44	Deviations from standard procedures recorded and signed by the supervisor?	☐ ☐ ☐		5.14
6.45	Special procedures for the production of antibiotics, hormones, etc.?	☐ ☐ ☐		5.19
6.46	• Campaign production?	☐ ☐ ☐		5.19
6.47	• Special monitoring?	☐ ☐ ☐		5.19
6.48	• Validated decontamination procedure?	☐ ☐ ☐		5.19
6.49	Double check on weight?	☐ ☐ ☐		5.34
6.50	Line clearance before start of production?	☐ ☐ ☐		5.35
6.51	Investigation of deviations in yields?	☐ ☐ ☐		5.39
6.52	Specification of max. storage time and storage conditions if products are not immediately filled or packaged?	☐ ☐ ☐		Suppl. 9
6.53	Validated procedures for reworking of rejected batches?	☐ ☐ ☐		5.62
6.54	Detailed procedures for the addition of previous batches?	☐ ☐ ☐		5.63
6.55	Special release procedure (QA) for those batches?	☐ ☐ ☐		5.64
6.56	Use of protective clothing (hair cover, shoes, masks, gloves)?	☐ ☐ ☐		2.16
6.57	Clothing regulation for visitors?	☐ ☐ ☐		2.11

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Water			
6.58	Loop system for purified water?	☐ ☐ ☐		Suppl. 4
6.59	Antimicrobial treatment of purified water?	☐ ☐ ☐		Suppl. 4
6.60	Loop system for water for injection?	☐ ☐ ☐		Suppl. 4
	Storage temperature of water for injection:			Suppl. 4
6.61	Loop system constructed to avoid dead legs?	☐ ☐ ☐		Suppl. 4
6.62	Regular microbiological monitoring?	☐ ☐ ☐		Suppl. 4
6.63	Regular endotoxin control?	☐ ☐ ☐		Suppl. 4
	Special requirements for sterile and aseptic products			Suppl.
	Rooms and equipment			
6.64	Access of staff and materials to clean areas *only* through air locks?	☐ ☐ ☐		1
6.66	Rooms classified according to the EC Guide?	☐ ☐ ☐		3
	Classification for products to be sterilized:			
6.67	• Solution preparation (EC: class C, with special precautions class D):	Class:		5
6.68	• Filling (EC: under LF in class C):	Class:		5
	Classification for aseptic products:			
6.69	• Handling of starting materials that can be sterile filtered (EC: class C):	Class:		6
6.70	• Handling of starting materials that cannot be sterile filtered (EC: class A in class B):	Class:		6
6.71	• Handling and filling of bulk (EC: class A in Class B):	Class:		6
6.72	All rooms easy to clean disinfect?	☐ ☐ ☐		17
6.73	Doors, windows, frames, lighting, etc. without edges?	☐ ☐ ☐		18
6.74	Suspended ceilings (if yes: sealed?)?	☐ ☐ ☐		19
6.75	Traps constructed to avoid microb. contamination?	☐ ☐ ☐		21
6.76	Appropriate constructed changing rooms?	☐ ☐ ☐		22
6.77	Measures against opening of both doors of air locks?	☐ ☐ ☐		23
6.78	Overpressure gradient from cleanest areas to others?	☐ ☐ ☐		24
6.79	AHU validated and regularly revalidated?	☐ ☐ ☐		25
6.80	Control instruments for pressure gradient?	☐ ☐ ☐		26
6.81	Warning system for errors in air supply?	☐ ☐ ☐		26
6.82	Recording of pressure gradients?	☐ ☐ ☐		26
6.83	Do conveyor belts leave sterile areas?	☐ ☐ ☐		28
6.84	Maintenance works outside from clean areas possible?	☐ ☐ ☐		28
6.85	Cleaning and disinfection procedure after maintenance works?	☐ ☐ ☐		29
6.86	Regular revalidation of all equipment and systems?	☐ ☐ ☐		30
6.87	Water prepared, circulated, and stored to exclude microb. contamination?	☐ ☐ ☐		31
6.88	Cleaning and disinfection of rooms according to validated SOPs rooms?	☐ ☐ ☐		32
	• Disinfection methods?			
6.89	Microb. monitoring of cleaning and disinfection agents?	☐ ☐ ☐		33

		Compliance 1 2 3[a]	Remarks	EU-Guide
6.90	Microb. monitoring program of production areas?	☐ ☐ ☐		35
6.91	Results recorded and considered for the release?	☐ ☐ ☐		35
	Personnel and hygiene			
6.92	Minimal no. of personnel in clean areas?	☐ ☐ ☐		7
6.93	Special and regular training?	☐ ☐ ☐		8
6.94	Regular medical examinations?	☐ ☐ ☐		10
6.95	Appropriate clean room clothes (material, and design)?	☐ ☐ ☐		12
6.96	Protective clothes worn correctly?	☐ ☐ ☐		12
6.97	Prohibition of cosmetics, jewelry, and watches?	☐ ☐ ☐		13
6.98	New clean room clothes for each working cycle?	☐ ☐ ☐		15
6.99	Appropriate washing and sterilization of clothes?	☐ ☐ ☐		16
	Operations			
6.100	Validation (media filling) in regular intervals?	☐ ☐ ☐		38
	Monitoring of water preparation system, frequency:			
6.101	• microbiological			40
6.102	• chemical			40
6.103	• particles			40
6.104	• endotoxins			40
6.105	Microbiological monitoring of starting materials?	☐ ☐ ☐		42
6.106	Max. storage times defined for sterilized equipment?	☐ ☐ ☐		45
6.107	Max. storage time defined between solution preparation and filtration?	☐ ☐ ☐		46
6.108	Material transfer to clean areas through double door autoclaves?	☐ ☐ ☐		48
	Sterilization processes			
6.109	All processes validated?	☐ ☐ ☐		50
6.110	Sterilized and not sterilized materials clearly separated?	☐ ☐ ☐		54
	Trays and boxes clearly labeled with			
6.111	• product name and code	☐ ☐ ☐		54
6.112	• batch no.	☐ ☐ ☐		54
6.113	• status: sterilized or nonsterilized	☐ ☐ ☐		54
	Sterilizers			
6.114	• Recording of temp., pressure, and time?	☐ ☐ ☐		55
6.115	• Coldest point determined?	☐ ☐ ☐		55
6.116	• Independent counter check probe?	☐ ☐ ☐		55
6.117	• Heat-up time for each product determined?	☐ ☐ ☐		56
6.118	• Sterile cooling media?	☐ ☐ ☐		57
6.119	• Tightness tests for vacuum autoclaves?	☐ ☐ ☐		58
6.120	• Clean steam for steam autoclaves?	☐ ☐ ☐		58
6.121	• Circulated air with overpressure?	☐ ☐ ☐		61
6.122	• Recirculated air: sterile filtered?	☐ ☐ ☐		61
6.123	• Ethylene oxide autoclaves: humidity, temp., and time recorded?	☐ ☐ ☐		69
6.124	• Ethylene oxide autoclaves: use of bioindicators?	☐ ☐ ☐		70

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Filtration			
6.125	Double filtration?	☐ ☐ ☐		75
6.126	Integrity testing of filters immediately after use?	☐ ☐ ☐		77
6.127	Are results part of the batch protocol?	☐ ☐ ☐		77
6.128	Optical control of each single container of ampoules, vials, and infusions?	☐ ☐ ☐		82
	IPC			
6.129	Written IPC procedures and SOPs?	☐ ☐ ☐		
	Particle testing of			
6.130	• rooms	☐ ☐ ☐		
6.131	• primary packaging materials	☐ ☐ ☐		
6.132	• system of warning and action limits?	☐ ☐ ☐		
	Microbiological monitoring of			
6.133	• rooms			
6.134	• personnel			
6.135	• euipment			
6.136	Residual O_2 of ampoules, infusions, and syrups?	☐ ☐ ☐		
6.137	Endotoxin testing of water and packaging materials?	☐ ☐ ☐		
6.138	Calibration of equipment?	☐ ☐ ☐		
6.139	Regular revalidation of equipment?	☐ ☐ ☐		
7	**PACKAGING**			
	Operations carried out: • Blistering • Foil–packaging • Filling into tablet glasses • Effervescent packaging • Powder filling • Syrup/drops filling • Ointment filling	 ☐ ☐ ☐ ☐ ☐ ☐ ☐		
	Rooms			
7.1	Suitable for the intended use?	☐ ☐ ☐		3
7.2	• adequate size?	☐ ☐ ☐		3
7.3	• clean?	☐ ☐ ☐		3
7.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
7.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
7.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
7.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
7.8	Recording of temperature and humidity?	☐ ☐ ☐		
7.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
7.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
7.11	Adequate separation of the packaging lines?	☐ ☐ ☐		3.15
	Operations			
7.12	Only *one* product per line?	☐ ☐ ☐		5.44

		Compliance 1 2 3[a]	Remarks	EU-Guide
7.13	Check list for clearance before processing a new product/new batch?	☐ ☐ ☐		5.45
7.14	Adequate labeling of the lines (product name and code)?	☐ ☐ ☐		5.46
7.15	Check of all materials delivered to the line (quantity, identity, conformity with order)?	☐ ☐ ☐		5.47
7.16	Cleaning of primary packaging materials?	☐ ☐ ☐		5.48
7.17	Immediate labeling after filling?	☐ ☐ ☐		5.49
7.18	Careful check of all printing processes (code, and expiry date)?	☐ ☐ ☐		5.50
7.19	Special safety measures for off-line printing?	☐ ☐ ☐		5.51
7.20	Regular checks of all control devices (code reader, counter, etc.)?	☐ ☐ ☐		5.52
7.21	Printings clear and durable?	☐ ☐ ☐		5.53
7.22	Balancing of printed packaging materials and bulk?	☐ ☐ ☐		5.56
7.23	Destruction of excessive coded packaging material after completion of an order?	☐ ☐ ☐		5.57
7.24	Are the finished products kept in quarantine until final release?	☐ ☐ ☐		5.58
7.25	Appropriate storage after release?	☐ ☐ ☐		5.60
	IPC			
7.26	Checks on identity of bulk and packaging materials?	☐ ☐ ☐		5.47
	Regular line checks on			
7.27	• aspect of the packages	☐ ☐ ☐		5.54a
7.28	• completeness	☐ ☐ ☐		5.54b
7.29	• conformity of quantity and quality of materials with packaging order	☐ ☐ ☐		5.54c
7.30	• correct imprint	☐ ☐ ☐		5.54d
7.31	• correct function of control devices	☐ ☐ ☐		5.54d
	Are the following IPC checks performed?			
7.32	• Leaking	☐ ☐ ☐		
7.33	• Release torque of screw caps	☐ ☐ ☐		
7.34	• pH, density, drop weight, viscosity, sedimentation	☐ ☐ ☐		
8	**DOCUMENTATION**			
	Specifications			
8.1	Specifications for raw/packaging materials available?	☐ ☐ ☐		4.10
	Do they include			
8.2	• internal name and code	☐ ☐ ☐		4.11
8.3	• name of supplier and/or manufacturer?	☐ ☐ ☐		4.11
8.4	• reference sample (printed pack. mat.)?	☐ ☐ ☐		4.11
8.5	• sampling procedure?	☐ ☐ ☐		4.11
8.6	• qualitative/quantitative specifications with limits?	☐ ☐ ☐		4.11
8.7	• storage conditions?	☐ ☐ ☐		4.11
8.8	• maximum storage period?	☐ ☐ ☐		4.11
	Goods receiving			
8.9	Written procedures for the reception of deliveries?	☐ ☐ ☐		4.19

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Do records receipt include			
8.10	• product name on labels and delivery note?	☐ ☐ ☐		4.20
8.11	• internal name and code?	☐ ☐ ☐		4.20
8.12	• receiving date?	☐ ☐ ☐		4.20
8.13	• name of supplier and/or manufacturer?	☐ ☐ ☐		4.20
8.14	• batch number of supplier?	☐ ☐ ☐		4.20
8.15	• total quantity and number of containers?	☐ ☐ ☐		4.20
8.16	• allocated internal batch number?	☐ ☐ ☐		4.20
8.17	SOPs for labeling, quarantine, and storage conditions of all incoming goods available?	☐ ☐ ☐		4.21
	SOPs include			
8.18	• authorized sampling personnel?	☐ ☐ ☐		4.22
8.19	• methods, equipment, and quantities?	☐ ☐ ☐		4.22
8.20	• safety measures?	☐ ☐ ☐		4.22
	Master formulae			
8.21	Are master formulae for each product and batch size available?	☐ ☐ ☐		4.3
8.22	Is the master formula approved and signed by the authorized persons?	☐ ☐ ☐		4.3
	The master formula includes			
8.23	• product name and code?	☐ ☐ ☐		4.14a
8.24	• description of galenical form, dosage, and batch size?	☐ ☐ ☐		4.14b
8.25	• all active ingredients with name, code, and weight?	☐ ☐ ☐		4.14c
8.26	• all excipients used during manufacture with name, code, and weight?	☐ ☐ ☐		4.14c
8.27	• yields with limits?	☐ ☐ ☐		4.14d
	Does the working procedure include			
8.28	• the production line?	☐ ☐ ☐		4.15a
8.29	• equipment to be used?	☐ ☐ ☐		4.15a
8.30	• reference to methods for cleaning, assembling, and calibration of machines?	☐ ☐ ☐		4.15b
8.31	• detailed stepwise manufacturing prescription?	☐ ☐ ☐		4.15c
8.32	• IPCs to be performed with limits?	☐ ☐ ☐		4.15d
8.33	• precautions to be followed?	☐ ☐ ☐		4.15e
8.34	Are batch records kept for each batch processed?	☐ ☐ ☐		4.17
	Do batch records include			
8.35	• protocol of line clearance?	☐ ☐ ☐		4.17
8.36	• name of the product and batch no.?	☐ ☐ ☐		4.17a
8.37	• date and time of start and end of production?	☐ ☐ ☐		4.17b
8.38	• name and initials of responsible workers for each step?	☐ ☐ ☐		4.17c, d
8.39	• batch and analytical no. and actual weight of all starting materials?	☐ ☐ ☐		4.17e
8.40	• equipment used?	☐ ☐ ☐		4.17f
8.41	• results of IPCs with initials of person who carries them out?	☐ ☐ ☐		4.17g
8.42	• yields of the relevant manufacturing steps?	☐ ☐ ☐		4.17h
8.43	• detailed notes on problems and process deviations?	☐ ☐ ☐		4.17i

		Compliance 1 2 3[a]	Remarks	EU-Guide
8.44	Records on reprocessing of batches?	☐ ☐ ☐		
	Packaging instructions			
8.45	Packaging instructions for each product, package size, and presentation?	☐ ☐ ☐		4.16
	Do they include			
8.46	• product name?	☐ ☐ ☐		4.16a
8.47	• description of galenical form and strength?	☐ ☐ ☐		4.16b
8.48	• package size?	☐ ☐ ☐		4.17c
8.49	• list of all packaging materials with code for a standard batch size?	☐ ☐ ☐		4.17d
8.50	• samples of printed packaging materials?	☐ ☐ ☐		4.17e
8.51	• special precautions?	☐ ☐ ☐		4.17f
8.52	• description of the process and equipment?	☐ ☐ ☐		4.17g
8.53	• IPCs to be performed with sampling instruction?	☐ ☐ ☐		4.17h
8.54	Are packaging batch records kept for each batch or part batch?	☐ ☐ ☐		4.18
	Do the packaging batch records include			
8.55	• protocol of line clearance?	☐ ☐ ☐		4.18
8.56	• name of the product?	☐ ☐ ☐		4.18a
8.57	• date and time when operations have been performed?	☐ ☐ ☐		4.18b
8.58	• name of the responsible person?	☐ ☐ ☐		4.18c
8.59	• initials of workers carrying out operations?	☐ ☐ ☐		4.18d
8.60	• notes on identity checks and conformity with packaging instructions?	☐ ☐ ☐		4.18e
8.61	• results of IPCs	☐ ☐ ☐		4.18e
8.62	• details of operations and equipment used?	☐ ☐ ☐		4.18f
8.63	• samples of printed packaging materials with codes (MFD, EXP, batch no. etc.)?	☐ ☐ ☐		4.18g
8.64	• record of problems and process deviations?	☐ ☐ ☐		4.18h
8.65	• quantities of packaging materials delivered, used, destroyed, or returned?	☐ ☐ ☐		4.18i
8.66	• no. of packs consumed?	☐ ☐ ☐		4.18j
	Testing			
	Do the written testing procedures include			
8.67	• test methods?	☐ ☐ ☐		4.23
8.68	• equipment for testing?	☐ ☐ ☐		4.23
8.69	Tests documented?	☐ ☐ ☐		4.23
	Others			
8.70	Procedures for release and rejection of materials and finished products?	☐ ☐ ☐		4.24
8.71	Final release by authorized person?	☐ ☐ ☐		4.24
8.72	Records about distribution of each batch?	☐ ☐ ☐		4.25
	Procedures and protocols about			
8.73	• validation?	☐ ☐ ☐		4.26
8.74	• set up and calibration of equipment?	☐ ☐ ☐		4.26
8.75	• maintenance, cleaning, and disinfection?	☐ ☐ ☐		4.26

		Compliance 1 2 3[a]	Remarks	EU-Guide
8.76	• training records?	☐ ☐ ☐		4.26
8.77	• environmental monitoring of production areas?	☐ ☐ ☐		4.26
8.78	• pest control?	☐ ☐ ☐		4.26
8.79	• complaints?	☐ ☐ ☐		4.26
8.80	• recalls?	☐ ☐ ☐		4.26
8.81	• returned goods?	☐ ☐ ☐		4.26
8.82	Instructions for use of manufacturing and testing equipment?	☐ ☐ ☐		4.27
	Log books for major equipment incl. date and name of persons who performed			
8.83	• validation?	☐ ☐ ☐		4.28
8.84	• calibration?	☐ ☐ ☐		4.28
8.85	• maintenance, cleaning, and repair works?	☐ ☐ ☐		4.28
8.86	Chronological records of use of major equipment and manufacturing areas?	☐ ☐ ☐		4.29
9	**QUALITY CONTROL**			**6**
	General requirements			
9.1	Independent QC department available?	☐ ☐ ☐		6.1
9.2	Head of QC well qualified and sufficiently experienced?	☐ ☐ ☐		6.1
9.3	Qualified personnel available?	☐ ☐ ☐		2.1
9.4	Organization charts available?	☐ ☐ ☐		2.2
9.5	Job descriptions available?	☐ ☐ ☐		2.2
9.6	Responsibilities clearly defined?	☐ ☐ ☐		2.2
9.7	Continuous training programs for QC staff?	☐ ☐ ☐		2.2
9.8	Initial job training for all employees?	☐ ☐ ☐		2.9
9.9	Training records?	☐ ☐ ☐		
9.10	QC personnel admitted to the production rooms for sampling?	☐ ☐ ☐		
	QC laboratories			
9.11	Suitable for the intended use?	☐ ☐ ☐		3.26
9.12	Laboratories of adequate size?	☐ ☐ ☐		3.26
9.13	Appropriate level of maintenance?	☐ ☐ ☐		3.1
9.14	Adequate separation from the production area?	☐ ☐ ☐		3.26
9.15	Controlled access of authorized personnel only?	☐ ☐ ☐		3.5
9.16	Special laboratory to handle biological samples available?	☐ ☐ ☐		3.29
9.17	Special laboratory to handle radioactive material available?	☐ ☐ ☐		3.29
9.18	Separate recreation rooms for the personnel available?	☐ ☐ ☐		3.30
9.19	Animal laboratories present?	☐ ☐ ☐		3.33
9.20	Animal laboratories separated from other areas?	☐ ☐ ☐		3.33
9.21	Animal laboratories equipped with a separate air-handling system?	☐ ☐ ☐		3.33
	QC Documentation			
9.22	Do procedures exist for • self-inspection? • release or rejection of products or raw material? • product complaints? • product recalls?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		

		Compliance 1 2 3[a]	Remarks	EU-Guide
	• local stability testing? • storage of reference samples? • validation of analytical procedures?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		
9.23	Specifications available for • raw materials? • bulk products? • packaging materials?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		6.7
9.24	Analytical procedures for every product?	☐ ☐ ☐		
9.25	Are Basel methods followed?	☐ ☐ ☐		
9.26	Validation of locally developed test methods?	☐ ☐ ☐		
9.27	Sampling procedures available for • raw materials? • bulk products? • packaging materials?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		6.7
9.28	Suppliers certificates available?	☐ ☐ ☐		6.7
9.29	Calibration program for analytical instruments installed?	☐ ☐ ☐		6.7
9.30	Maintenance program for analytical instruments?	☐ ☐ ☐		6.7
9.31	Retention system for QC records?	☐ ☐ ☐		6.8
9.32	Batch documents stored for expiry + 1 year or 5 years (EEC 75/319, article 22) minimum?	☐ ☐ ☐		6.8
9.33	Are original data like notebooks stored in addition to the batch documents?	☐ ☐ ☐		6.10
9.34	Can the original data be traced back easily and quickly from the analytical report number or batch number?	☐ ☐ ☐		6.10
9.35	Are trend analyses being performed for • analytical results? • yields? • environmental monitoring data?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		6.9
	Sampling			
9.36	Written procedures for taking samples?	☐ ☐ ☐		6.11
9.37	Do procedures define • method of sampling? • necessary equipment? • quantity of the sample? • subdivision of the sample? • sample container? • labeling of samples? • storage conditions? • cleaning and storage of sampling equipment? • identification of containers sampled	 ☐		
9.38	Are samples representative for the batch they are taken from (sampling plan)?	☐ ☐ ☐		6.12
9.39	Are critical steps being surveilled and validated by additional sampling (e.g., beginning or end of a process).	☐ ☐ ☐		6.12
9.40	Sample containers labeled with • name of the content • batch number • date of sampling • batch containers sampled	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		6.13
9.41	Are samples taken by QC/QA?	☐ ☐ ☐		

		Compliance 1 2 3[a]	Remarks	EU-Guide
9.42	Reference samples retained for validity +1 year?	☐ ☐ ☐		6.14
9.43	Storage of reference samples under the recommended storage conditions?	☐ ☐ ☐		6.14
9.44	Finished products stored in the final packaging?	☐ ☐ ☐		6.14
9.45	Quantity of the reference sample makes 1 (better 2) complete reanalysis possible?	☐ ☐ ☐		6.14
9.46	Sample room secure?	☐ ☐ ☐		
9.47	Sample room neatly organized and not overcrowded?	☐ ☐ ☐		
	Testing			
9.48	Are the applied analytical methods validated?	☐ ☐ ☐		6.15
9.49	Analytical methods in compliance with the registration?	☐ ☐ ☐		6.16
9.50	Are all results recorded and checked for correctness?	☐ ☐ ☐		6.16
9.51	Are all calculations checked?	☐ ☐ ☐		6.16
9.52	Do the testing protocols contain			6.17
	• name and galenical form of material?	☐ ☐ ☐		
	• batch number?	☐ ☐ ☐		
	• supplier if applicable?	☐ ☐ ☐		
	• specification reference?	☐ ☐ ☐		
	• method reference?	☐ ☐ ☐		
	• analytical results?	☐ ☐ ☐		
	• reference to analytical certificates?	☐ ☐ ☐		
	• date of the analysis?	☐ ☐ ☐		
	• name of the analyst?	☐ ☐ ☐		
	• name of the person verifying the data?	☐ ☐ ☐		
	• statement of release or rejection?	☐ ☐ ☐		
	• date and signature of the release person?	☐ ☐ ☐		
9.53	Are all IPC methods in production approved by QC?	☐ ☐ ☐		6.18
9.54	Are written methods available for the preparation of reagents and volumetric solutions?	☐ ☐ ☐		6.19
9.55	Is a record maintained of standardization of volumetric solutions?	☐ ☐ ☐		6.2
9.56	Are reagents for prolonged use labeled with			6.20
	• date of the preparation?	☐ ☐ ☐		
	• sign of the preparator?	☐ ☐ ☐		
9.57	Are unstable reagents labeled with			6.20
	• expiry date?	☐ ☐ ☐		
	• storage conditions?	☐ ☐ ☐		
9.58	Are volumetric solutions labeled with			6.20
	• the last date of standardization?	☐ ☐ ☐		
	• last current factor?	☐ ☐ ☐		
9.59	Are reference standards labeled with			6.21
	• name and potency	☐ ☐ ☐		
	• suppliers' reference	☐ ☐ ☐		
	• date of receipt	☐ ☐ ☐		
	• date of expiry	☐ ☐ ☐		
9.60	Are reference standards stored properly and under the control of a designated person?	☐ ☐ ☐		
9.61	• Are animals used for testing of components, materials, or products?	☐ ☐ ☐		
	• Quarantined before use?	☐ ☐ ☐		
	• Checked for suitability?	☐ ☐ ☐		
	• Are records maintained showing the history of their use?			

		Compliance 1 2 3[a]	Remarks	EU-Guide
10	**COMPLAINTS AND PRODUCT RECALLS**			**8**
	Complaints			8.1
10.1	Does a written complaint procedure exist?	☐ ☐ ☐		8.2
10.2	Are product complaints carefully reviewed?	☐ ☐ ☐		8.1
10.3	Is a person designated to handle complaints and to decide on measures to be taken?	☐ ☐ ☐		8.1
10.4	Is each complaint concerning a product recorded with all original details?	☐ ☐ ☐		8.3
10.5	Are product complaints thoroughly investigated?	☐ ☐ ☐		8.3
10.6	Is a responsible person of QC involved in the study?	☐ ☐ ☐		8.3
10.7	Is it considered that other batches might be concerned as well?	☐ ☐ ☐		8.4
10.8	Are decisions and measures as a result recorded?	☐ ☐ ☐		8.5
10.9	Is this record added to the corresponding batch documents?	☐ ☐ ☐		8.5
10.10	Are the complaint records regularly revised with respect to specific or recurring problems?	☐ ☐ ☐		8.6
10.11	Are the authorities informed of serious quality problems with a product?	☐ ☐ ☐		8.7
	Recalls			8.8
10.12	Does a written recall procedure exist?	☐ ☐ ☐		8.9
10.13	Is a person nominated responsible for the execution and coordination of a recall?	☐ ☐ ☐		8.8
10.14	Responsible person independent of the marketing and sales organization?	☐ ☐ ☐		8.8
10.15	Are the competent authorities informed of an imminent recall?	☐ ☐ ☐		8.11
10.16	Does the person responsible for a recall have access to the distribution records?	☐ ☐ ☐		8.12
10.17	Do the distribution records contain sufficient information on customers with • addresses? • phone numbers inside or outside working hours? • batches and amounts delivered? • medical samples?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		8.12
10.18	Are recalled products stored separately in a secure area?	☐ ☐ ☐		8.13
10.19	Is a final record made including a reconciliation between the delivered and recovered quantities?	☐ ☐ ☐		8.14
10.20	Is the effectiveness of the arrangements for recalls checked critically from time to time?	☐ ☐ ☐		8.15
11	**SELF-INSPECTION**			**9**
11.1	Does a self-inspection procedure exist which defines frequency and program?	☐ ☐ ☐		9.1
11.2	Are self-inspections carried out to check compliance with GMP rules?	☐ ☐ ☐		9.1
11.3	Are self-inspections conducted in an independent and detailed way? by designated competent persons from the company or external experts?	 ☐ ☐ ☐ ☐ ☐ ☐		9.2
11.4	Are self-inspections recorded?	☐ ☐ ☐		9.3

		Compliance 1 2 3[a]	Remarks	EU-Guide
11.5	Do reports contain • the observations made during a self-inspection? • proposals for corrective measures?	 ☐ ☐ ☐ ☐ ☐ ☐		9.3
11.6	Are actions subsequently taken recorded?	☐ ☐ ☐		9.3
12	**CONTRACT MANUFACTURE AND ANALYSIS**			**7**
12.1	Written contract between contract giver and contract acceptor available?	☐ ☐ ☐		7.1
12.2	Are responsibilities and duties clearly defined?	☐ ☐ ☐		7
12.3	All arrangements in accordance with the marketing authorization of the product concerned?	☐ ☐ ☐		7.2
	The contract giver			
12.4	Competence of the acceptor to carry out the work successful and according to GMP assessed?	☐ ☐ ☐		7.3
12.5	Acceptor provided with all the informations necessary to carry out the contract work?	☐ ☐ ☐		7.4
12.6	Acceptor informed of safety aspects?	☐ ☐ ☐		7.4
12.7	Conformance of products supplied by the acceptor ensured?	☐ ☐ ☐		7.5
12.8	Product released by a qualified person on the acceptor's side?	☐ ☐ ☐		7.5
	The contract acceptor			
12.9	Does the acceptor have • adequate premises and equipment? • knowledge and experience? • competent personnel? • a manufacturing authorization?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		7.6
12.10	Does the acceptor ensure that all products or materials delivered to him are suitable?	☐ ☐ ☐		7.7
12.11	There must be no work passed to a third party without the permission of the giver.	☐ ☐ ☐		7.8
12.12	If a third party is involved it must have the necessary manufacturing and analytical information.	☐ ☐ ☐		7.8
	The contract			
12.13	Does the written contract specify the responsibilities?	☐ ☐ ☐		7.10
12.14	Have technical aspects been drawn-up by competent persons?	☐ ☐ ☐		7.10
12.15	Release of material and check for compliance with the marketing authorization defined?	☐ ☐ ☐		7.11
12.16	Is defined who is responsible for • purchasing of materials? • IPC controls • testing and release of materials? • manufacturing and quality control? • sampling? • storage of batch documentation?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		7.12
12.17	Are manufacturing, analytical, and distribution records available to the contract giver?	☐ ☐ ☐		7.13
12.18	Contract permits the giver to visit the facilities of the acceptor?	☐ ☐ ☐		7.14
12.19	In the case of contract analysis: Does the contract acceptor understand that he is subject to inspection by the competent authorities?	☐ ☐ ☐		7.15

		Compliance 1 2 3[a]	Remarks	EU-Guide
13	**AUDIT OF SUPPLIERS**			**2.7**
13.1	Supplier audits performed for • excipients? • active substances? • packaging material?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		

[a] 1. Fulfilled or available; 2. partially fulfilled; 3. not fulfilled or not available.

GLOSSARY

Acceptance Criteria—Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active Pharmaceutical Ingredient (API) (or Drug Substance)—Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Air Lock—An enclosed space with two or more doors, which is interposed between two or more rooms, for example, of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An air lock is designed for use either by people or for goods and/or equipment.

API Starting Material—A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in house. API Starting Materials are normally of defined chemical properties and structure.

Authorized Person—The person recognized by the national regulatory authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested, and approved for release in compliance with the laws and regulations in force in that country.

Batch (or Lot)—A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of subbatches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

Batch Number (or Lot Number)—A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined. A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records, and corresponding certificates of analysis, and so on.

Batch Records—All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

Bioburden—The level and type (e.g., objectionable or not) of microorganisms that can be present in raw materials, API starting materials, intermediates, or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Bulk Product—Any product that has completed all processing stages up to, but not including, final packaging.

Calibration—The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

Clean Area—An area with defined environmental control of particulate and microbial contamination, constructed, and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

Computer System—A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions. A process or operation integrated with a computer system.

Consignment (or Delivery)—The quantity of a pharmaceutical(s), made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

Contamination—The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, and storage or transport.

Contract Manufacturer—A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

Critical—Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Critical Operation—An operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product.

Cross-Contamination—Contamination of a material or product with another material or product. Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

Deviation—Departure from an approved instruction or established standard.

Drug (Medicinal) Product—The dosage form in the final immediate packaging intended for marketing. (Reference Q1A)

Drug Substance—See Active Pharmaceutical Ingredient.

Expiry Date (or Expiration Date)—The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

Finished Product—A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labeling.

Impurity—Any component present in the intermediate or API that is not the desired entity.

Impurity Profile—A description of the identified and unidentified impurities present in an API.

In-Process Control (or Process Control)—Checks performed during production in order to monitor and, if appropriate, to adjust the process, and/or to ensure that the intermediate or API conforms to its specifications.

In-process Control—Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Intermediate—A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

Large-Volume Parenterals—Sterile solutions intended for parenteral application with a volume of 100 mL or more in one container of the finished dosage form.

Lot—See Batch.

Lot Number—See Batch Number.

Manufacture—All operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs and related controls.

Manufacturer—A company that carries out operations such as production, packaging, repackaging, labeling, and relabeling of pharmaceuticals.

Marketing Authorization (Product License, Registration Certificate)—A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling, and shelf life.

Master Formula—A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

Master Record—A document or set of documents that serve as a basis for the batch documentation (blank batch record).

Material—A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs, and packaging and labeling materials.

Mother Liquor—The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API, and/or impurities. It may be used for further processing.

Packaging—All operations, including filling and labeling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.

Packaging Material—Any material intended to protect an intermediate or API during storage and transport. Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Pharmaceutical Product—Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

Procedure—A documented description of the operations to be performed, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

Process Aids—Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g., filter aid, activated carbon, and so on).

Process Control—See In-Process Control.

Production—All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labeling and relabeling, to completion of the finished product.

Qualification—Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality Assurance (QA)—The sum total of the organised arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC)—Checking or testing that specifications are met.

Quality Unit(s)—An organizational unit independent of production which fulfills both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine—The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection, or reprocessing.

Raw Material—A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reconciliation—A comparison between the theoretical quantity and the actual quantity.

Recovery—The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.

Reference Standard, Primary—A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity.

Reference Standard, Secondary—A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Reprocessing—Subjecting all or part of a batch or lot of an in-process drug, bulk process intermediate (final biological bulk intermediate) or bulk product of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary for biological drugs and, in such cases, are validated and preapproved as part of the marketing authorization.

Retest Date—The date when a material should be reexamined to ensure that it is still suitable for use.

Reworking—Subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not preapproved as part of the marketing authorization.

Self-Contained Area—Premises which provide complete and total separation of all aspects of an operation, including personnel and equipment movement, with well established procedures, controls, and monitoring. This includes physical barriers as well as separate air-handling systems, but does not necessarily imply two distinct and separate buildings.

Signature (Signed)—See definition for signed.

Signed (Signature)—The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

Solvent—An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Specification—A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Standard Operating Procedure (SOP)—An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g., equipment operation, maintenance, and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Starting Material—Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

Validation—A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria. Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity, or system actually leads to the expected results (see also qualification).

Validation Protocol—A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Yield, Expected—The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, Theoretical—The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.

3

Inspection of Sterile Product Manufacturing Facilities

I. INTRODUCTION

Typically, a sterile drug contains no viable microorganisms and is nonpyrogenic. Drugs for intravenous injection, for irrigation, and those used as ophthalmic preparations meet these criteria. In addition, other dosage forms might be labeled as sterile, for instance, an ointment applied to a puncture wound or skin abrasion.

Parenteral drugs must be nonpyrogenic, because the presence of pyrogens can cause a febrile reaction in humans. Pyrogens are the products of the growth of microorganisms. Therefore, any condition that permits bacterial growth should be avoided in the manufacturing process. Pyrogens may develop in water located in stills, storage tanks, dead-legs, and piping, or from surface contamination of containers, closures, or other equipment. Parenterals may also contain chemical contaminants that produce a pyretic response in humans or animals although no pyrogens are present.

The sterile product manufacturing system includes measures that minimize the hazard of contamination with microorganisms and particulates of sterile drugs. This chapter describes what manufacturers should evaluate about their facilities regarding compliance with the existing (and, in some instances, upcoming) standards of inspection. Highlighted in this chapter are the areas of concern to regulatory inspectors, the problem areas, the often-overlooked systems, and, above all, the attributes where most inspections fail. It is assumed that the manufacturer is fully cognizant of the existing current good manufacturing practice (cGMP) compliance conditions as described in the Code of Federal Regulations (CFR).

This chapter includes an outline of the general cGMP compliance requirements [particularly those laid out by the U.S. Food and Drug Aministration (FDA)] for sterile manufacturing areas, detailed description of compliance problem areas regarding aseptic processing, terminal sterilization, blow-fill sealing, lyophilization, and the quality of water systems. Portions of the watch list provided here are still in the draft phase at the regulatory agencies, but might be fully adopted by the time this book is published. The guidelines given therefore present state-of-the-art sterile product manufacturing inspection audit requirements.

II. cGMP COMPLIANCE BASICS

A. Personnel

Greater emphasis is placed by regulatory agencies on the training of personnel involved in the manufacturing of sterile products than any other type. The company must always assure that the training program ensures that personnel performing production and control procedures have experience and training commensurate with their intended duties. It is important that personnel be trained in aseptic procedures. The employees must be properly gowned and use good aseptic techniques.

B. Buildings

The nonsterile preparation areas for sterile drugs should also be controlled. Refer to subpart C of the proposed Current Good Manufacturing Practice Requirements for large volume parenterals (LVPs) for further details. Evaluate the air cleanliness classification of the area. For guidance in this area, review Federal Standard #209E entitled "Airborne Particulate Cleanliness Classes in Clean-Rooms and Clean Zones." The formulation practices or procedures used in the preparation areas are important in minimizing routes of contamination. It is best to minimize traffic and unnecessary activity in the preparation area. The filling rooms and other aseptic areas should be so constructed as to eliminate possible areas for microbiological or particulate contamination, for instance, in the dust-collecting ledges or porous surfaces. Detailed plans of the cleaning and maintenance of aseptic areas should be developed and appropriate records kept assuring compliance.

C. Air

Air supplied to the nonsterile preparation or formulation area for manufacturing solutions prior to sterilization should be filtered as necessary to control particulates. Air supplied to product exposure areas where sterile drugs are processed and handled should be high-efficiency particulate air (HEPA) filtered under positive pressure. The system description for HEPA filters should include certification or dioctyl phthalate (DOP) testing, indicating the frequency of testing, or both.

The compressed air system requires that the air be filtered at the point of use to control particulates. Diagrams of the HEPA-filtered and compressed air systems should be made and be readily available for inspection.

D. Environmental Controls

Specifications for viable and nonviable particulates must be established. Specifications for viable particulates must include provisions for both air and surface sampling of aseptic processing areas and equipment. A comprehensive environmental control program, specifications, and test data should be available, particularly the procedures for reviewing out-of-limit test results. Review of environmental test data should be included as a part of the release procedures. (*Note*: In the preparation of media for environmental air and surface sampling, suitable inactivating agents should be added; e.g., the addition of penicillinase to media used for monitoring sterile penicillin operations and cephalosporin products.)

E. Equipment

Instructions should be available on how the equipment operates, including cleaning and maintenance practices. How the equipment used in the filling room is sterilized, and if the sterilization cycle has been validated, should be properly documented. The practice of resterilizing equipment if sterility has been compromised should be clearly described.

A listing of the type of filters used; the purpose of the filters; and how they are assembled, cleaned, and inspected

for damage should be maintained. Microbial retentive filters require an integrity testing (i.e., bubble point testing before and after the filtration operation).

F. Water for Injection

Water used in the production of sterile drugs must be controlled to assure that it meets USP (United States Pharmacopoeia) specifications. A detailed description of water quality systems is presented later in the chapter. The description of the system used for producing water for injection (WFI) storage and of the delivery system should be present in a written form and in sufficient detail for the operators to understand it fully. The stills, filters, storage tanks, and pipes should be installed and operated in a manner that will not contaminate the water. The procedures and specifications that assure the quality of the WFI should be periodically audited for compliance and records of audit available for inspection.

G. Containers and Closures

The system for handling and storing containers and closures should be established to show that cleaning, sterilization, and depyrogenization are adequate and have been validated.

H. Sterilization

1. Methods

Depending on the method of sterilization used, appropriate guidelines should be followed. A good source of reference material on validation of various sterilization processes is the *Parenteral Drug Association Technical Reports*. For instance, Technical Report No. 1 covers validation of steam sterilization cycles. Establish that the validation data are in order.

If steam under pressure is used, an essential control is a mercury thermometer and a recording thermometer installed in the exhaust line. The time required to heat the center of the largest container to the desired temperature must be known. Steam must expel all air from the sterilizer chamber to eliminate cold spots. The drain lines should be connected to the sewer by means of an air break to prevent back siphoning. The use of paper layers or liners and other practices that might block the flow of steam should be avoided. Charts of time, temperature, and pressure should be filed for each sterilizer load.

If sterile filtration is used, establish criteria for selecting the filter and the frequency of changing. Review the filter validation data. Know what the bioburden of the drug is and develop the procedures for filter integrity testing. If filters are not changed after each batch is sterilized, establish data to justify the integrity of the filters for the time used and that "grow through" has not occurred.

If ethylene oxide sterilization is used, establish tests for residues and degradation. A record of the ethylene oxide (EtO) sterilization cycle, including preconditioning of the product, EtO concentration, gas exposure time, chamber and product temperature, and chamber humidity should be available.

2. Indicators

Establish which type of indicator will be used to assure sterility, such as lag thermometers, peak controls, Steam Klox, test cultures, or biological indicators (BIs). (*Caution:* When spore test strips are used to test the effectiveness of ethylene oxide sterilization, be aware that refrigeration may cause condensation on removal to room temperature. Moisture on the strips converts the spore to the more susceptible vegetative forms of the organism, which may affect the reliability of the sterilization test. Do not store the spore strips where they could be exposed to low levels of ethylene oxide.)

If BIs are used, assure that the current USP guidelines on sterilization and BIs are followed. In some cases, testing BIs may become all or part of the sterility testing.

BIs are of two forms, each incorporating a viable culture of a single species of microorganism. In one form, the culture is added to representative units of the lot to be sterilized or to a simulated product that offers no less resistance to sterilization than the product to be sterilized. The second form is used when the first form is not practical, as in the case of solids. In the second form, the culture is added to disks or strips of filter paper, or metal, glass, or plastic beads. Data on the use of BIs include the following:

- Surveys of the types and numbers of organisms in the product before sterilization.
- Data on the resistance of the organism to the specific sterilization process.
- Data used to select the most resistant organism and its form (spore or vegetative cell).
- Studies of the stability and resistance of the selected organism to the specific sterilization process.
- Studies on the recovery of the organism used to inoculate the product.
- If a simulated product or surface similar to the solid product is used, validation of the simulation or similarity is required. The simulated product or similar surface must not affect the recovery of the numbers of indicator organisms applied.
- Validation of the number of organisms used to inoculate the product, simulated product, or similar surface, to include stability of the inoculum during the sterilization process.

Because qualified personnel are crucial to the selection and application of these indicators, their qualifications, including experience dealing with the process, expected contaminants, testing of resistance of organisms, and technique, should be frequently reviewed and records kept current. Policies regarding use, control, and testing of the BI by product, including a description of the method used to demonstrate presence or absence of viable indicator in or on the product, should be established.

Check data used to support the use of the indicator each time it is used. Include the counts of the inoculum used; recovery data to control the method used to demonstrate the sterilization of the indicator organism; counts on unprocessed, inoculated material to indicate the stability of the inoculum for the process time; and results of sterility testing specifically designed to demonstrate the presence or absence of the indicator organism for each batch or filling operation. In using indicators, assure that the organisms are handled so they do not contaminate the drug manufacturing area and product.

3. Filled Containers

Challenge the procedure of how the filled vials or ampoules leave the filling room. Is the capping or sealing done in the sterile fill area? If not, how is sterility maintained until capped? Review the tests done on finished vials, ampoules, or other containers to assure proper fill and seal, for instance, leak and torque tests.

Keep a good record of examinations made for particulate contamination. Know that inspectors can quickly check for suspected particulate matter by using a polariscope. Practice this in-house on a representative sample of production frequently. Employees doing visual examinations online

must be properly trained. If particle counts are done by machine, this operation must be validated. Know that even when 100% inspection is performed, defective vials and ampoules are picked up afterward.

I. Personnel Practices

Establish how employees sterilize and operate the equipment used in the filling area. Be critical of filling room personnel practices. Are the employees properly dressed in sterile gowns, masks, caps, and shoe coverings? Establish the gowning procedures, and determine whether good aseptic technique is maintained in the dressing and filling rooms. Check on the practices after lunch and other absences. Is fresh sterile garb supplied, or are soiled garments reused? If the dressing room is next to the filling area, how employees and supplies enter the sterile area is important.

J. Laboratory Controls

Pharmaceutical quality control laboratories are subject to strict guidelines established by the FDA. Review the "FDA Guide to Inspections of Pharmaceutical Quality Control Laboratories" and the "FDA Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories." Clear standard operating procedures (SOPs) should be established.

1. Retesting for Sterility

See the USP for guidance on sterility testing. Sterility retesting is acceptable provided the cause of the initial nonsterility is known, thereby invalidating the original results. It cannot be assumed that the initial sterility test failure is a false positive. This conclusion must be justified by sufficient documented investigation. Additionally, spotty or low-level contamination may not be identified by repeated sampling and testing. Review sterility test failures and determine the incidence, procedures for handling, and final disposition of the batches involved.

2. Retesting for Pyrogens

As with sterility, pyrogen retesting can be performed provided it is known that the test system was compromised. It cannot be assumed that the failure is a false positive without documented justification. Review any initial pyrogen test failures and establish a justification for retesting.

3. Particulate Matter Testing

Particulate matter consists of extraneous, mobile, and undissolved substances other than gas bubbles unintentionally present in parenteral solutions. Cleanliness specifications or levels of nonviable particulate contamination must be established. Limits are usually based on the history of the process. The particulate matter test procedure and limits for LVPs in the USP can be used as a general guideline. However, the levels of particulate contamination in sterile powders are generally greater than in LVPs. LVP solutions are filtered during the filling operation. However, sterile powders, except powders lyophilized in vials, cannot include filtration as a part of the filling operation. Considerable particulate contamination is also present in sterile powders that are spray dried due to charring during the process.

Establish the particulate matter test procedure and release criteria. Have available production and control records of any batches for which complaints of particulate matter have been received.

4. Production Records

Production records should be similar to those for other dosage forms. Critical steps, such as integrity testing of filter, should be signed and dated by a second responsible person. The production records must ensure that directions for significant manufacturing steps are included and reflect a complete history of production.

III. ASEPTIC PROCESSING

A. Introduction

There are basic differences between the production of sterile drug products by aseptic processing and by terminal sterilization. Terminal sterilization usually involves filling and sealing product containers under conditions of a high-quality environment; the product, container, and closure in most cases have low bioburden but are not sterile. The environment in which filling and sealing is performed is of high quality in order to minimize the microbial content of the in-process product and to help ensure that the subsequent sterilization process is successful. The product in its final container is then subjected to a sterilization process such as heat or radiation. Because of their nature, certain products are aseptically processed from either an earlier stage in the process or in their entirety. Cell-based therapy products are an example. All components and excipients for these products are rendered sterile, and release of the final product is contingent on determination of sterility.

In aseptic processing, the drug product, container, and closure are subjected to sterilization processes separately, as appropriate, and then brought together. Because there is no further processing to sterilize the product after it is in its final container, it is critical that containers be filled and sealed in an environment of extremely high quality. Manufacturers should be aware that there are more variables associated with aseptic processing than with terminal sterilization. Before aseptic assembly, different parts of the final product are generally subjected to different sterilization processes, such as dry heat for glass containers, moist-heat sterilization for rubber closures, and sterile filtration for a liquid dosage form. Each of the processes of the aseptic manufacturing operation requires thorough validation and control. Each also introduces the possibility of error that might ultimately lead to the distribution of contaminated product. Any manual or mechanical manipulation of the sterilized drug, components, containers, or closures prior to or during aseptic assembly poses a risk of contamination and thus necessitates careful control. The terminally sterilized drug product, on the other hand, undergoes a single sterilization process in a sealed container, thus limiting the possibilities for error. Nearly all drugs recalled due to nonsterility or lack of sterility assurance from 1980 to 2000 were produced via aseptic processing. Manufacturers should have a keen awareness of the public health implication of distributing a nonsterile drug purporting to be sterile. Poor cGMP conditions at a manufacturing facility can ultimately pose a life-threatening health risk to a patient.

B. Buildings and Facilities

Section 211.42, "Design and Construction Features," of CFR requires, in part, that aseptic processing operations be "performed within specifically defined areas of adequate size. There shall be separate or defined areas for the operations to prevent contamination or mix-ups." Aseptic processing operations must also "include, as appropriate, an air supply

Table 1 Room Area Classification

Clean-Area Classification	>0.5-mm Particles/ft^3	>0.5-mm Particles/m^3	Microbiological Limits[b] CFU/10 ft^3	CFU/m^3
100	100	3500	<1[c]	<3[c]
1000	1000	35,000	<2	<7
10,000	10,000	350,000	<5	<18
100,000	100,000	3,500,000	<25	<88

[a] All classifications based on data measured in the vicinity of exposed articles during periods of activity.
[b] Alternative microbiological standards may be established where justified by the nature of the operation.
[c] Samples from Class 100 environments should normally yield no microbiological contaminants
Source: From Ref. Cleanrooms and Associated Controlled Environments (1972). These classifications are now replaced by ISO 14644–1 (see chapter 13).

filtered through HEPA filters under positive pressure," as well as systems for "monitoring environmental conditions" and "maintaining any equipment used to control aseptic conditions." Section 211.46, "Ventilation, Air Filtration, Air Heating and Cooling," states, in part, that "equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product." This regulation also states that "air filtration systems, including prefilters and particulate matter air filters, shall be used when appropriate on air supplies to production areas."

In aseptic processing, various areas of operation require separation and control, with each area having different degrees of air quality depending on the nature of the operation. Area design is based on satisfying microbiological and particulate standards defined by the equipment, components, and products exposed as well as the particular operation conducted in the given area. Critical and support areas of the aseptic processing operation should be classified and supported by microbiological and particulate data obtained during qualification studies. Initial clean-room qualification includes some assessment of air quality under as-built and static conditions, whereas the final room or area classification should be derived from data generated under dynamic conditions, that is, with personnel present, equipment in place, and operations ongoing. The aseptic processing facility-monitoring program should assess on a routine basis conformance with specified clean-area classifications under dynamic conditions. Table 1 summarizes clean-area air classifications (Cleanrooms and Associated Controlled Environments, 1972). Two clean areas are of particular importance to sterile drug product quality: the critical area and the supporting clean areas associated with it.

1. Critical Area (Class 100)

A critical area is one in which the sterilized drug product, containers, and closures are exposed to environmental conditions designed to preserve sterility. Activities conducted in this area include manipulations (e.g., aseptic connections, sterile ingredient additions) of sterile materials prior to and during filling and closing operations. This area is critical because the product is not processed further in its immediate container and is vulnerable to contamination. To maintain product sterility, the environment in which aseptic operations are conducted should be of appropriate quality throughout operations. One aspect of environmental quality is the particulate content of the air. Particulates are significant because they can enter a product and contaminate it physically or, by acting as a vehicle for microorganisms, biologically. Particle content in critical areas should be minimized by effective air systems.

Air in the immediate proximity of exposed sterilized containers or closures and filling or closing operations is of acceptable particulate quality when it has a per-cubic-foot particle count of no more than 100 in a size range of 0.5 mm and larger (Class 100) when counted at representative locations normally not more than 1 ft away from the work site, within the airflow, and during filling or closing operations. Deviations from this critical area monitoring parameter should be documented as to origin and significance.

Measurements to confirm air cleanliness in aseptic processing zones should be taken with the particle counting probe oriented in the direction of oncoming airflow and at specified sites where sterilized product and container/closure are exposed. Regular monitoring should be performed during each shift. Nonviable particulate monitoring with a remote counting system is generally less invasive than the use of portable particle counting units and provides the most comprehensive data.

Some powder-filling operations can generate high levels of powder particulates that, by their nature, do not pose a risk of product contamination. It may not, in these cases, be feasible to measure air quality within the 1-ft distance and still differentiate "background noise" levels of powder particles from air contaminants. In these instances, air should be sampled in a manner that, to the extent possible, characterizes the true level of extrinsic particulate contamination to which the product is exposed. Initial certification of the area under dynamic conditions without the actual powder-filling function should provide some baseline information on the nonproduct particle generation of the operation.

Air in critical areas should be supplied at the point of use as HEPA-filtered laminar flow air at a velocity sufficient to sweep particulate matter away from the filling or closing area and maintain laminarity during operations. The velocity parameters established for each processing line should be justified, and appropriate to maintain laminarity and air quality under dynamic conditions within a defined space (Cleanrooms and Associated Controlled Environments, 1972). (A velocity of 90–100 ft/min is generally established, with a range of ±20% around the set point. Higher velocities may be appropriate in operations generating high levels of particulates.)

Proper design and control should prevent turbulence or stagnant air in the aseptic processing line or clean zone. Once relevant parameters are established, airflow patterns should be evaluated for turbulence. Air pattern or "smoke" studies demonstrating laminarity and sweeping action over and away from the product under dynamic conditions should be conducted. The studies should be well documented with written conclusions. Videotape or other recording mechanisms have been found to be useful in assessing airflow initially as well as facilitating evaluation of subsequent equipment configuration changes. However, even successfully qualified systems can be compromised by poor personnel or operational or maintenance practices. Active air monitoring of critical areas should normally yield no microbiological contaminants. Contamination in this environment should receive investigative attention.

2. Supporting Clean Areas

Supporting clean areas include various classifications and functions. Many support areas function as zones in which nonsterile components, formulated product, in-process materials, equipment, and containers or closures are prepared, held, or transferred. These environments should be designed to minimize the level of particulate contaminants in the final product and control the microbiological content (bioburden) of articles and components that are subsequently sterilized.

The nature of the activities conducted in a supporting clean area should determine its classification. An area classified as Class 100,000 is used for less critical activities (such as initial equipment preparation). The area immediately adjacent to the aseptic processing line should, at a minimum, meet Class 10,000 standards (see Table 1) under dynamic conditions. Depending on the operation, manufacturers can also classify this area as Class 1000 or maintain the entire aseptic filling room at Class 100.

3. Clean Area Separation

Adequate separation is necessary between areas of operation to prevent contamination. To maintain air quality in areas of higher cleanliness, it is important to achieve a proper airflow and a positive pressure differential relative to adjacent less clean areas. Rooms of higher classification should have a positive pressure differential relative to adjacent lower classified areas of generally at least 0.05 in H_2O (with doors closed). When doors are open, outward airflow should be sufficient to minimize ingress of contamination (Ljungqvist and Reinmuller, 1997). Pressure differentials between clean rooms should be monitored continuously throughout each shift and frequently recorded, and deviations from established limits investigated.

An adequate air change rate should be established for a clean room. For Class 100,000 supporting rooms, airflow sufficient to achieve at least 20 air changes per hour is typically acceptable.

Facility monitoring systems should be established to rapidly detect atypical changes that can compromise the facility's environment. Operating conditions should be restored to established, qualified levels before reaching action levels. For example, pressure differential specifications should enable prompt detection (i.e., alarms) of any emerging low-pressure problem in order to preclude ingress of unclassified air into a classified room.

4. Air Filtration

a. Membrane (Compressed Gases)

A compressed gas should be of appropriate purity (e.g., free from oil and water vapor) and its microbiological and particulate quality should be equal to or better than air in the environment into which the gas is introduced. Compressed gases such as air, nitrogen, and carbon dioxide are often used in clean rooms and are frequently employed in operations involving purging or overlaying.

Membrane filters allow for the filtration of compressed gases to meet an appropriate high-quality standard, and can be used to produce a sterile compressed gas. A sterile-filtered gas is used when the gas contacts a sterilized material. Certain equipment should also be supplied with a sterile-filtered gas. For example, sterile bacterial retentive membrane filters should be used for autoclave air lines, lyophilizer vacuum breaks, vessels containing sterilized materials, and hot-air sterilizer vents. Sterilized tanks or liquids should be held under continuous overpressure to prevent microbial contamination. Safeguards should be in place to prevent a pressure change that can result in contamination due to backflow of nonsterile air or liquid.

Gas filters (including vent filters) should be dry. Condensate in a gas filter can cause blockage or microbial contamination. Frequent replacement, heating, and use of hydrophobic filters prevent moisture residues in a gas supply system. These filters also should be integrity tested on installation and periodically thereafter (e.g., including at end of use). Integrity test failures should be investigated.

b. High-Efficiency Particulate Air

The same broad principles can be applied to ultra-low particulate air (ULPA) filters as described here for HEPA filters. An essential element in ensuring aseptic conditions is the maintenance of HEPA filter integrity. Integrity testing should be performed at installation to detect leaks around the sealing gaskets, through the frames or through various points on the filter media. Thereafter, integrity tests should be performed at suitable time intervals for HEPA filters in the aseptic processing facility. For example, such testing should be performed twice a year for the aseptic processing room. Additional testing may be needed when air quality is found to be unacceptable, or as part of an investigation into a media fill or drug product sterility failure. Among the filters that should be integrity tested are those installed in dry-heat depyrogenation tunnels commonly used to depyrogenate glass vials.

One recognized method of testing the integrity of HEPA filters is use of a DOP aerosol challenge. However, alternative aerosols may be acceptable. Poly-alpha-olefin can also be used, provided it meets specifications for critical physicochemical attributes such as viscosity. Some alternative aerosols are problematic because they pose a risk of microbial contamination of the environment being tested. It should be ensured that any alternative does not promote microbial growth.

An intact HEPA filter is capable of retaining at least 99.97% of particulates greater than 0.3 mm in diameter. It is important to ensure that the aerosol used for the challenge has a sufficient number of particles of this size range. Performing an integrity test without introducing particles of known size upstream of the filter is ineffective to detect leaks. The DOP challenge should introduce the aerosol upstream of the filter in a concentration of 80 to l00 mg/L of air at the filter's designed airflow rating. The downstream side of the filter is then scanned with an appropriate photometer probe at a sampling rate of at least 1 ft^3/min. Scanning should be conducted on the entire filter face and frame at a position about 1 to 2 in from the face of the filter. This comprehensive scanning of HEPA filters should be fully documented. Although vendors often provide these services, the drug manufacturer is responsible to ensure that these essential certification activities are conducted satisfactorily.

A single probe reading equivalent to 0.01% of the upstream challenge should be considered as indicative of a significant leak and should result in replacement of the HEPA filter or perhaps repair in a limited area. A subsequent confirmatory retest should be performed in the area of any repair. Whereas there is a major difference between filter integrity testing and efficiency testing, the purpose of regularly scheduled integrity testing is to detect leaks from the filter media, filter frame, and seal.

The challenge is a polydispersed aerosol usually composed of particles ranging in size from 1 to 3 mm. The test is done in place and the filter face is scanned with a probe; the measured downstream leakage is taken as a percent of the

upstream challenge. The efficiency test, on the other hand, is a test used only to determine the rating of the filter. (The efficiency test uses a monodispersed aerosol of particles of size 0.3 μm, relates to filter media, and usually requires specialized testing equipment. Downstream readings represent an average over the entire filter surface. Therefore, the efficiency test is not intended to test for leakage in a filter.)

HEPA filter integrity testing alone is not sufficient to monitor filter performance. This testing is usually done only on a semiannual basis. It is important to conduct periodic monitoring of filter attributes such as uniformity of velocity across the filter (and relative to adjacent filters). Variations in velocity generally increase the possibility of contamination, as these changes (e.g., velocity reduction) can have an effect on the laminarity of the airflow. Airflow velocities are measured 6 in from the filter face or at a defined distance proximal to the work surface for each HEPA filter. For example, velocity monitoring as frequently as weekly may be appropriate for the clean zone in which aseptic processing is performed. HEPA filters should be replaced when inadequate airflow (e.g., due to blockage) or nonuniformity of air velocity across an area of the filter is detected.

5. Design

Section 211.42 requires that aseptic processing operations be "performed within specifically defined areas of adequate size. There shall be separate or defined areas for the firm's operations to prevent contamination or mix-ups." Section 211.42 further states that "flow of components, drug products containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination." HEPA-filtered air as appropriate, as well as "floors, walls and ceilings of smooth, hard surfaces that are easily cleanable" are some additional requirements of this section. Section 211.63 states that equipment "shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance." Section 211.65 states that "equipment shall be constructed so that surfaces that contact the components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."

Section 211.68 includes requirements for "automatic, mechanical and electronic equipment." Section 211.113 states that "appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed."

An aseptic process is designed to minimize exposure of sterile articles to dynamic conditions and potential contamination hazards presented by the operation. Limiting the duration of open container exposure, providing the highest possible environmental control, and designing equipment to prevent entrainment of lower quality air into the Class 100 zone are essential to this goal (Ljungqvist and Reinmuller, 1997).

Any intervention or stoppage during an aseptic process can increase the risk of contamination. Personnel and material flow should be optimized to prevent unnecessary activities that increase the potential for introducing contaminants to exposed product, container/closures, or the surrounding environment. The layout of equipment should provide for ergonomics that optimize comfort and movement of operators. The flow of personnel should be designed to limit the frequency with which entries and exits are made to and from the aseptic processing room and, more significantly, its critical area. To prevent changes in air currents that introduce lower quality air, movement adjacent to the critical area should be limited. For example, personnel intervention can be reduced by integrating an on-line weight check device, thus eliminating a repeated manual activity within the critical zone. It is also important to minimize the number of personnel in the aseptic processing room.

Transfer of products should be performed under appropriate clean-room conditions. For example, lyophilization processes include transfer of aseptically filled product in partially sealed containers. To prevent contamination, partially closed sterile product should be staged and transferred only in critical areas. Facility design should assure that the area between a filling line and the lyophilizer, and the transport and loading procedures, provide Class 100 protection. The sterile product and container closures should also be protected from activities occurring adjacent to the line. Carefully designed curtains, rigid plastic shields, or other barriers should be used in appropriate locations to partially segregate the aseptic processing line. Airlocks and interlocking doors facilitate better control of air balance throughout the aseptic processing area. Airlocks should be installed between the aseptic processing area entrance and the adjoining uncontrolled area. Other interfaces such as personnel entries, or the juncture of the aseptic processing room and its adjacent room, are also appropriate locations for airlocks. Clean rooms are normally designed as functional units with specific purposes. A well-designed clean room is constructed with material that allows for ease of cleaning and sanitizing. Examples of adequate design features include seamless and rounded floor-to-wall junctions as well as readily accessible corners. Floors, walls, and ceilings are constructed of smooth, hard surfaces that can be easily cleaned (section 211.42). Ceilings and associated HEPA filter banks should be designed to protect sterile materials from contamination. Clean rooms also should not contain unnecessary equipment, fixtures, or materials.

Processing equipment and systems should be equipped with sanitary fittings and valves. Drains are not considered appropriate for rooms in classified areas of the aseptic processing facility. When applicable, equipment must be suitably designed for ease of sterilization (section 211.63). The effect of equipment layout and design on the clean-room environment should be addressed. Flat surfaces or ledges that accumulate dust and debris should be avoided. Equipment should not obstruct airflow and, in critical zones, its design should not perturb airflow.

C. Personnel Training, Qualification, and Monitoring

Section 211.22 states that "the quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product." Section 211.113(b) addresses the procedures designed to prevent microbiological contamination, stating that "appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed." Section 211.25, "Personnel Qualifications," requires that:

> Each person engaged in manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. . . . Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the

> drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess.

This section also requires "an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product." Section 211.25 also requires that continuing training in cGMP "shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with cGMP requirements applicable to them." The training "shall be in the particular operations that the employee performs and in cGMP (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations), as they relate to the employee's functions."

Section 211.28, "Personnel Responsibilities," states that "personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform." It also states that "personnel shall practice good sanitization and health habits" and specifies that "protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination." It also states:

> Any person shown at any time (either by medical examination or supervisory examination) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products.

This section also addresses restrictions on entry into limited-access areas: "Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas." Section 211.42 requires the establishment of a "system for monitoring environmental conditions."

1. Manufacturing Personnel

A well-designed aseptic process minimizes personnel intervention. As operator activities increase in an aseptic processing operation, the risk to finished product sterility also increases. It is essential that operators involved in aseptic manipulations adhere to the basic principles of aseptic technique at all times to assure maintenance of product sterility. Appropriate training should be conducted before an individual is permitted to enter the aseptic processing area and perform operations. For example, such training should include aseptic technique, clean-room behavior, microbiology, hygiene, gowning, and patient safety hazard posed by a nonsterile drug product, and the specific written procedures covering aseptic processing area operations. After initial training, personnel should be updated regularly by an ongoing training program. Supervisory personnel should routinely evaluate each operator's conformance to written procedures during actual operations. Similarly, the quality control unit should provide regular oversight of adherence to established, written procedures, and basic aseptic techniques during manufacturing operations.

Adherence to basic aseptic technique is a continuous requirement for operators in an aseptic processing operation. The following are some techniques aimed at maintaining sterility of sterile items and surfaces:

1. Contact sterile materials with sterile instruments only. Always use sterile instruments (e.g., forceps) while handling sterilized materials. Between uses, place instruments in sterilized containers only. Replace these instruments as necessary throughout the operation. Regularly sanitize initial gowning and sterile gloves to minimize the risk of contamination. Personnel should not directly contact sterile products, containers, closures, or critical surfaces.
2. Move slowly and deliberately. Rapid movements can create unacceptable turbulence in the critical zone. Such movements disrupt the sterile field, presenting a challenge beyond intended clean-room design and control parameters. Follow the principle of slow, careful movement throughout the clean room.
3. Keep the entire body out of the path of laminar air. Laminar airflow design is used to protect sterile equipment surfaces, container/closures, and product. Personnel should not disrupt the path of laminar flow air in the aseptic processing zone.
4. Approach a necessary manipulation in a manner that does not compromise sterility of the product. To maintain sterility of nearby sterile materials, approach a proper aseptic manipulation from the side and not above the product (in vertical laminar flow operations). Also, speaking when in direct proximity to an aseptic processing line is not an acceptable practice.
5. Personnel who have been qualified and permitted access to the aseptic processing area should be appropriately gowned. An aseptic processing-area gown should provide a barrier between the body and exposed sterilized materials, and prevent contamination from particles generated by, and microorganisms shed from, the body. Gowns need to be sterile and nonshedding, and should cover the skin and hair. Face masks, hoods, beard or moustache covers, protective goggles, elastic gloves, clean-room boots, and shoe overcovers are examples of common elements of gowns. An adequate barrier should be created by the overlapping of gown components (e.g., gloves overlapping sleeves). If an element of the gown is found to be torn or defective, change it immediately. There should be an established program to regularly assess or audit conformance of personnel to relevant aseptic manufacturing requirements. An aseptic gowning qualification program should assess the ability of a clean-room operator to maintain the sterile quality of the gown after performance of gowning procedures. Gowning qualification should include microbiological surface sampling of several locations on a gown (e.g., glove fingers, facemask, forearm, chest, and other sites). Following an initial assessment of gowning, periodic requalification should monitor various gowning locations over a suitable period to ensure the consistent acceptability of aseptic gowning techniques. Semiannual or yearly requalification is acceptable for automated operations where personnel involvement is minimized. To protect exposed sterilized product, personnel are expected to maintain sterile gown quality and aseptic method standards in a consistent manner. Written procedures should adequately address circumstances under which personnel should be retrained, requalified, or reassigned to other areas.

2. Laboratory Personnel

The basic principles of training, aseptic technique, and personnel qualification in aseptic manufacturing are equally applicable to those performing aseptic sampling and microbiological laboratory analyses. Processes and systems cannot be

considered to be under control and reproducible if there is any question regarding the validity of data produced by the laboratory.

3. Monitoring Program

Personnel can have substantial impact on the quality of the environment in which the sterile product is processed. A vigilant and responsive personnel-monitoring program should be established. Monitoring should be accomplished by obtaining surface samples of each aseptic processing operator's gloves on at least a daily basis or in association with each batch. This sampling should be accompanied by an appropriate frequency of sampling for other strategically selected locations of the gown (Current Practices in the Validation of Aseptic Processing, 2002). The quality control unit should establish a more comprehensive monitoring program for operators involved in operations that are especially labor intensive, that is, those requiring repeated or complex aseptic manipulations. Asepsis is fundamental to an aseptic processing operation. An ongoing goal for manufacturing personnel in the aseptic processing room is to maintain contamination-free gloves throughout operations. Sanitizing gloves just prior to sampling is inappropriate because it can prevent recovery of microorganisms that were present during an aseptic manipulation. When operators exceed established levels or show an adverse trend, an investigation should be conducted promptly. Follow-up actions may include increased sampling, increased observation, retraining, gowning requalification, and, in certain instances, reassigning the individual to operations outside of the aseptic processing area. Microbiological trending systems and assessment of the impact of atypical trends are discussed in more detail under the section on laboratory controls.

D. Components and Containers/Closures

1. Components

Section 210.3(b)(3) defines a component as "any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product." Section 211.80, "General Requirements," requires, in part, "the establishment of written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures. . . . Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination."

Section 211.84, "Testing and Approval or Rejection of Components, Drug Product Containers, and Closures," requires that "each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use."

A drug product produced by aseptic processing can become contaminated by use of one or more components (e.g., active ingredients, excipients, WFI) contaminated with microorganisms or endotoxins. It is important to characterize the microbial content of each component liable to contamination and establish appropriate acceptance or rejection limits based on information on bioburden. Knowledge of bioburden is critical in assessing whether the sterilization process is adequate.

In aseptic processing, each component is individually sterilized or several components are combined, with the resulting mixture sterilized. There are several methods to sterilize components. A widely used method is filtration of a solution formed by dissolving the component(s) in a solvent such as USP WFI. The solution is passed through a sterilizing membrane or cartridge filter. Filter sterilization is used when the component is soluble and is likely to be adversely affected by heat. A variation of this method involves subjecting the filtered solution to aseptic crystallization and precipitation of the component as a sterile powder. However, this method involves more handling and manipulation and therefore has a higher potential for contamination during processing. If a component is not adversely affected by heat and is soluble, it may be made into a solution and subjected to steam sterilization, typically in an autoclave or a pressurized vessel. Dry-heat sterilization is a suitable method for components that are heat stable and insoluble. However, carefully designed heat penetration and distribution studies should be performed for powder sterilization because of the insulating effects of the powder.

Ethylene oxide exposure is often used for surface sterilization. Such methods should be carefully controlled and validated if used for powders to evaluate whether consistent penetration of the sterilant is achieved and to minimize residual ethylene oxide and by-products.

Parenteral products are intended to be nonpyrogenic. There should be written procedures and appropriate specifications for acceptance or rejection of each lot of components that might contain endotoxins. Any components failing to meet endotoxin specifications should be rejected.

2. Containers/Closures

Section 211.94, "Drug Product Containers and Closures," states that "drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use." It also states that "standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures." Section 211.113(b) requires "validation of any sterilization process" as part of designing procedures "to prevent microbiological contamination of drug products purporting to be sterile."

a. Preparation

Containers and closures should be rendered sterile and, for parenteral drug products, pyrogen-free. The type of processes used will depend primarily on the nature of the material comprising the container or closure, or both. The validation study for any such process should be adequate to demonstrate its ability to render materials sterile and pyrogen-free. Written procedures should specify the frequency of revalidation of these processes as well as time limits for holding sterile, depyrogenated containers and closures.

Presterilization preparation of glass containers usually involves a series of wash-and-rinse cycles. These cycles serve an important role in removing foreign matter. Rinse water should be of high purity so as not to contaminate containers. For parenteral products, final rinse water should meet the specifications of WFI, USP.

The adequacy of the depyrogenation process can be assessed by spiking containers or closures with known quantities of endotoxin, followed by measuring endotoxin content after depyrogenation. The challenge studies should be performed with a reconstituted endotoxin solution applied directly onto the surface being tested and air-dried. Positive controls should be used to measure the percentage of endotoxin recovery by the test method. Validation study data

should demonstrate that the process reduces the endotoxin content by at least 99.9% (3 logs).

Glass containers are generally subjected to dry heat for sterilization and depyrogenation. Validation of dry-heat sterilization or depyrogenation should include appropriate heat distribution and penetration studies as well as the use of worst-case process cycles, container characteristics (e.g., mass), and specific loading configurations to represent actual production runs.

Pyrogen on plastic containers can be generally removed by multiple WFI rinses. Plastic containers can be sterilized with an appropriate gas, irradiation, or other suitable means. For gases such as EtO, the parameters and limits of the EtO sterilization cycle (e.g., temperature, pressure, humidity, gas concentration, exposure time, degassing, aeration, and determination of residuals) should be specified and monitored closely. BIs are of special importance in demonstrating the effectiveness of EtO and other gas sterilization processes.

Rubber closures (e.g., stoppers and syringe plungers) are cleaned by multiple cycles of washing and rinsing prior to final steam or irradiation sterilization. At minimum, the initial rinses for the washing process should employ purified water USP of minimal endotoxin content, followed by final rinse(s) with WFI for parenteral products. Normally, depyrogenation is achieved by multiple rinses of hot WFI. The time between washing and sterilizing should be minimized because moisture on the stoppers can support microbial growth and the generation of endotoxins. Because rubber is a poor conductor of heat, extra attention should be given to the validation of processes that use heat to sterilize rubber stoppers. Validation data should also demonstrate successful endotoxin removal from rubber materials.

A potential source of contamination is the siliconization of rubber stoppers. Silicone used in the preparation of rubber stoppers should be rendered sterile and not have an adverse effect on the safety, quality, or purity of the drug product. It is important to establish production time limits for the holding of sterilized containers and closures.

Contract facilities that perform sterilization and depyrogenation of containers and closures are subject to the same cGMP requirements as those established for in-house processing. The finished dosage from the manufacturer is subject to the review and approval of the contractor's validation protocol and final validation report.

b. Inspection of Container/Closure System

A container–closure system that permits penetration of air, or microorganisms, is unsuitable for a sterile product. Any damaged or defective units should be detected and removed during inspection of the final sealed product. Safeguards should be implemented to strictly preclude shipment of product that may lack container–closure integrity and lead to nonsterility. Equipment suitability problems or incoming container or closure deficiencies have caused loss of container–closure system integrity. As examples, failure to detect vials fractured by faulty machinery or by mishandling of bulk finished stock has led to drug recalls. If damage that is not readily detected leads to loss of container–closure integrity, improved procedures should be rapidly implemented to prevent and detect such defects.

Functional defects in delivery devices (e.g., syringe device defects, delivery volume) can also result in product quality problems, and should be monitored by appropriate in-process testing.

Any defects or results outside the specifications established for in-process and final inspection should be investigated in accord with section 211.192.

E. Endotoxin Control

Section 211.63, "Equipment Design, Size, and Location," states that equipment "shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance." Section 211.65, "Equipment Construction," requires, in part, that equipment shall be constructed so that surfaces that contact the components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."

Section 211.67, "Equipment Cleaning and Maintenance," states that "equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements." Section 211.94 states that "drug product containers and closures shall be clean, and where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use." Section 211.167 states: "For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed."

Endotoxin contamination of an injectable product can be a result of poor cGMP controls. Certain patient populations (e.g., neonates), those receiving other injections concomitantly, or those administered a parenteral in atypically large volumes or doses, can be at greater risk for pyrogenic reaction than that anticipated by the established limits based on body weight of a normal healthy adult (Grandics, 2000; Lord and Levchuk, 1989; Current Practices in the Validation of Aseptic Processing, 2002). Such clinical concerns reinforce the need for appropriate cGMP controls to prevent generation of endotoxin. Drug product components, container/closures, equipment, and storage time limitations are among the concerns to address in establishing endotoxin control.

Adequate cleaning, drying, and storage of equipment provide for control of bioburden and prevent contribution of endotoxin load. Equipment should be designed such that it is easily assembled and disassembled, cleaned, sanitized, and sterilized. Endotoxin control should be exercised for all product contact surfaces both prior to and after sterile filtration. Endotoxin on equipment surfaces is inactivated by high-temperature dry heat, or removed from equipment surfaces by validated cleaning procedures. Some clean-in-place procedures employ initial rinses with appropriate high-purity water or a cleaning agent (e.g., acid, base, surfactant), or both, followed by final rinses with heated WFI. Equipment should be dried following cleaning. Sterilizing filters and moist-heat sterilization have not been shown to be effective in removing endotoxins. Processes that are designed to achieve depyrogenation should demonstrate a 3-log reduction of endotoxin.

F. Time Limitations

Section 211.111, "Time Limitations on Production," states: "When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product."

Time limits should be established for each phase of aseptic processing. Time limits should include, for example,

the period between the start of bulk product compounding and its filtration; filtration processes; product exposure while on the processing line; and storage of sterilized equipment, containers, and closures. Maintenance of in-process quality at different production phases should be supported by data. Bioburden and endotoxin load should be assessed when establishing time limits for stages such as the formulation processing stage. The total time for product filtration should be limited to an established maximum in order to prevent microorganisms from penetrating the filter. Such a time limit should also prevent a significant increase in upstream bioburden and endotoxin load. Sterilizing filters should generally be replaced following each manufactured lot. Because they can provide a substrate for microbial attachment, maximum use times for those filters used upstream for solution clarification or particle removal should also be established and justified.

G. Process Validation and Equipment Qualification

Section 211.113(b), "Control of Microbiological Contamination," states: "Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process." Section 211.63 is "Equipment, Design, Size, and Location"; section 211.65 is "Equipment Construction"; and section 211.67 is "Equipment Cleaning and Maintenance." Section 211.84(c)(3) states that "sterile equipment and aseptic sampling techniques shall be used when necessary."

The following sections primarily discuss routine qualification and validation study expectations. Change control procedures are only briefly addressed, but they are an important part of the quality systems. A change in equipment, process, test method, or systems requires evaluation through the written change control program and should trigger an evaluation of the need for revalidation or requalification.

1. Process Simulations

To ensure the sterility of products purporting to be sterile, both sterilization and aseptic filling or closing operations must be adequately validated (section 211.113). The goal of even the most effective sterilization processes can be defeated if the sterilized elements of a product (the drug, the container, and the closure) are brought together under conditions that contaminate those elements. Similarly, product sterility is compromised when the product elements are nonsterile at the time they are assembled.

Validation of an aseptic processing operation should include the use of a microbiological growth nutrient medium in place of product. This has been termed a *media fill* or *process simulation.* The nutrient medium is exposed to product contact surfaces of equipment, container systems, critical environments, and process manipulations to closely simulate the same exposure that the product itself will undergo. The sealed containers filled with the media are then incubated to detect microbial contamination. The results are interpreted to determine the potential for any given unit of drug product to become contaminated during actual operations (e.g., start-up, sterile ingredient additions, aseptic connections, filling, and closing). Environmental monitoring data is integral to the validation of an aseptic processing operation.

a. Study Design

A validation protocol should detail the overall strategy, testing requirements, and acceptance criteria for the media fill. Media-fill studies should simulate aseptic manufacturing operations as closely as possible, incorporating a worst-case approach. A media-fill study should address applicable issues such as

- factors associated with the longest permitted run on the processing line;
- ability to produce sterile units when environmental conditions impart a greater risk to the product;
- number and type of normal interventions, atypical interventions, unexpected events (e.g., maintenance), stoppages, equipment adjustments, or transfers;
- lyophilization, when applicable;
- aseptic assembly of equipment (e.g., at start-up, during processing);
- number of personnel and their activities;
- number of aseptic additions (e.g., charging containers and closures as well as sterile ingredients);
- shift changes, breaks, and gown changes (when applicable);
- number and type of aseptic equipment disconnections or connections;
- aseptic sample collections;
- line speed and configurations;
- manual weight checks;
- operator fatigue;
- container/closure systems (e.g., sizes, type, compatibility with equipment);
- temperature and humidity set point extremes; and
- specific provisions of aseptic processing–related SOPs (conditions permitted before line clearance is mandated, etc.).

A written batch record documenting conditions and activity simulated should be prepared for each media fill run. The same vigilance should be observed in both media fill and routine production runs. Media fills cannot be used to validate an unacceptable practice.

b. Frequency and Number of Runs

When a processing line is initially validated, separate media fills should be repeated enough times to ensure that results are consistent and meaningful. This approach is important because a single run can be inconclusive, whereas multiple runs with divergent results signal a process that is not in control. A minimum of three consecutive separate successful runs should be performed during initial line qualification. Subsequently, routine semiannual revalidation runs should be conducted for each shift and processing line to evaluate the state of control of the aseptic process. All personnel who enter the aseptic processing area, including technicians and maintenance personnel, should participate in a media fill at least once a year.

Each change to a product or line change should be evaluated by a written change control system. Any changes or events that appear to affect the ability of the aseptic process to exclude contamination from the sterilized product should be assessed through additional media fills. For example, facility and equipment modification, line configuration change, significant changes in personnel, anomalies in environmental testing results, container/closure system changes, or end-product sterility testing showing contaminated products may be cause for revalidation of the system.

When a media fill's data indicate that the process may not be in control, a comprehensive documented investigation should be conducted to determine the origin of the contamination and the scope of the problem. Once corrections are instituted, multiple repeat process simulation runs should be performed to confirm that deficiencies in practices and

procedures have been corrected and the process has returned to a state of control. However, when an investigation fails to reach well-supported, substantive conclusions as to the cause of the media fill failure, three consecutive successful runs and increased scrutiny (i.e., extra supervision, monitoring) of the production process should be implemented.

c. Size and Duration of Runs

The duration of aseptic processing operations is a major consideration in determining the size of the media fill run. Although the most accurate simulation model would be the full batch size and duration because it most closely simulates the actual production run, other appropriate models can be justified. In any study protocol, the duration of the run and the overall study design should adequately mimic worst-case operating conditions and cover all manipulations that are performed in the actual processing operation. Adequate batch sizes are needed to simulate commercial production conditions and accurately assess the potential for commercial batch contamination. The number of units filled should be sufficient to reflect the effects of potential operator fatigue, as well as the maximum number of interventions and stoppages. The run should be large enough to accurately simulate production conditions and sensitive enough to detect a low incidence of contaminated units. For batches produced over multiple shifts or yielding an unusually large number of units, the media fill protocol should adequately encompass conditions and any potential risks associated with the larger operation. Although conventional manufacturing lines are highly automated, often operate at relatively high speeds, and are designed to limit operator intervention, some processes include considerable operator involvement. When aseptic processing employs manual filling or closing, or extensive manual manipulations, the duration of the process simulation should generally be no less than the length of the actual manufacturing process in order to best simulate operator fatigue.

For simulation of lyophilization operations, unsealed containers should be exposed to pressurization and partial evacuation of the chamber in a manner that is representative of process stresses. Vials should not be frozen, as this may inhibit the growth of microorganisms.

d. Line Speed

The media fill program should adequately address the range of line speeds (e.g., by bracketing all vial sizes and fill volumes) employed during production. In some cases, more than one line speed should be evaluated in the course of a study.

Each individual media fill run should evaluate a single worst-case line speed, and the speed chosen for each batch during a study should be justified. For example, use of high line speed is justified for manufacturing processes characterized by frequent interventions or a significant degree of manual manipulation. Use of slow line speed is justified for manufacturing processes characterized by prolonged exposure of sterile components in the aseptic area.

e. Environmental Conditions

Media fills should be conducted under environmental conditions that simulate normal as well as worst-case conditions of production. An inaccurate assessment (making the process appear cleaner than it actually is) can result from conducting a media fill under extraordinary air particulate and microbial quality, or under production controls and precautions taken in preparation for the media fill. To the extent SOPs permit stressful conditions, it is crucial that media fills should include rigorous challenges in order to support the validity of these studies.

f. Media

In general, a microbiological growth medium such as soybean casein digest medium should be used. Use of anaerobic growth media (e.g., fluid thioglycollate medium) is appropriate in special circumstances. Media selected should be demonstrated to promote growth of USP Media units should be incubated for a sufficient time (a period of not less than 14 days) at a temperature adequate to enhance detection of organisms that can otherwise be difficult to culture. Each media-filled unit should be examined for contamination by personnel with appropriate education, training, and experience in microbiological techniques. There should be direct quality control unit oversight throughout any such examination. Clear containers with otherwise identical physical properties should be used as a substitute for amber or other opaque containers to allow visual detection of microbial growth.

When a final product inspection is performed of units immediately following the media fill run, all integral units should proceed to incubation. Units found to have defects not related to integrity (e.g., cosmetic defect) should be incubated; units that lack integrity should be rejected. (Separate incubation of certain categories of rejected units may nonetheless provide valuable information with respect to contamination that may arise from container/closure integrity deficiencies.) Erroneously rejected units should be returned promptly for incubation with the media fill lot.

After incubation is underway, any unit found to be damaged should be included in the data for the media fill batch, because the incubation of the units simulates release to the market. Any decision to exclude such incubated units (i.e., nonintegral) from the final batch tally should be fully justified, and the deviation explained in the media fill report. If a correlation emerges between difficult-to-detect damage and microbial contamination, a thorough investigation should be conducted to determine its cause.

Written procedures regarding aseptic interventions should be clear and specific (e.g., intervention type, quantity of units removed), providing for consistent production practices and assessment of these practices during media fills. If written procedures and batch documentation are adequate, these intervention units do not need to be incubated during media fills. Where procedures lack specificity, there would be insufficient justification for exclusion of units removed during an intervention from incubation. As an example, if a production procedure requires removal of 10 units after an intervention at the stoppering station infeed, batch records (i.e., for production and media fills) should clearly document conformance with this procedure. In no case should more units be removed during a media fill intervention than would be cleared during a production run. The ability of a media fill run to detect potential contamination from a given simulated activity should not be compromised by a large-scale line clearance, which can result in removal of a positive unit caused by an unrelated event or intervention. If unavoidable, appropriate study provisions should be made to compensate in such instances.

Appropriate criteria should be established for yield and accountability. Batch record reconciliation documentation should include an accurate accounting and description of units rejected from a batch.

g. Interpretation of Test Results

The process simulation run should be observed, and contaminated units should be reconcilable with the approximate time and the activity being simulated during the media fill. Videotaping of a media fill has been found to be useful in identifying personnel practices that could negatively impact on the aseptic process.

Any contaminated unit should be considered as objectionable and fully investigated. The microorganisms should be identified to species level. In the case of a media fill failure, a comprehensive investigation should be conducted, surveying all possible causes of the contamination. The impact on commercial drugs produced on the line since the last successful media fill should also be assessed.

Whenever contamination exists in a media fill batch, it should be considered as indicative of a potential production problem. The use of statistics has limitations for media fill evaluation in that the number of contaminated units should not be expected to increase in a directly proportional manner with the number of vials in the media fill run. Test results should show, with a high degree of confidence, that the units produced by an aseptic processing operation are sterile. Modern aseptic processing operations in suitably designed facilities have demonstrated a capability of meeting contamination levels approaching zero (Leahy and Sullivan, 1978) and should normally yield no media fill contamination. For example, a single contaminated unit in a 10,000-unit media fill batch should be fully investigated, but is normally not considered on its own to be sufficient cause for line revalidation. However, intermittent incidents at this media fill contamination level can be indicative of a persistent low-level contamination problem. Accordingly, any pattern of media fill batches with such low-level contamination should be comprehensively investigated and would be cause for line revalidation.

The use of media fill acceptance criteria allowing infrequent contamination does not mean that a distributed lot of drug product purporting to be sterile may contain a nonsterile unit. The purpose of an aseptic process is to prevent any contamination. A manufacturer is fully liable for the shipment of any nonsterile unit, an act that is prohibited under the FD&C Act. FDA also recognizes that there might be some scientific and technical limitations on how precisely and accurately validation can characterize a system of controls intended to exclude contamination.

As with any validation batch, it is important to note that "invalidation" of a media fill run should be a rare occurrence. A media fill lot should be aborted only under circumstances in which written procedures require commercial lots to be equally handled. Supporting documentation and justification should be provided in such cases.

2. Filtration Efficacy

Filtration is a common method of sterilizing drug product solutions. An appropriate sterilizing grade filter is one that reproducibly removes all microorganisms from the process stream, producing a sterile effluent. Such filters usually have a rated porosity of 0.2 mm or smaller. Whatever filter or combination of filters is used, validation should include microbiological challenges to simulate worst-case production conditions regarding the size of microorganisms in the material to be filtered and integrity test results of the filters used for the study. The microorganisms should be small enough to both challenge the nominal porosity of the filter and simulate the smallest microorganism that may occur in production. The microorganism *Brevundimonas diminuta* (ATCC 19146) when properly grown, harvested, and used can be satisfactory in this regard because it is one of the smallest bacteria (0.3-mm mean diameter). Bioburden of unsterilized bulk solutions should be determined in order to trend the characteristics of potentially contaminating organisms. In certain cases, when justified as equivalent or better than use of *B. diminuta*, it may be appropriate to conduct bacterial retention studies with a bioburden isolate. The number of microorganisms in the challenge is important because a filter can contain a number of pores larger than the nominal rating that have potential to allow passage of microorganisms (Pall et al, 1980). The probability of such passage is considered to increase as the number of organisms (bioburden) in the material to be filtered increases (Sterilizing Filtration of Liquids, 1998). A challenge concentration of at least 107 organisms/cm^2 effective filtration area of *B. diminuta* is generally used. Actual influent bioburden of a commercial lot should not include microorganisms of a size or concentration that would present a challenge beyond that considered by the validation study.

Direct inoculation into the drug formulation provides an assessment of the effect of drug product on the filter matrix and on the challenge organism. However, directly inoculating *B. diminuta* into products with inherent bactericidal activity or into oil-based formulations can lead to erroneous conclusions. When sufficiently justified, the effects of the product formulation on the membrane's integrity can be assessed by an appropriate alternative method. For example, the drug product could be filtered in a manner in which the worst-case combination of process specifications and conditions is simulated. This step could be followed by filtration of the challenge organism for a significant period of time, under the same conditions, using an appropriately modified product (e.g., lacking an antimicrobial preservative or other antimicrobial component) as the vehicle. Any divergence from a simulation using the actual product and conditions of processing should be justified. Factors that can affect filter performance normally include viscosity of the material to be filtered, pH, compatibility of the material or formulation components with the filter itself, pressures, flow rates, maximum use time, temperature, osmolality, and the effects of hydraulic shock.

When designing the validation protocol, it is important to address the effect of the extremes of processing factors on the filter capability to produce sterile effluent. Filter validation should be conducted by using the worst-case conditions, such as maximum filter use time and pressure (Pall et al, 1980; Parenteral Drug Association, 1998; Commentary on the Sterility Tests and Sterilization Chapters of the U.S. Pharmacopoeia, 1980). Filter validation experiments, including microbial challenges, need not be conducted in the actual manufacturing areas. However, it is essential that laboratory experiments simulate actual production conditions. The specific type of filter used in commercial production should be evaluated in filter validation studies. When the more complex filter validation tests go beyond the capabilities of the filter user, tests are often conducted by outside laboratories or by filter manufacturers. However, it is the responsibility of the filter user to review the validation data on the efficacy of the filter in producing a sterile effluent. The data should be applicable to the user's products and conditions of use because filter performance may differ significantly for various conditions and products.

After a filtration process is properly validated for a given product, process, and filter, it is important to ensure that identical filter replacements (membrane or cartridge) used in production runs perform in the same manner. Sterilizing

filters should be routinely discarded after processing a single batch. Normally, integrity testing of the filter is performed after the filter unit is assembled and sterilized prior to use. It is important that the integrity testing be conducted after filtration in order to detect any filter leaks or perforations that might have occurred during the filtration. Forward flow and bubble point tests, when appropriately employed, are two acceptable integrity tests. A production filter's integrity test specification should be consistent with data generated during filtration efficacy studies.

3. Sterilization of Equipment and Containers/Closures

To maintain sterility, equipment surfaces that contact sterilized drug product or sterilized container/closure surfaces must be sterile so as not to alter purity of the drug (sections 211.63 and 211.113). Surfaces in the vicinity of the sterile product or not directly in contact with the product should also be rendered sterile where reasonable contamination potential exists. It is as important in aseptic processing to properly validate the processes used to sterilize such critical equipment as it is to validate processes used to sterilize the drug product and its container/closure. Moist-heat and dry-heat sterilization are most widely used as the primary processes discussed in this document. It should be noted that many of the heat-sterilization principles discussed in this document are also applicable to other sterilization methods.

Sterility of aseptic processing equipment (e.g., stopper hoppers) should be maintained by batch-by-batch sterilization. Following sterilization of equipment, containers, or closures, any transportation or assembly needs to be performed in a manner in which its sterile state is protected and sustained, with adherence to strict aseptic methods.

a. Sterilizer Qualification and Validation

Validation studies should be conducted demonstrating the efficacy of the sterilization cycle. Requalification studies should also be performed on a periodic basis. For both the validation studies and routine production, use of a specified load configuration should be documented in the batch records.

Unevacuated air's insulating properties prevent moist heat from penetrating or heating up materials, and achieving the lethality associated with saturated steam. Consequently, there is a far slower thermal energy transfer and rate of kill from the dry heat in insulated locations in the load. It is important to remove all of the air from the autoclave chamber during the sterilization cycle. Special attention should be given to the nature or type of the materials to be sterilized and the placement of BI within the sterilization load. *D*-value of the BI can vary widely depending on the material (e.g., glass vs. Teflon) to be sterilized. Difficult-to-reach locations within the sterilizer load and specific materials should be an important part of the evaluation of sterilization cycle efficacy. Thereafter, requalification or revalidation should continue to focus on load areas identified as the most difficult to penetrate or heat [e.g., worst-case locations of tightly wrapped or densely packed supplies (Clinical sepsis and death in a newborn nursery associated with contaminated medications, 1998), securely fastened load articles, lengthy tubing, the sterile filter apparatus, hydrophobic filters, stopper load]. The formal program providing for regular (i.e., semiannual, annual) revalidation should consider the age of the sterilizer and its past performance. Change control procedures should adequately address issues such as a load configuration change or a modification of the sterilizer.

i. *Qualification: Empty Chamber*
   Temperature distribution studies evaluate numerous locations throughout an empty sterilizing unit (e.g., steam autoclave, dry-heat oven) or equipment train (e.g., large tanks, immobile piping). It is important that these studies assess temperature uniformity at various locations throughout the sterilizer to identify potential "cold spots" where there can be insufficient heat to attain sterility. These heat uniformity or "temperature mapping" studies should be conducted by placing calibrated temperature measurement devices in numerous locations throughout the chamber.
ii. *Validation: Loaded Chamber*
   Heat penetration studies should be performed using the established sterilizer load(s). Validation of the sterilization process with a loaded chamber demonstrates the effects of loading on thermal input to the items being sterilized, and may identify cold spots where there is insufficient heat to attain sterility. The placement of BIs at numerous positions in the load, including the most difficult-to-sterilize places, is a direct means of demonstrating the efficacy of any sterilization procedure.

In general, the thermocouple is placed adjacent to the BI so as to assess the correlation between microbial lethality and thermal input. Sterilization can be validated by a partial or half-cycle approach. In some cases, the bioburden-based cycle is used for sterilization validation. For further information on validation by moist-heat sterilization, refer to FDA guidance "Guideline for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" (November 1994).

Sterilization cycle specifications are based on the delivery of adequate thermal input to the slowest-to-heat locations. When determining which articles are most difficult to sterilize, special attention should be given to the sterilization of filters. For example, some filter installations in piping cause a significant pressure differential across the filter, resulting in a significant temperature drop on the downstream side. BIs should be placed at appropriate downstream locations of this equipment to determine whether the drop in temperature affects the thermal input at these sites. Established load configuration should be part of batch record documentation. A sterility assurance level of 10^6 or better should be demonstrated for the sterilization process.

b. Equipment Controls and Instrument

Calibration For both validation and routine process control, the reliability of the data generated by sterilization cycle monitoring devices should be considered to be of utmost importance. Devices that measure cycle parameters should be routinely calibrated. Written procedures should be established to ensure that these devices are maintained in a calibrated state. Temperature monitoring devices for heat sterilization should be calibrated at suitable intervals, as well as before and after validation runs. Devices used to monitor dwell time in the sterilizer should be periodically calibrated. The microbial count and *D*-value of a BI should be confirmed before a validation study. Instruments used to determine the purity of steam should be calibrated. For dry-heat depyrogenation tunnels, devices (e.g., sensors and transmitters) used to measure belt speed should be routinely calibrated.

Sterilizing equipment should be properly maintained to allow for consistently satisfactory function. Evaluation of sterilizer performance attributes such as equilibrium

("come up") time studies should be helpful to assess whether the unit continues to operate properly.

H. Laboratory Controls

Section 211.160, "General Requirements," states: "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." Sections 211.165 and 211.194 require that validation of test methods be established and documented. Section 211.22(c) states that "the quality control unit shall have the responsibility for approving or rejecting all procedures and specifications impacting on the identity, strength, quality, and purity of the drug product." Section 211.42 requires, for aseptic processes, the establishment of a "system for monitoring environmental conditions." Section 211.56 requires "written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities." The "written procedures shall be designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, or drug products and shall be followed." Section 211.113(b) requires that "appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed." Section 211.192 states that "all drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved, written procedures before a batch is released or distributed."

1. Environmental Monitoring

a. General Written Program

In aseptic processing, one of the most important laboratory controls is the establishment of an environmental monitoring program. This monitoring provides meaningful information on the quality of the aseptic processing environment when a given batch is being manufactured as well as environmental trends of the manufacturing area. An adequate program identifies potential routes of contamination, allowing for implementation of corrections before product contamination occurs (sections 211.42 and 211.113).

Evaluating the quality of air and surfaces in the clean-room environment should start with a well-defined written program and validated methods. The monitoring program should cover all production shifts and include air, floors, walls, and equipment surfaces, including the critical surfaces in contact with product and container/closures. Written procedures should include a list of locations to be sampled. Sample timing, frequency, and location should be carefully selected based on their relationship to the operation performed. Samples should be taken throughout the aseptic processing facility (e.g., aseptic corridors, gowning rooms) by appropriate, scientifically sound sampling procedures, standards, and test limits.

Locations posing the most microbiological risk to the product are a critical part of the program. It is especially important to monitor the microbiological quality of the aseptic processing clean zone to determine whether aseptic conditions are maintained during filling/closing activities. Critical surfaces which contact sterile product should be sterile. Critical surface sampling should be performed at the conclusion of the aseptic processing operation to avoid direct contact with sterile surfaces during processing. Air and surface samples should be taken at the actual working site and at locations where significant activity or product exposure occurs during production.

Environmental monitoring methods do not always recover microorganisms present in the sampled area. In particular, low-level contamination can be particularly difficult to detect. Because of the likelihood of false negatives, consecutive growth results are only one type of adverse trend. Increased incidence of contamination over a given period in comparison to that normally detected is an equally significant trend to be tracked.

All environmental monitoring locations should be described in SOPs with sufficient detail to allow for reproducible sampling of a given location surveyed. Written SOPs should also address areas such as frequency of sampling, when the samples are taken (i.e., during or at the conclusion of operations), duration of sampling, sample size (e.g., surface area, air volume), specific sampling equipment and techniques, alert and action limits, and appropriate response to deviations from alert or action limits.

b. Establishing Limits and a Trending Program

Microbiological monitoring limits should be established based on the relationship of the sampled location to the operation. The limits should be based on the need to maintain adequate microbiological control throughout the entire sterile manufacturing facility. One should also consider environmental monitoring data from historical databases, media fills, clean-room qualification, and sanitization procedure studies in developing monitoring limits. Microbiological environmental monitoring should include both alert and action limits. Each individual sample result should be evaluated for its significance by comparing to the alert or action limits. Averaging of results can mask unacceptable localized conditions. A result at the alert limit urges attention to the approaching action conditions. A result at the action level should prompt a more thorough investigation. Written procedures should be established, detailing data review frequency, identification of contaminants, and actions to be taken. The quality control unit should provide routine oversight of near-term (e.g., daily, weekly, monthly, or quarterly) and long-term trends in environmental and personnel monitoring data. Trend reports should include data generated by location, shift, lot, room, operator, or other search parameters. The quality control unit is responsible for producing specialized data reports (e.g., a search on a particular atypical isolate over a year period) in order to investigate results beyond established limits and identify any appropriate follow-up actions. In addition to microbial counts beyond alert and action limits, the presence of any atypical microorganisms in the clean-room environment should be investigated, with any appropriate corrective action promptly implemented. Written procedures should define the system whereby the most responsible managers are regularly informed and updated on trends and investigations.

c. Sanitization Efficacy

The suitability, efficacy, and limitations of sanitization agents should be assessed with their implementation for use in clean areas. The effectiveness of these sanitization procedures should be measured by their ability to ensure that potential contaminants are adequately removed from surfaces (i.e., via obtaining samples before and after sanitization). On preparation, disinfectants should be rendered sterile and used for a

limited time, as specified by written procedures. Disinfectants should retain efficacy against the normal microbial flora and be effective against spore-forming microorganisms. Many common sanitizers are ineffective against spores; for example, 70% isopropyl alcohol is not effective against spores of *Bacillus* species. A sporicidal agent should be used regularly to prevent contamination of the manufacturing environment with otherwise difficult to eradicate spore-forming bacteria or fungi. After the initial assessment of sanitization procedures, ongoing sanitization efficacy should be frequently monitored through specific provisions in the environmental monitoring program, with a defined course of action in the event samples are found to exceed limits.

d. Monitoring Methods

The following are some acceptable methods of monitoring the microbiological quality of the environment.

i. *Surface Monitoring*
Environmental monitoring should include testing of various surfaces for microbiological quality. For example, product contact surfaces, floors, walls, ceilings, and equipment should be tested on a regular basis. Routinely used for such tests are touch plates, swabs, and contact plates. Other surfaces in controlled areas should be tested to show the adequacy of cleaning and sanitizing procedures.

ii. *Active Air Monitoring*
The method of assessing the microbial quality of air should involve the use of active devices such as slit to agar samplers, those using liquid impingement and membrane filtration, or centrifugal samplers. Each device has certain advantages and disadvantages, although all allow a quantitative testing of the number of organisms per volume of air sampled. The use of such devices in aseptic areas is considered an essential part of evaluating the environment during each production shift at carefully chosen critical locations. Manufacturers should be aware of a device's air-monitoring capabilities and should determine suitability of any new or current devices with respect to sensitivity and limit of quantification.

iii. *Passive Air Monitoring (Settling Plates)*
Another method is the use of passive air samplers such as settling plates (petri dishes containing nutrient growth medium exposed to the environment). These settling plates lack value as quantitative air monitors because only microorganisms that settle onto the agar surface will be detected. Their value as qualitative indicators in critical areas is enhanced by positioning plates in locations that pose the greatest risk of product contamination. As part of methods validation, the quality control laboratory should evaluate what media exposure conditions optimize recovery of low levels of environmental isolates. Exposure conditions should preclude desiccation (e.g., caused by lengthy sampling periods or high airflows), which inhibits recovery of microorganisms. The data generated by passive air sampling can be useful when considered in combination with results from other types of air samples.

2. Microbiological Media and Identification

The environmental monitoring program should include routine characterization of recovered microorganisms. Monitoring of critical and immediately surrounding areas as well as personnel should include routine identification of microorganisms to the species (or, where appropriate, genus) level. In some cases, environmental trending data have revealed migration of microorganisms into the aseptic processing room from either uncontrolled or lesser-controlled areas. To detect such trends, an adequate program of differentiating microorganisms in lesser-controlled environments (e.g., Class 100,000) should be in place. At minimum, the program should require species (or, where appropriate, genus) identification of microorganisms in ancillary environments at frequent intervals to establish a valid, current database of contaminants present in the facility during processing (and to demonstrate that cleaning and sanitization procedures continue to be effective). Environmental isolates often correlate with the contaminants found in a media fill or product sterility testing failure, and the overall environmental picture provides valuable information for the associated investigation.

The goal of microbiological monitoring is to reproducibly detect microorganisms for purposes of monitoring the state of environmental control. Consistent methods will yield a database that allows for sound data comparisons and interpretations. The microbiological culture media used in environmental monitoring should be validated as capable of detecting fungi (i.e., yeasts and molds) as well as bacteria, and incubated at appropriate conditions of time and temperature. Total aerobic bacterial count can be obtained by incubating at 30°C to 35°C for 48 to 72 hours. Total combined yeast and mold count is generally obtained by incubating at 20°C to 25°C for 5 to 7 days.

Incoming lots of environmental monitoring media should include positive and negative controls. Growth promotion testing should be performed on all lots of prepared media. Where appropriate, inactivating agents should be used to prevent inhibition of growth by clean-room disinfectants.

a. Prefiltration Bioburden

For any parenteral manufacturing process, prefiltration bioburden should be minimal. In addition to increasing the challenge to the sterilizing filter, high bioburden can contribute endotoxin or other impurities to the drug formulation. An in-process limit for bioburden level for each formulated product (generally sampled immediately preceding sterile filtration) should be established.

b. Particulate Monitoring

Routine particle monitoring is useful in detecting significant deviations in air cleanliness from qualified processing norms (e.g., clean-area classification). A result outside the established specifications at a given location should be investigated consistent with the severity of the "excursion." Appropriate corrective action should be implemented to prevent future deviations.

I. Sterility Testing

Section 211.167, "Special Testing Requirements," states: "For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed." Section 211.165 states that "for each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product . . . prior to release." Section 211.165(e) requires methods for testing to be validated as reliable and reproducible (e.g., bacteriostasis/fungistasis, method robustness, etc.), stating: "The accuracy, sensitivity, specificity, and reproducibility

of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with section 211.194(a)(2)." Section 211.110 requires, in part, that sampling procedures be established in order to ensure batch uniformity. The "control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product." Section 211.160 requires the establishment of sound and appropriate sampling plans representative of the batch.

Section 210 defines "representative sample" as one based on rational criteria that provide an "accurate portrayal" of the material or batch being sampled. Section 211.180 requires a review of "at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures." Investigations conducted under section 211.192 for each drug product are required to be addressed within this annual review.

Certain aspects of sterility testing are of particular importance, including controlling the testing environment, understanding the test limitations, and the investigating manufacturing systems following a positive test. The testing laboratory environment should employ facilities and controls comparable to those used for filling or closing operations. Poor or deficient sterility test facilities or controls can result in a high rate of test failures. If production facilities and controls are significantly better than those for sterility testing, there is the danger of attributing the cause of a positive sterility test result to the faulty laboratory even when the product tested could have, in fact, been nonsterile. Therefore, some manufacturing deficiency may go undetected. The use of isolators to perform sterility testing is a well-established means to minimize false positives.

1. Choice of Methods

Sterility testing methodologies are required to be accurate and reproducible, in accord with sections 211.194 and 211.165. The methodology selected should present the lowest potential for yielding a false positive. The USP specifies membrane filtration as the method of choice, when feasible. As a part of methods validation, appropriate bacteriostasis or fungistasis testing should be conducted. Such testing should demonstrate reproducibility of the method in recovering each of a panel of representative microorganisms. Study documentation should include evaluation of whether microbial recovery from inoculated controls and product samples is comparable throughout the incubation period. If growth is inhibited, modifications (e.g., increased dilution, additional membrane filter washes, addition of inactivating agents) in the methodology should be implemented to optimize recovery. Ultimately, methods validation studies should demonstrate that the methodology does not provide an opportunity for false negatives.

2. Media

It is essential that the media used to perform sterility testing be rendered sterile and demonstrated as growth promoting.

3. Personnel

Personnel performing sterility testing should be qualified and trained for the task. A written program should be in place to regularly update training of personnel and confirm acceptable sterility testing practices.

4. Sampling and Incubation

Sterility tests are limited in their ability to detect low levels of contamination. For example, statistical evaluations indicate that the USP sterility test sampling plan has been described by USP as "only enabling the detection of contamination in a lot in which 10% of the units are contaminated about nine times out of ten in making the test." (Price, 1998) To further illustrate, if a 10,000-unit lot with a 0.1% contamination level is sterility tested using 20 units, there is a 98% chance that the batch will pass the test. This limited sensitivity makes it necessary to ensure that for batch release purposes, an appropriate number of units are tested and that the samples uniformly represent the following:

- *Entire batch*. Samples should be taken at the beginning, middle, and end of the aseptic processing operation.
- *Batch processing circumstances*. Samples should be taken in conjunction with processing interventions or excursions. Because of the limited sensitivity of the test, any positive result is considered a serious cGMP issue and should be thoroughly investigated.

5. Investigation of Sterility Positives

Care should be taken in the performance of the sterility test to preclude any activity that allows for possible sample contamination. When microbial growth is observed, the lot should be considered to be nonsterile. It is inappropriate to attribute a positive result to laboratory error on the basis of a retest that exhibits no growth. [Underscoring this regulatory standard, USP XXV, Section <71>, states that an initial positive test is invalid only in an instance in which "microbial growth can be without a doubt ascribed to" laboratory error (as described in the monograph).]

The evaluation of a positive sterility test result should include an investigation to determine whether the growth observed in the test arose from product contamination or from laboratory error. Although it is recognized that such a determination may not be reached with absolute certainty, it is usually possible to acquire persuasive evidence showing that causative laboratory error is absent. When available evidence is inconclusive, batches should be rejected as not conforming to sterility requirements.

It would be difficult to support invalidation of a positive sterility test. Only if conclusive and documented evidence clearly shows that the contamination occurred as part of testing should a new test be performed.

After considering all relevant factors concerning the manufacture of the product and testing of the samples, the comprehensive written investigation should include specific conclusions and identify corrective actions. The investigation's persuasive evidence of the origin of the contamination should be based on at least the following factors.

a. Identification (Speciation) of the Organism in the Sterility Test

Identification of the sterility test isolate(s) should be to the species level. Microbiological monitoring data should be reviewed to determine whether the organism is also found in laboratory and production environments, personnel, or product bioburden.

b. Record of Laboratory Tests and Deviations

Review of trends in laboratory findings can help to eliminate or implicate the laboratory as the source of contamination. If the organism is seldom found in the laboratory environment, then product contamination is likely. If the organism is

found in laboratory and production environments, it can indicate product contamination. Proper handling of deviations is an essential aspect of laboratory control. When a deviation occurs during sterility testing, it should be documented, investigated, and remedied. If any deviation is considered to have compromised the integrity of the sterility test, the test should be invalidated immediately without incubation.

Deviation and sterility test positive trends should be evaluated periodically (e.g., quarterly, annually) to provide an overview of operations. A sterility positive result can be viewed as indicative of production or laboratory problems and should be investigated globally because such problems often can extend beyond a single batch.

To more accurately monitor potential contamination sources, it is useful to keep separate trends by product, container type, filling line, and personnel. If the degree of sterility test sample manipulation is similar for a terminally sterilized product and an aseptically processed product, a higher rate of initial sterility failures for the latter should be taken as indicative of aseptic processing production problems.

Microbial monitoring of the laboratory environment and personnel over time can also reveal trends that are informative. Upward trends in the microbial load in the laboratory should be promptly investigated as to cause, and corrected. In some instances, such trends can appear to be more indicative of laboratory error as a possible source of a sterility test failure.

A good error record can help eliminate a laboratory as a source of contamination because chances are higher that the contamination arose from production. However, the converse is not true. Specifically, if the laboratory has a poor track record, it should not be automatically assumed that the contamination is more attributable to an error in the laboratory and consequently overlook a genuine production problem. Accordingly, all sterility positives should be thoroughly investigated.

c. Monitoring of Production Area Environment
Of particular importance is trend analysis of microorganisms in the critical and immediately adjacent area. Trends are an important tool in investigating the product as the possible source of a sterility failure. Consideration of environmental microbial loads should not be limited to results of monitoring the production environment for the lot, day, or shift associated with the suspect lot. For example, results showing little or no recovery of microorganisms can be misleading, especially when preceded or followed by a finding of an adverse trend or atypically high microbial counts. It is therefore important to look at both short- and long-term trend analysis.

d. Monitoring of Personnel
Daily personnel monitoring data and associated trends should be reviewed and can in some cases strongly indicate a route of contamination. The adequacy of personnel practices and training should also be considered.

e. Product Presterilization Bioburden
Trends in product bioburden should be reviewed (counts and identity). Adverse bioburden trends occurring during the time period of the test failure should be considered in the investigation.

f. Production Record Review
Complete batch and production control records should be reviewed to detect any signs of failures or anomalies that could have a bearing on product sterility. For example, the investigation should evaluate batch and trending data that indicate whether utility or support systems (e.g., HVAC, WFI) are functioning properly. Records of air quality monitoring for filling lines should show a time at which there was improper air balance, an unusual high particulate count, etc.

g. Manufacturing History
The manufacturing history of the product or similar products should be reviewed as part of the investigation. Past deviations, problems, or changes (e.g., process, components, equipment) are among the factors that can provide an indication of the origin of the problem.

J. Batch Record Review: Process Control Documentation

Sections 211.100, 211.186, and 211.188 address documentation of production and control of a batch, including recording various production and process control activities at the time of performance. Section 211.100(b) requires a documented record and evaluation of any deviation from written procedures. Section 211.192 states

> All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and follow-up.

Maintaining process and environmental control is a daily necessity for an aseptic processing operation. The requirement for review of all batch records and data for conformance with written procedures, operating parameters, and product specifications prior to arriving at the final release decision for an aseptically processed batch calls for an overall review of process and system performance for that given cycle of manufacture. All in-process data must be included with the batch record documentation per Section 211.188. Review of environmental monitoring data as well as other data relating to the acceptability of output from support systems (e.g., HEPA/HVAC, WFI, steam generator) and proper functioning of equipment (e.g., batch alarms report, integrity of various filters), should be viewed as essential elements of the batch release decision.

While interventions or stoppages are normally recorded in the batch record, the manner of documenting these occurrences varies. In particular, line stoppages and any unplanned interventions should be sufficiently documented in batch records with the associated time and duration of the event. In general, there is a correlation between product (or container/closure) dwell time in the aseptic processing zone and the probability of contamination. Sterility failures can be attributed to atypical or extensive interventions that have occurred as a response to an undesirable event during the aseptic process. Written procedures describing the need for line clearances in the event of certain interventions, such as machine adjustments and any repairs, should be established. Such interventions should be documented with more detail than minor events. Interventions that result in substantial activity near exposed product or container/closures or that last beyond a reasonable exposure time should, where appropriate, result in a local or full line clearance. Any disruption in

power supply, however momentary, during aseptic processing is a manufacturing deviation and must be included in batch records (sections 211.100 and 211.192).

IV. PROCESSING PRIOR TO FILLING AND SEALING OPERATIONS

The following aseptic processing activities that take place prior to the filling and sealing of the finished drug product require special consideration.

A. Aseptic Processing from Early Manufacturing Steps

Because of their nature, some products undergo aseptic processing at some or all manufacturing steps preceding the final product closing step. There is a point in the process after which a product can no longer be rendered sterile by filtration, and the product is handled aseptically in all subsequent steps. Some products are formulated aseptically because the formulated product cannot be sterilized by filtration. For example, products containing aluminum adjuvant are formulated aseptically because once they are alum-adsorbed, they cannot be sterile filtered. When a product is processed aseptically from early steps, the product and all components or other additions are rendered sterile prior to entering the manufacturing process. It is critical that all transfers, transports, and storage stages be carefully controlled at each step of the process to maintain sterility of the product.

Procedures that expose the product or product contact equipment surfaces to the environment, such as aseptic connections, should be performed under unidirectional airflow in a Class 100 environment. The environment of the room surrounding the Class 100 environment should be Class 10,000 or better. Microbiological and particulate monitoring should be performed during operations. Microbial surface monitoring should be performed at the end of operations but prior to cleaning. Personnel monitoring should be performed in association with operations.

Process simulation studies should be designed to incorporate all conditions, product manipulations, and interventions that could impact on the sterility of the product during manufacturing. The process simulation, from early process steps, should demonstrate that controls over the process are adequate to protect the product during manufacturing. These studies should incorporate all product manipulations, additions, and procedures involving exposure of product contact surfaces to the environment. The studies should include worst-case conditions such as maximum duration of open operations and maximum number of participating operators. However, process simulations do not need to mimic total manufacturing time if the manipulations that occur during manufacturing are adequately represented.

It is also important that process simulations incorporate storage of product or transport to other manufacturing areas. For instance, there should be assurance of bulk vessel integrity for specified holding times. The transport of bulk tanks or other containers should be simulated as part of the media fill. Process simulation studies for the formulation stage should be performed at least twice per year.

B. Aseptic Processing of Cell-Based Therapy Products (or of Products Intended for Use as Cell-Based Therapies)

Cell-based therapy products represent a subset of the products for which aseptic manipulations are used throughout the process. Where possible, closed systems should be used during production of this type of products. Cell-based therapy products often have short processing times at each manufacturing stage, even for the final product. Often, it is appropriate for these products to be administered to patients before final product sterility testing results are available. In situations where results of final sterility testing are not available before the product is administered, additional controls and testing should be considered. For example, additional sterility tests can be performed at intermediate stages of manufacture, especially after the last manipulation of the product prior to administration. Other tests that may indicate microbial contamination, such as microscopic examination, Gram stains, and endotoxin testing should be performed prior to product release.

V. ASEPTIC PROCESSING ISOLATORS

An emerging aseptic processing technology uses isolation systems to minimize the extent of personnel involvement and to separate the external clean-room environment from the aseptic processing line. A well-designed positive pressure barrier isolator, supported by adequate procedures for its maintenance, monitoring, and control, appears to offer an advantage over classical aseptic processing, including fewer opportunities for microbial contamination during processing. However, users should not adopt a false sense of security with these systems. Manufacturers should be also aware of the need to establish new procedures addressing issues unique to these systems.

A. Maintenance

1. General

Isolator systems have a number of special maintenance requirements. Although no isolator unit forms an absolute seal, very high integrity can be achieved in a well-designed unit. However, a leak in any of certain components of the system can constitute a significant breach of integrity. The integrity of gloves, half-suits, seams, gaskets, and seals require daily attention and a comprehensive preventative maintenance program. Replacement frequencies should be established in written procedures that require changing parts before they break down or degrade.

2. Glove Integrity

A faulty glove or sleeve (gauntlet) assembly represents a route of contamination and a critical breach of isolator integrity. The choice of durable glove materials coupled with a well-justified replacement frequency are two aspects of good manufacturing practice that should be addressed. With every use, gloves should be visually evaluated for any macroscopic physical defect. Mechanical integrity tests should also be performed routinely. This attentive preventative maintenance program is necessary to prevent use of gloves lacking integrity that would place the sterile product at risk. When such a breach is discovered, the operation should be terminated. Because of the potential for microbial migration through microscopic holes in gloves and the lack of a highly sensitive glove integrity test, the inner part of the installed glove should be sanitized regularly and the operator should also wear a second pair of thin gloves.

B. Design

1. Airflow

The design of an aseptic processing isolator normally employs unidirectional airflow that sweeps over and away from exposed sterile materials, avoiding any turbulence or stagnant airflow in the area of exposed sterilized materials,

product, and container/closures. In most sound designs, air showers over the critical zone once, and is then systematically exhausted. Air-handling systems should employ HEPA or ULPA filters, or both, in series.

2. Materials of Construction

As in any aseptic processing design, suitable materials should be chosen based on durability as well as ease of cleaning and sterilization. For example, rigid wall construction incorporating stainless steel and glass materials is widely used.

3. Pressure Differential

Isolators that include an open exit portal represent a potential compromise in achieving complete physical separation from the external environment. A positive air pressure differential adequate to achieve this full separation should be employed and supported by qualification studies. Positive air pressure differentials from the isolator to the surrounding environment have largely ranged from ca. 0.07 to 0.2 in water gauge. The appropriate minimum pressure differential specification established will be dependent on the system's design and, when applicable, its exit port. Air balance between the isolator and other direct interfaces (e.g., dry-heat tunnel) should also be qualified. The positive pressure differential should be coupled with appropriate protection at the product egress point(s) in order to overcome the potential for ingress of any airborne particles from the external environment by induction. Induction can result from local turbulent flow causing air swirls or pressure waves that can push extraneous particles into the isolator. Local Class 100 protection at an opening can provide a further barrier to induction of outside air into the isolator.

4. Clean-Area Classifications

The interior of the isolator should, at minimum, meet Class 100 standards. The classification of the environment surrounding the isolator should be based on the design of the product interfaces, such as transfer ports and discharge points, as well as the number of transfers into and out of the isolator. A Class 10,000 or Class 100,000 background is appropriate, depending on isolator design and manufacturing situations. The area surrounding the isolator should be justified. An isolator should not be located in an unclassified room.

C. Transfer of Materials and Supplies

The ability to maintain integrity and sterility of an isolator is impacted by the design of transfer ports. Various adaptations of differing capabilities allow for the transfer of supplies into and out of the isolator.

1. Introduction

Multiple material transfers are generally made during the processing of a batch. Frequently, transfers are performed via direct interface with a decontaminating transfer isolator or dry-heat depyrogenation tunnel with balanced airflow. Such provisions, if well designed, help ensure that microbiological ingress does not result from the introduction of supplies. Properly operated RTPs (rapid transfer ports) are also generally considered to be an effective transfer mechanism. The number of transfers should be kept to a minimum because the risk of ingress of contaminants increases with each successive material transfer.

Some transfer ports can have significant limitations, including marginal decontaminating capability [e.g., ultraviolet (UV)] or a design that would compromise isolation by allowing ingress of air from the surrounding room. In the latter case, localized HEPA-filtered laminar airflow cover in the area of such a port should be implemented.

2. Discharge

Isolators often include a "mousehole" or other exit port through which product is discharged, opening the isolator to the outside environment. The mousehole represents a potential route of contamination. Sufficient overpressure should be supplied and monitored on a continuous basis at this location to ensure that isolation is maintained.

D. Decontamination

1. Surface Exposure

Written procedures for decontamination of the isolator should be established. The decontamination process should provide full exposure of all isolator surfaces to the chemical agent. For example, to facilitate contact with the sterilant, the glove apparatus should be fully extended with glove fingers separated during the decontamination cycle.

2. Efficacy

A decontamination method should be developed that renders the inner surfaces of the isolator free of viable microorganisms. Decontamination can be accomplished by a number of vaporized agents, although these agents possess limited capability to penetrate obstructed or covered surfaces. Process development and validation studies should include a thorough determination of cycle capability. The characteristics of these agents generally preclude the use of reliable statistical methods (e.g., fraction negative) to determine process lethality. An appropriate, quantified BI challenge should be placed on various materials and in many locations throughout the isolator, including difficult-to-reach areas. Cycles should be developed with an appropriate margin of extra kill to provide confidence in the robustness of the decontamination processes. For most production applications, demonstration of a 6-log reduction of the challenge BI is recommended. The uniform distribution of the defined concentration of decontaminating agent should also be evaluated concurrently with these studies. Chemical indicators may also be useful as a qualitative tool to show that the decontaminating agent reached a given location.

3. Frequency

Although isolators vary widely in design, their interior and content should be designed to be frequently decontaminated. If an isolator is to be used for multiple days between decontamination cycles, the frequency adopted should include a built-in safety margin and be well justified. This frequency, established during validation studies, should be reevaluated and increased if production data indicate any deterioration of the microbiological quality of the isolator environment.

A breach of isolator integrity (e.g., power failure, glove or seam tear, other air leaks, valve failure, out-of-specification pressure) should lead to a decontamination cycle. Breaches of integrity should be investigated and any product that may have been impacted by the breach rejected.

E. Filling Line Sterilization

To ensure sterility of product contact surfaces from the start of each operation, the entire path of the sterile liquid stream should be sterilized. In addition, loose materials or equipment to be used within the isolator should be chosen based on their ability to withstand steam sterilization (or equivalent

method). It is expected that any materials that can be subjected to a steam sterilization cycle will, in fact, be autoclaved.

F. Environmental Monitoring

An appropriate environmental monitoring program should be established that routinely ensures acceptable microbiological quality of air, surfaces, and gloves (or half-suits) as well as particulate levels within the isolator. Air quality should be monitored periodically during each shift. As an example, the exit port should be monitored for particulates to detect any unusual results.

G. Personnel

Although clean-room apparel requirements are generally reduced, the contribution of human factor to contamination should not be overlooked. Isolation processes generally include periodic or even frequent use of one or more gloves for aseptic manipulations and handling of component transfers into and out of the isolator. Contaminated gloves can lead to product nonsterility. This concern is heightened because locations on gloves, sleeves, or half-suits can be among the more difficult-to-reach places during surface sterilization. Meticulous aseptic technique standards must be observed (section 211.113).

VI. BLOW-FILL-SEAL TECHNOLOGY

Blow-fill-seal (BFS) technology is an automated process by which containers are formed, filled, and sealed in a continuous operation. This manufacturing technology includes economies in container/closure processing and reduced human intervention, and is often used for filling and packaging of ophthalmics and less frequently for injectables. This section discusses some of the critical control points of this technology. Except where otherwise noted later, the aseptic processing standards discussed elsewhere in this document should be applied to the BFS technology.

A. Equipment Design and Air Quality

A BFS machine operates by (1) heating a plastic polymer resin, (2) extruding it to form a parison (a tubular form of the hot resin), (3) cutting the parison with a high temperature knife, (4) moving the parison under the blow-fill needle (mandrel), (5) inflating it to the shape of the mold walls, (6) filling the formed container with the liquid product, (7) removing the mandrel, and (8) sealing. Throughout this operation sterile air is used, for example, to form the parison and inflate it prior to filling. In most operations, the three steps that pose greatest potential for exposure to particle contamination or surrounding air are those in which the parison is cut, the parison is moved under the blow-fill mandrel, and the mandrel is removed (just prior to sealing).

BFS machinery and its surrounding barriers should be designed to prevent potential for extraneous contamination. As with any aseptic processing operation, it is critical that contact surfaces be sterile. A validated steam-in-place cycle should be used to sterilize the equipment path through which the product is conveyed. In addition, any other surface (e.g., above or nearby) that has potential to contaminate the sterile product needs to be sterile.

The classified environment surrounding BFS machinery should generally meet Class 10,000 standards, but special design provisions (e.g., isolation technology) can justify an alternative classification. HEPA-filtered or sterile air provided by membrane filters is necessary in the critical zone in which sterile product or materials are exposed (e.g., parison formation, container molding or filling steps). Air in the critical zone should meet Class 100 microbiological standards. A well-designed BFS system should also normally achieve Class 100 particulate levels. Equipment design should incorporate specialized measures to reduce particulate levels. In contrast to nonpharmaceutical applications that use BFS machinery, control of air quality (i.e., particulates) is critical for sterile drug product manufacture. Particles generated during the plastic extrusion, cutting, and sealing processes provide a potential means of transport for microorganisms into open containers prior to sealing. Provisions for carefully controlled airflow can protect the product by forcing generated particles outward while preventing any ingress from the adjacent environment. Furthermore, designs separating the filling zone from the surrounding environment are important in ensuring product protection. Barriers, pressure vacuums, microenvironments, and appropriately directed high velocities of sterile air have been found useful in preventing contamination (United States Pharmacopoeia). Smoke studies and multilocation particulate data are vital when performing qualification studies to assess whether proper particulate control dynamics have been achieved throughout the critical area.

In addition to suitable design, an adequate preventative maintenance program should be established. For example, because of its potential to contaminate the sterile drug product, the integrity of the boiling system (e.g., mold plates, gaskets) should be carefully monitored and maintained.

B. Validation and Qualification

Advantages of BFS processing are known to include rapid container/closure processing and minimized interventions. However, a properly functioning process is necessary to realize these advantages. Equipment qualification or requalification and personnel practices should be given special attention. Equipment sterilization, media fills, polymer sterilization, endotoxin removal, product–plastic compatibility, forming and sealing integrity, and unit weight variation are among the key issues that should be covered by validation and qualification studies.

Appropriate data should ensure that BFS containers are sterile and nonpyrogenic. This can generally be achieved by validating that time–temperature conditions of the extrusion process destroy the worst-case endotoxin load on the polymeric material.

The plastic polymer material chosen should be pharmaceutical grade, safe, pure, and pass USP criteria for plastics. Polymer suppliers should be qualified and monitored for raw material quality.

C. Batch Monitoring and Control

In-process monitoring should include various control parameters (e.g., container weight variation, fill weight, leakers, or air pressure) to ensure ongoing process control. Environmental monitoring is particularly important. Samples should be taken during each shift at specified locations under dynamic conditions. Because of the generation of high levels of particles near the exposed drug product, continuous monitoring of particles can provide valuable data relative to the control of a BFS operation. Container/closure defects can be a major problem in control of a BFS operation. It is necessary for the operation to be designed and set up to uniformly manufacture leakproof units. As a final measure, inspection of each unit of a batch should employ a reliable, sensitive final product examination capable of detecting a defective unit

(e.g., leakers). Significant defects due to heat or mechanical problems, such as mold thickness, container/closure interface deficiencies, poorly formed closure, or other deviations should be investigated in accord with sections 211.100 and 211.192.

VII. LYOPHILIZATION OF PARENTERALS

A. Introduction

Lyophilization or freeze-drying is a process in which water is removed from a product after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapor without passing through the liquid phase. The process consists of three separate, unique, and interdependent processes: freezing, primary drying (sublimation), and secondary drying (desorption). The advantages of lyophilization include the following:

- Ease of processing a liquid, which simplifies aseptic handling
- Enhanced stability of a dry powder
- Removal of water without excessive heating of the product
- Enhanced product stability in a dry state
- Rapid and easy dissolution of reconstituted product

Disadvantages of lyophilization include the following:

- Increased handling and processing time
- Need for sterile diluent on reconstitution
- Cost and complexity of equipment

The lyophilization process generally includes the following steps:

- Dissolving the drug and excipients in a suitable solvent, generally WFI
- Sterilizing the bulk solution by passing it through a 0.22-mm bacteria-retentive filter
- Filling into individual sterile containers and partially stoppering the containers under aseptic conditions
- Transporting the partially stoppered containers to the lyophilizer and loading into the chamber under aseptic conditions
- Freezing the solution by placing the partially stoppered containers on cooled shelves in a freeze-drying chamber or prefreezing in another chamber
- Applying a vacuum to the chamber and heating the shelves in order to evaporate the water from the frozen state
- Complete stoppering of the vials usually by hydraulic or screw rod stoppering mechanisms installed in the lyophilizers

Many new parenteral products, including anti-infectives, biotechnology-derived products, and in vitro diagnostics, are manufactured as lyophilized products. Numerous potency, sterility, and stability problems are associated with the manufacture and control of lyophilized products. It is recognized that there is complex technology associated with the manufacture and control of a lyophilized pharmaceutical dosage form. Some of the important aspects of these operations include the formulation of solutions, filling of vials, and validation of the filling operation, sterilization and engineering aspects of the lyophilizer, scale-up and validation of the lyophilization cycle, and testing of the end product. This discussion will address some of the problems associated with the manufacture and control of a lyophilized dosage form.

B. Product Type and Formulation

Products are manufactured in the lyophilized form due to their instability when in solution. Many antibiotics, such as some of the semisynthetic penicillins, cephalosporins, and some of the salts of erythromycin, doxycycline, and chloramphenicol, are made by the lyophilization process. Because they are antibiotics, low bioburden of these formulations would be expected at the time of batching. However, some of the other dosage forms that are lyophilized, such as hydrocortisone sodium succinate, methylprednisolone sodium succinate, and many of the biotechnology-derived products, have no antibacterial effect when in solution.

For these types of products, bioburden should be minimal; the bioburden should be determined prior to sterilization of these bulk solutions prior to filling. Obviously, the batching or compounding of these bulk solutions should be controlled to prevent any increase in microbiological levels that may occur up to the time the bulk solutions are filtered (sterilized). The concern with any microbiological level is the possible increase in endotoxins. Good practice for the compounding of lyophilized products would also include batching in a controlled environment and in sealed tanks, particularly if the solution is to be held for any length of time prior to sterilization.

In some cases, manufacturers have performed bioburden testing on bulk solutions after prefiltration and prior to final filtration. Although the testing of such solutions may be meaningful in determining the bioburden for sterilization, it does not provide any information regarding the potential formation or presence of endotoxins. The testing of 0.1-mL samples by LAL methods of bulk solution for endotoxins is of value, but testing of at least 100-mL size samples prior to prefiltration, particularly for the presence of gram-negative organisms, would be of greater value in evaluating the process. For example, the presence of *Pseudomonas* species in the bioburden of a bulk solution has been identified as an objectionable condition.

C. Filling

The filling of vials that are to be lyophilized has some problems that are somewhat unusual. The stopper is placed on top of the vial and is ultimately seated in the lyophilizer. As a result, the contents of the vial are subject to contamination until they are actually sealed. Validation of filling operations should include media fills and the sampling of critical surfaces and air during active filling (dynamic conditions).

Because of the active involvement of people in filling and aseptic manipulations, an environmental program should also include an evaluation of microbiological levels on people working in aseptic processing areas. One method of evaluating the training of operators working in aseptic processing facilities is the surface monitoring of gloves and gowns on a daily basis. Manufacturers are actively sampling the surfaces of personnel working in aseptic processing areas. A reference that provides for this type of monitoring is the USP discussion of the interpretation of sterility test results. It states under the heading of "Interpretation of Quality Control Tests" that review consideration should be paid to environmental control data, including microbial monitoring, records of operators, gowns, gloves, and garbing practices. In those situations wherein manufacturers have failed to perform some type of personnel monitoring or monitoring has shown unacceptable levels of contamination, regulatory situations have resulted.

Typically, vials to be lyophilized are partially stoppered by machine. However, some filling lines have been noted in which an operator places each stopper on top of the vial by hand. At this time, it would seem difficult for a manufacturer to justify a hand-stoppering operation, even if sterile forceps are employed, in any type of operation other than filling a clinical batch or a very small number of units. Significant regulatory situations have resulted from this practice. Again, the concern is the immediate avenue of contamination offered by the operator. It is well recognized that people are the major source of contamination in an aseptic processing filling operation. The longer a person works in an aseptic operation, the more the microorganisms shed and the greater the probability of contamination.

Once filled and partially stoppered, vials are transported and loaded into the lyophilizer. The transfer and handling, such as loading of the lyophilizer, should take place under primary barriers, such as the laminar flow hoods under which the vials were filled. Validation of this handling should also include the use media fills.

Regarding the filling of sterile media, there are some manufacturers who carry out a partial lyophilization cycle and freeze the media. Although this could seem to greater mimic the process, the freezing of media could reduce microbial levels of some contaminants. Because the purpose of the media fill is to evaluate and justify the aseptic capabilities of the process, the people, and the system, the possible reduction of microbiological levels after aseptic manipulation by freezing would not be warranted. The purpose of a media fill is not to determine the lethality of freezing and its effect on any microbial contaminants that might be present.

In an effort to identify the particular sections of filling and aseptic manipulation that might introduce contamination, several manufacturers have resorted to expanded media fills. That is, they have filled ca. 9000 vials during a media fill and segmented the fill into three stages: the first stage of filling 3000 vials and stoppering on line; the second stage of filling 3000 vials, transporting to the lyophilizer, and then stoppering; and a third stage of filling 3000 vials, loading in the lyophilizer, and exposure to a portion of the nitrogen flush and then stoppering. Because sterilization of lyophilizer and sterilization of the nitrogen system used to backfill require separate validation, media fills should primarily validate the filling, transporting, and loading aseptic operations.

The question of the number of units needed for media fills when the capacity of the process is less than 3000 units is frequently asked, particularly for clinical products. Again, the purpose of the media fill is to assure that the product can be aseptically processed without contamination under operating conditions. It would seem, therefore, that the maximum number of units of media filled be equivalent to the maximum batch size if it is less than 3000 units.

In the transport of vials to the lyophilizer, because they are not sealed, there is concern for the potential for contamination. During inspections and in the review of new facilities, the failure to provide laminar flow coverage or a primary barrier for the transport and loading areas of a lyophilizer has been regarded as an objectionable condition. The solutions include use of laminar flow carts or locating filling lines close to the lyophilizer to minimize exposure. The use of laminar flow units should validate that the air turbulence created in the area does not itself produce a contamination problem. The media fills and smoke studies should be done to identify and correct these problems. Typically, the lyophilization process includes the stoppering of vials in the chamber.

Another major concern with the filling operation is assurance of fill volumes. Obviously, a low fill would represent a subpotency in the vial. Unlike a powder or liquid fill, a low fill would not be readily apparent after lyophilization, particularly for a biopharmaceutical drug product in which the active ingredient may be only a milligram. Because of the clinical significance, subpotency in a vial can be a very serious situation.

On occasion, it has been seen that production operators monitoring fill volumes record these fill volumes only after adjustments are made. Therefore, good practice and a good quality assurance program would include the frequent monitoring of the volume of fill, such as every 15 minutes. Good practice would also include provision for the isolation of particular sections of filling operations when low or high fills are encountered.

Some atypical filling operations have not been discussed. For example, there have also been some situations in which lyophilization is performed on trays of solution rather than in vials. Based on the current technology available, it would seem that for a sterile product, it would be difficult to justify this procedure.

The dual chamber vial also presents additional requirements for aseptic manipulations. Media fills should include the filling of media in both chambers. Also, the diluent in these vials should contain a preservative. (Without a preservative, the filling of diluent would be analogous to the filling of media. In such cases, a 0% level of contamination would be expected.)

D. Lyophilization Cycle and Controls

After sterilization of the lyophilizer and aseptic loading, the initial step is freezing the solution. In some cycles, the shelves are at the temperature needed for freezing, whereas for other cycles, the product is loaded and then the shelves are taken to the freezing temperature necessary for product freeze. In those cycles wherein the shelves are precooled prior to loading, there is concern for any ice formation on shelves prior to loading. Ice on shelves prior to loading can cause partial or complete stoppering of vials prior to lyophilization of the product. It is noteworthy that even 100% vial inspection can fail to identify defective vials. Typically, the product is frozen at a temperature well below the eutectic point.

The scale-up and change of lyophilization cycles, including the freezing procedures, have presented some problems. Studies have shown the rate and manner of freezing may affect the quality of the lyophilized product. For example, slow freezing leads to the formation of larger ice crystals. This results in relatively large voids, which aid in the escape of water vapor during sublimation. On the other hand, slow freezing can increase concentration shifts of components. Also, the rate and manner of freezing have been shown to have an effect on the physical form (polymorph) of the drug substance.

It is desirable after freezing and during primary drying to hold the drying temperature (in the product) at least 4°C to 5°C below the eutectic point. Obviously, the manufacturer should know the eutectic point and have the necessary instrumentation to assure the uniformity of product temperatures. The lyophilizer should also have the necessary instrumentation to control and record the key process parameters. These include shelf temperature, product temperature, condenser temperature, chamber pressure, and condenser pressure. The manufacturing directions should provide for time, temperature, and pressure limits necessary for a lyophilization cycle for a product. The monitoring

of product temperature is particularly important for those cycles for which there are atypical operating procedures, such as power failures or equipment breakdown.

Electromechanical control of a lyophilization cycle has utilized cam-type recorder-controllers. However, newer units provide for microcomputer control of the freeze–drying process. A very basic requirement for a computer-controlled process is a flow chart or logic. Typically, operator involvement in a computer-controlled lyophilization cycle primarily occurs at the beginning. It consists of loading the chamber, inserting temperature probes in product vials, and entering cycle parameters such as shelf temperature for freezing, product freeze temperature, freezing soak time, primary drying shelf temperature and cabinet pressure, product temperature for establishment of fill vacuum, secondary drying shelf temperature, and secondary drying time.

In cases where manufacturers continuously make adjustments in cycles as they are being run, the lyophilization process would be nonvalidated.

Validation of the software program of a lyophilizer follows the same criteria as those for other processes. Basic concerns include software development, modifications, and security. The "Guide to Inspection of Computerized Systems in Drug Processing" contains a discussion of potential problem areas relating to computer systems. The "Guide to the Inspection of Software Development Activities" is a reference that provides a more detailed review of software requirements.

Leakage into a lyophilizer may originate from various sources. As in any vacuum chamber, leakage can occur from the atmosphere into the vessel itself. Other sources are media employed within the system to perform the lyophilizing task. These would be the thermal fluid circulated through the shelves for product heating and cooling, the refrigerant employed inside the vapor condenser cooling surface, and oil vapors that may migrate back from the vacuum pumping system.

Any one source, or a combination of all, can contribute to the leakage of gases and vapors into the system. It is necessary to monitor the leak rate periodically to maintain the integrity of the system. It is also necessary, should the leak rate exceed specified limits, to determine the actual leak site for purposes of repair.

Thus, it would be beneficial to perform a leak test at some time after sterilization, possibly at the beginning of the cycle or prior to stoppering. The time and frequency for performing the leak test will vary and will depend on the data developed during the cycle validation. The pressure rise found acceptable at validation should be used to determine the acceptable pressure rise during production. A limit and what action is to be taken if excessive leakage is found should be addressed in some type of operating document.

To minimize oil vapor migration, some lyophilizers are designed with a tortuous path between the vacuum pump and chamber. For example, one fabricator installed an oil trap in the line between the vacuum pump and chamber in a lyophilizer with an internal condenser. Leakage can also be identified by sampling surfaces in the chamber after lyophilization for contaminants. One could conclude that if contamination is found on a chamber surface after lyophilization, then dosage units in the chamber could also be contaminated. It is a good practice, as part of the validation of cleaning of the lyophilization chamber, to sample the surfaces both before and after cleaning.

Because of the lengthy cycle runs and strain on machinery, it is not unusual to see equipment malfunction or fail during a lyophilization cycle. There should be provisions in place for the corrective action to be taken when these atypical situations occur. In addition to documentation of the malfunction, there should be an evaluation of the possible effects on the product (e.g., partial or complete meltback; refer to subsequent discussion). Merely testing samples after the lyophilization cycle is concluded may be insufficient to justify the release of the remaining units. For example, the leakage of chamber shelf fluid into the chamber or a break in sterility would be cause for rejection of the batch.

E. Cycle Validation

Many manufacturers file (in applications) their normal lyophilization cycles and validate the lyophilization process based on these cycles. Unfortunately, such data would be of little value to substantiate shorter or abnormal cycles. In some cases, manufacturers are unaware of the eutectic point. It would be difficult for a manufacturer to evaluate partial or abnormal cycles without knowing the eutectic point and the cycle parameters needed to facilitate primary drying.

Scale-up for the lyophilized product requires knowledge of the many variables that can affect the product. Some of the variables include freezing rate and temperature ramping rate. As with the scale-up of other drug products, there should be a development report that discusses the process and logic for the cycle. Probably more so than any other product, scale-up of the lyophilization cycle is very difficult.

Some manufacturers market multiple strengths, vial sizes, and different batch sizes. Separate validation should be performed for each product and extrapolation from one cycle to another is not proper.

F. Lyophilizer Sterilization and Design

The sterilization of the lyophilizer is one of the more frequently encountered problems noted during inspections. Some of the older lyophilizers cannot tolerate steam under pressure, and sterilization is marginal at best. These lyophilizers can only have their inside surfaces wiped with a chemical agent that may be a sterilant but usually has been found to be a sanitizing agent. Unfortunately, piping such as that for the administration of inert gas (usually nitrogen) and sterile air for backfill or vacuum break is often inaccessible to such surface "sterilization" or treatment. It would seem very difficult for a manufacturer to demonstrate satisfactory validation of sterilization of a lyophilizer by chemical "treatment."

Another method of sterilization that has been practiced is the use of gaseous ethylene oxide. As with any ethylene oxide treatment, humidification is necessary. Providing a method of introducing the sterile moisture with uniformity has been found to be difficult.

To employ WFI as a final wash or rinse of the lyophilizer and while the chamber is wet, sterilizing by ethylene oxide gas may be satisfactory for the chamber but inadequate for associated plumbing. Another problem associated with ethylene oxide is the residue. A common ethylene oxide and nitrogen supply line to a number of lyophilizers connected in parallel to the system may result in some ethylene oxide in the nitrogen supply line during the backfilling step. Obviously, this type of system is objectionable.

A generally recognized, acceptable method of sterilizing the lyophilizer is through the use of moist steam under pressure. Sterilization procedures should parallel that of an autoclave, and a typical system should include two independent temperature-sensing systems, one to control and record temperatures of the cycle as with sterilizers and the other in the cold spot of the chamber. As with autoclaves, lyophilizers

should have drains with atmospheric breaks to prevent back siphonage.

As discussed, there should also be provisions for sterilizing the inert gas or air and the supply lines. Some manufacturers have chosen to locate the sterilizing filters in a port of the chamber. The port is steam sterilized when the chamber is sterilized, and then the sterilizing filter, previously sterilized, is aseptically connected to the chamber. Some manufacturers have chosen to sterilize the filter and downstream piping to the chamber in place. Typical sterilization-in-place of filters may require steaming of both to obtain sufficient temperatures. In this type of system, there should be provision for removing or draining condensate. The failure to sterilize nitrogen and air filters and the piping downstream leading into the chamber has been identified as a problem on a number of inspections.

Because these filters are used to sterilize inert gas or air, or both, there should be some assurance of their integrity. Some inspections have disclosed a lack of integrity testing of the inert gas or air filter. The question frequently asked is how often the vent filter should be tested for integrity. As with many decisions made by manufacturers, there is a level of risk associated with the operation, process, or system, which only the manufacturer can determine. If the sterilizing filter is found to pass the integrity test after several uses or batches, then one can claim its integrity for the previous batches. However, if the filter is tested only after several batches have been processed and if found to fail the integrity test, then one can question the sterility of all of the previous batches processed. To minimize this risk, some manufacturers have resorted to redundant filtration.

For most cycles, stoppering occurs within the lyophilizer. Typically, the lyophilizer has some type of rod or rods (ram), which enter the immediate chamber at the time of stoppering. Once the rod enters the chamber, there is the potential for contamination of the chamber. However, because the vials are stoppered, there is no avenue for contamination of the vials in the chamber, which are now stoppered. Generally, lyophilizers should be sterilized after each cycle because of the potential for contamination of the shelf support rods. Additionally, the physical act of removing vials and cleaning the chamber can increase levels of contamination.

In some of the larger units, the shelves are collapsed after sterilization to facilitate loading. Obviously, the portions of the ram entering the chamber to collapse the shelves enter from a nonsterile area. Attempts to minimize contamination have included wiping the ram with a sanitizing agent prior to loading. Control aspects have included testing the ram for microbiological contamination, testing it for residues of hydraulic fluid, and testing the fluid for its bacteriostatic effectiveness. One practice is to provide a flexible "skirt" to cover the ram. In addition to microbiological concerns with hydraulic fluid, there is also the concern with product contamination.

During steam sterilization of the chamber, there should be space between shelves that permit passage of free-flowing steam. Some manufacturers have placed "spacers" between shelves to prevent their total collapse. Others have resorted to a two-phase sterilization of the chamber. The initial phase provides for sterilization of the shelves when they are separated. The second phase provides for sterilization of the chamber and piston with the shelves collapsed.

Typically, BIs are used in lyophilizers to validate the steam sterilization cycle. One manufacturer of a biopharmaceutical product was found to have a positive BI after sterilization at 121°C for 45 minutes. During the chamber sterilization, trays used to transport vials from the filling line to the chamber were also sterilized. The trays were sterilized in an inverted position on shelves in the chamber. It is believed that the positive BI is the result of poor steam penetration under these trays.

The sterilization of condensers is also a major issue that warrants discussion. Most of the newer units provide for the capability of sterilization of the condenser along with the chamber, even if the condenser is external to the chamber. This provides a greater assurance of sterility, particularly in those situations in which there is some equipment malfunction and the vacuum in the chamber is deeper than in the condenser.

Malfunctions that can occur, indicating that sterilization of the condenser is warranted, include vacuum pump breakdown, refrigeration system failures, and the potential for contamination by the large valve between the condenser and chamber. This is particularly true for units that have separate vacuum pumps for both the condenser and chamber. When there are problems with the systems in the lyophilizer, contamination could migrate from the condenser back to the chamber. It is recognized that it is not possible to sterilize the condenser in many of the older units, and this represents a major problem, particularly in those cycles in which there is some equipment or operator failure.

As referenced previously, leakage during a lyophilization cycle can occur, and the door seal or gasket presents an avenue of entry for contaminants. If steam leaks from a unit during sterilization, air could possibly enter the chamber during lyophilization.

Some of the newer lyophilizers have double doors, one for loading and the other for unloading. The typical single-door lyophilizer opens in the clean area only, and contamination between loads is minimal. This clean area, as previously discussed, represents a critical processing area for a product made by aseptic processing. In most units, only the piston raising or lowering shelves is the source of contamination. For a double-door system, unloading the lyophilizer in a nonsterile environment, other problems may occur. The nonsterile environment presents a direct avenue of contamination of the chamber when unloading, and door controls similar to double-door sterilizers should be in place.

Obviously, the lyophilizer chamber is to be sterilized between batches because of the direct means of contamination. A significant problem is that of leakage through the door seal. For the single-door unit, leakage before stoppering around the door seal is not a major problem from a sterility standpoint because single-door units open only into sterile areas. However, leakage from a door gasket or seal from a nonsterile area will present a significant microbiological problem. To minimize the potential for contamination, it is recommended that the lyophilizers be unloaded in a cleanroom area to minimize contamination. After steam sterilization, there is often some condensate remaining on the floor of the chamber. Some manufacturers remove this condensate through the drain line while the chamber is still pressurized after sterilization. Nonsterile air could contaminate the chamber through the drain line. Some manufacturers attempt to dry the chamber by blowing sterile nitrogen gas through the chamber at a pressure above atmospheric pressure. Residual of condensate in the chamber is often a cause of *Pseudomonas* contamination.

G. Finished Product Testing

Several aspects of finished product testing are of concern to the lyophilized dosage form. These include dose uniformity testing, moisture and stability testing, and sterility testing.

1. Dose Uniformity

The USP includes two types of dose uniformity testing: content uniformity and weight variation. It states that weight variation may be applied to solids, with or without added substances that have been prepared from true solutions and freeze-dried in final containers. However, when other excipients or other additives are present, weight variation may be applied, provided there is correlation with the sample weight and potency results. For example, in the determination of potency, it is sometimes common to reconstitute and assay the entire contents of a vial without knowing the weight of the sample. Performing the assay in this manner will provide information on the label claim of a product, but without knowing the sample weight, one has no information about dose uniformity. One should correlate the potency result obtained from the assay with the weight of the sample tested.

2. Stability Testing

An obvious concern with the lyophilized product is the amount of moisture present in vials. The manufacturer's data for the establishment of moisture specifications for both product release and stability should be reviewed. As with other dosage forms, the expiration date and moisture limit should be established based on worst-case data. That is, a manufacturer should have data that demonstrate adequate stability at the moisture specification.

As with immediate release potency testing, stability testing should be performed on vials with a known weight of sample. For example, testing a vial (sample) which had a higher fill weight (volume) than the average fill volume of the batch would provide higher potency results and not represent the potency of the batch. Also, the expiration date and stability should be based on those batches with the higher moisture content. Such data should also be considered in the establishment of a moisture specification.

For products showing a loss of potency due to aging, there are generally two potency specifications. There is a higher limit for the dosage form at the time of release. This limit is generally higher than the official USP or filed specification that is official throughout the entire expiration date period of the dosage form. The USP points out that compendial standards apply at any time in the life of the article.

Stability testing should also include provision for the assay of aged samples and subsequent reconstitution of these aged samples for the maximum amount of time specified in the labeling. On some occasions, manufacturers have established expiration dates without performing label claim reconstitution potency assays at the various test intervals and particularly the expiration date test interval. Additionally, this stability testing of reconstituted solutions should include the most concentrated and the least concentrated reconstituted solutions. The most concentrated reconstituted solution will usually exhibit degradation at a faster rate than less concentrated solutions.

3. Sterility Testing

With respect to sterility testing of lyophilized products, there is concern with the solution used to reconstitute the lyophilized product. Although products may be labeled for reconstitution with bacteriostatic WFI, sterile WFI should be used to reconstitute products. Because of the potential toxicities associated with bacteriostatic WFI, many hospitals use WFI only. Bacteriostatic WFI may kill some of the vegetative cells if present as contaminants, and thus mask the true level of contamination in the dosage form. As with other sterile products, sterility test results that show contamination on the initial test should be identified and reviewed.

H. Finished Product Inspection—Meltback

The USP points out that it is good pharmaceutical practice to perform 100% inspection of parenteral products. This includes sterile lyophilized powders. Critical aspects include the presence of correct volume of cake and the cake appearance. With regard to cake appearance, one of the major concerns is *meltback*.

Meltback is a form of cake collapse and is caused by the change from the solid to liquid state; that is, there is incomplete sublimation (change from the solid to vapor state) in the vial. Associated with this problem is a change in the physical form of the drug substance or a pocket of moisture, or both. These may result in greater instability and increased product degradation.

Another problem may be poor solubility. Increased time for reconstitution at the user stage may result in partial loss of potency if the drug is not completely dissolved, because it is common to use in-line filters during administration to the patient.

Manufacturers should be aware of the stability of lyophilized products that exhibit partial or complete meltback. Literature shows that for some products, such as the cephalosporins, the crystalline form is more stable than the amorphous form of lyophilized product. The amorphous form may exist in the meltback portion of the cake where there is incomplete sublimation.

VIII. HIGH-PURITY WATER SYSTEMS

High-purity water systems are used for the manufacture of many types of pharmaceutical products, particularly parenteral and ophthalmic products. The pharmacopoeia describes several specifications for water such as WFI, purified water, and potable water. Because adequate controls in the supply of water systems are considered critical, along with other environmental factors, a detailed description of high-purity water systems is provided here.

A. System Design

One of the basic considerations in the design of a system is the type of product that is to be manufactured. For parenteral products where there is a concern for pyrogens, it is expected that WFI will be used. This applies to the formulation of products, as well as to the final washing of components and equipment used in their manufacture. Distillation and reverse osmosis (RO) filtration are the only acceptable methods listed in the USP for producing WFI. However, in the bulk pharmaceutical and biotechnology industries and some foreign companies, ultra filtration (UF) is employed to minimize endotoxins in those drug substances that are administered parenterally.

It is expected that WFI be used in the formulation of some ophthalmic products such as the ophthalmic irrigating solution and some inhalation products such as sterile water for inhalation, where there are pyrogen specifications. However, purified water is used in the formulation of most inhalation and ophthalmic products. This also applies to topicals, cosmetics, and oral products.

Another design consideration is the temperature of the system. It is recognized that hot (65°C–80°C) systems are self-sanitizing. Although the cost of other systems may be less

expensive for a company, the cost of maintenance, testing, and potential problems may be higher than the cost of energy saved. Whether a system is circulating or one-way is also an important design consideration. Obviously, water in constant motion is less liable to have high levels of contaminant. A one-way water system is basically a "dead-leg."

The final, and possibly the most important, consideration is the risk assessment or level of quality that is desired. It should be recognized that different products require different quality waters. Parenterals require very pure water with no endotoxins. Topical and oral products require less pure water and do not have a requirement for endotoxins. Even with topical and oral products there are factors that dictate different qualities for water. For example, preservatives in antacids are marginally effective, so more stringent microbial limits have to be set. The quality control department should assess each product manufactured with the water from their system and determine the microbial action limits based on the most microbial sensitive product. In lieu of stringent water action limits in the system, the manufacturer can add a microbial reduction step in the manufacturing process for the sensitive drug product(s).

B. System Validation

A basic reference used for the validation of high-purity water systems is the Parenteral Drug Association Technical Report No. 4, "Design Concepts for the Validation of a Water for Injection System."

The introduction provides guidance and states that validation often involves the use of an appropriate challenge. In this situation, it would be undesirable to introduce microorganisms into an on-line system; therefore, reliance is placed on periodic testing for microbiological quality and on the installation of monitoring equipment at specific checkpoints to ensure that the total system is operating properly and continuously fulfilling its intended function.

In the review of a validation report or in the validation of a high-purity water system, several aspects should be considered. Documentation should include a description of the system along with a print. The drawing needs to show all equipment in the system from the water feed to points of use. It should also show all sampling points and their designations. If a system has no print, it is usually considered an objectionable condition. The thinking is that if there is no print, it is not possible for the system to be validated. How can a quality control manager or microbiologist know where to sample? In facilities observed without updated prints, serious problems have been identified in these systems. The print should be compared with the actual system annually to ensure its accuracy, to detect unreported changes, and confirm reported changes to the system.

After all the equipment and piping has been verified as installed correctly and working as specified, the initial phase of the water system validation can begin. During this phase, the operational parameters and the cleaning and sanitization procedures and frequencies will be developed. Sampling should be daily after each step in the purification process and at each point of use for 2 to 4 weeks. The sampling procedure for point-of-use sampling should reflect how the water is to be drawn; for example, if a hose is usually attached, the sample should be taken at the end of the hose. If the SOP calls for the line to be flushed before use of the water from that point, then the sample is taken after the flush.

The second phase of the system validation is to demonstrate that the system will consistently produce the desired water quality when operated in conformance with the SOPs. The sampling is performed as in the initial phase and for the same time period. At the end of this phase, the data should demonstrate that the system will consistently produce the desired quality of water.

The third phase of validation is designed to demonstrate that when the water system is operated in accordance with the SOPs over a long period of time, it will consistently produce water of the desired quality. Any variations in the quality of the feedwater that could affect the operation and ultimately the water quality will be picked up during this phase of the validation. Sampling is performed according to routine procedures and frequencies. For WFI systems, the samples should be taken daily from a minimum of one point of use, with all points of use tested weekly. The validation of the water system is completed when there is at least a full year's worth of data.

Although the above validation scheme is not the only way a system can be validated, it contains the necessary elements for validation of a water system. First, there must be data to support the SOPs. Second, there must be data demonstrating that the SOPs are valid and that the system is capable of consistently producing water that meets the desired specifications. Finally, there must be data to demonstrate that seasonal variations in the feedwater do not adversely affect the operation of the system or the water quality.

The last part of the validation is the compilation of the data, with any conclusions into the final report. The final validation report must be signed by the appropriate people responsible for operation and quality assurance of the water system.

A typical problem is the failure of operating procedures to preclude contamination of the system with nonsterile air remaining in a pipe after drainage. A typical problem occurs when a washer or hose connection is flushed and then drained at the end of the operation. After draining, this valve (the second off of the system) is closed. If, on the next day or start-up of the operation, the primary valve off the circulating system is opened, then the nonsterile air remaining in the pipe after drainage will contaminate the system. The solution is to provide for operational procedures that provide for opening the secondary valve before the primary valve to flush the pipe prior to use.

Another major consideration in the validation of high-purity water systems is the acceptance criteria. Consistent results throughout the system over a period of time constitute the primary element.

C. Microbial Limits

1. WFI Systems

Regarding microbiological results for WFI, it is expected that they be essentially sterile. Because sampling frequently is performed in nonsterile areas and is not truly aseptic, occasional low-level counts due to sampling errors may occur. The U.S. FDA policy is that less than 10 CFU/100 mL is an acceptable action limit. None of the limits for water are pass or fail limits; all limits are action limits. When action limits are exceeded, the cause of the problem must be investigated. Action must be taken to correct the problem and assess the impact of the microbial contamination on products manufactured with the water. The results of the investigation must then be documented.

With regard to sample size, 100 to 300 mL is preferred when sampling WFI systems. Sample volumes less than 100 mL are unacceptable.

The real concern in WFI is endotoxins. Because WFI can pass the LAL endotoxin test and still fail the above microbial action limit, it is important to monitor WFI systems for both endotoxins and microorganisms.

2. Purified Water Systems

For purified water systems, microbiological specifications are not as clear. The USP specifications, that it complies with federal Environmental Protection Agency (EPA) regulations for drinking water, are recognized as being minimal specifications. There have been attempts by some to establish meaningful microbiological specifications for purified water. The CFTA proposed a specification of not more than 500 organisms/mL. The USP has an action guideline of not greater than 100 organisms/mL. Although microbiological specifications have been discussed, none (other than EPA standards) have been established. The U.S. FDA policy is that any action limit over 100 CFU/mL for a purified water system is unacceptable.

The purpose of establishing any action limit or level is to assure that the water system is under control. Any action limit established will depend on the overall purified water system and further processing of the finished product and its use. For example, purified water used to manufacture drug products by cold processing should be free of objectionable organisms. Objectionable organisms are any organisms that can cause infections when the drug product is used as directed or any organism capable of growth in the drug product—the specific contaminant rather than the number is generally more significant.

Organisms exist in a water system either as freely floating in the water or attached to the walls of the pipes and tanks. When they are attached to the walls, they are known as biofilm, which continuously sloughs off organisms. Thus, contamination is not uniformly distributed in a system, and the sample may not be representative of the type and level of contamination. A count of 10 CFU/mL in one sample and 100 or even 1000 CFU/mL in a subsequent sample would not be unrealistic.

Thus, establishing the level of contamination allowed in a high-purity water system used in the manufacture of a nonsterile product requires an understanding of the use of the product, the formulation (preservative system), and manufacturing process. For example, antacids, which do not have an effective preservative system, require an action limit below the 100 CFU/mL maximum.

The USP gives some guidance in their monograph, *Microbiological Attributes of Non-Sterile Products*. It points out that, "The significance of microorganisms in nonsterile pharmaceutical products should be evaluated in terms of the use of the product, the nature of the product, and the potential harm to the user." Thus, not just the indicator organisms listed in some of the specific monographs present problems. It is up to manufacturers to evaluate their product and the way it is manufactured, and establish an acceptable action level of contamination, not to exceed the maximum, for the water system, based on the highest risk product manufactured with the water.

D. WFI Systems

In establishing a validated WFI system, there are several concerns. Pretreatment of feedwater is recommended by most manufacturers of distillation equipment and is definitely required for RO units. The incoming feedwater quality may fluctuate during the life of the system depending on seasonal variations and other external factors beyond the control of the pharmaceutical facility. For example, in the spring (at least in the northeast United States), increases in gram-negative organisms have been known. Also, new construction or fires can deplete water stores in old mains, causing an influx of water heavily contaminated with different flora.

A water system should be designed to operate within these anticipated extremes. Obviously, the only way to know the extremes is to periodically monitor feedwater. If the feedwater is from a municipal water system, reports from the municipality testing can be used in lieu of in-house testing.

E. Still

Most of the new systems now use multieffect stills. Endotoxins find their way into the system through many channels, such as when there is a malfunction of the feedwater valve and level control in the still, which results in droplets of feedwater being carried over in the distillate or water lying in the condenser for several days (i.e., over the weekend). This may produce unacceptable levels of endotoxins. More common, however, is the failure to adequately treat feedwater to reduce levels of endotoxins. Many of the still fabricators will only guarantee a 2.5-log to 3-log reduction in the endotoxin content. Therefore, it is not surprising that in systems in which the feedwater occasionally spikes to 250 EU/mL, unacceptable levels of endotoxins may occasionally appear in the distillate (WFI). This requires having a satisfactory pretreatment system to assure validity of system. Typically, conductivity meters are used on water systems to monitor chemical quality but have no meaning regarding microbiological quality.

Petcocks or small sampling ports between each piece of equipment, such as after the still and before the holding tank, are placed in the system to isolate major pieces of equipment. This is necessary for the qualification of the equipment and to enable easy investigation of any problems that might occur due to these petcocks and sampling ports.

F. Heat Exchangers

One principal component of the still is the heat exchanger. Because of the similar ionic quality of distilled and deionized water, conductivity meters cannot be used to monitor microbiological quality. Positive pressure such as in vapor compression or double-tubesheet design should be employed to prevent possible feedwater-to-distillate contamination in a leaky heat exchanger.

There are potential design-related problems associated with heat exchangers. There are two methods to prevent contamination by leakage: one is to provide gauges to constantly monitor pressure differentials to ensure that the higher pressure is always on the clean fluid side, and the other is to use the double-tubesheet type of heat exchanger.

In some systems, heat exchangers are used to cool water at use points. For the most part, cooling water is not circulated through them when not in use. In a few situations, pinholes have formed in the tubing after they were drained (on the cooling waterside) and not in use. A small amount of moisture remaining in the tubes when combined with air can corrode the stainless steel tubes on the cooling waterside. Thus, it is recommended that, when not in use, heat exchangers not be drained of the cooling water.

G. Holding Tank

In hot systems, temperature is usually maintained by applying heat to a jacketed holding tank or by placing a heat exchanger in the line prior to an insulated holding tank. The one component of the holding tank that requires great attention is the vent filter. It is expected that there be some program for

integrity-testing this filter to assure that it is intact. Typically, filters are now jacketed to prevent condensate or water from blocking the hydrophobic vent filter. If the vent filter becomes blocked, possibly either the filter will rupture or the tank will collapse. There are methods for integrity testing of vent filters in place. It is expected, therefore, that the vent filter be located in a position on the holding tank where it is readily accessible. Just because a WFI system is relatively new and distillation is employed, it is not necessarily problem free. Other considerations such as how it is integrated with the rest of the system are equally important.

H. Pumps

Pumps burn out and parts wear. Also, if pumps are static and not continuously in operation, their reservoir can be a static area where water will lie. A drain from the low point in a pump housing may become a source of contamination if the pump is only periodically operational.

I. Piping

Piping in WFI systems usually consists of highly polished stainless steel. In a few cases, manufacturers have begun to use PVDF (polyvinylidene fluoride) piping. It is purported that this piping can tolerate heat with no extractables being leached. A major problem with PVDF tubing is that it requires considerable support. When this tubing is heated, it tends to sag and may stress the weld (fusion) connection and result in leakage. Additionally, initially at least, fluoride levels are high. This piping is of benefit in product delivery systems wherein low-level metal contamination may accelerate the degradation of drug product, such as in the biotech industry.

One common problem with piping is that of "dead-legs," which are defined as "not having an unused portion greater in length than six diameters of the unused pipe measured from the axis of the pipe in use." It should be pointed out that this was developed for hot (75°C–80°C), circulating systems. With colder systems (65°C–75°C), any drops or unused portion of any length of piping has the potential of forming a biofilm and should be eliminated, if possible, or have special sanitizing procedures. There should be no threaded fittings in a pharmaceutical water system. All pipe joints must use sanitary fittings or be butt-welded. Sanitary fittings are usually used where the piping meets valves, tanks, and other equipment that must be removed for maintenance or replacement. Therefore, the procedures for sanitization, as well as the actual piping, should be established and well documented.

J. Reverse Osmosis

Another acceptable method for manufacturing WFI is RO. However, because these systems are cold, and because RO filters are not absolute, microbiological contamination is not unusual. Because RO filters are not absolute, the filter manufacturers recommend that at least two be in series. There may be an UV light in the system downstream from the RO units to control microbiological contamination.

The ball valves in these systems are not considered sanitary valves because the center of the valve can have water in it when the valve is closed. This is a stagnant pool of water that can harbor microorganisms and provide a starting point for biofilm.

As an additional comment on RO systems, with the recognition of microbiological problems, some manufacturers have installed heat exchangers immediately after the RO filters to heat the water to 75°C to 80°C to minimize microbiological contamination.

With the development of biotechnology products, many small companies are using RO and UF systems to produce high-purity water. Most of these systems employ PVC or some type of plastic tubing. Because the systems are typically cold, the many joints in the system are subject to contamination. Another potential problem with PVC tubing is extractables. Without demonstration to the contrary, it is not possible to evaluate from the design of the system whether the extractables would pose any problem.

The systems also contain 0.2-mm point-of-use filters that can mask the level of microbiological contamination in the system. Although it is recognized that endotoxins are the primary concern in such a system, a filter will reduce microbiological contamination but not necessarily endotoxin contamination. If filters are used in a water system, there should be a stated purpose for the filter, for example, particulate removal or microbial reduction, and an SOP stating the frequency with which the filter is to be changed, which is based on data generated during the validation of the system.

As previously discussed, because of the volume of water actually tested (1 mL for endotoxins vs. 100 mL for WFI), the microbiological test offers a good index of the level of contamination in a system. Therefore, unless the water is sampled before the final 0.2-mm filter, microbiological testing has little meaning.

The FDA strongly recommends that the nonrecirculating water systems be drained daily and water not be allowed to sit in the system, as this practice is bound to produce highly erratic contamination levels.

K. Purified Water Systems

Many of the comments regarding equipment for WFI systems are applicable to purified water systems. One type system that has been used to control microbiological contamination uses ozone. For optimum effectiveness, it is required that dissolved ozone residual remain in the system. This presents both employee safety problems and use problems when drugs are formulated. Problems arise once the ozone generator is turned off or ozone is removed prior to placing the water in the recirculating system, particularly if the levels fall below 0.45 mg/L; also, if sampling is performed immediately after sanitization, results cannot be meaningful.

Purified water systems can be problematic if there is a one-way and not a recirculating system. Even if a heat exchanger is used to heat the water on a weekly basis and sanitize the system, this system shall be classified as "dead."

If a 0.2-mm in-line filter is used to sanitize the purified water on a daily basis, the filter housing provides a good environment for microbiological contamination; a typical problem is water hammer that can cause "ballooning" of the filter. If a valve downstream from the filter is shut too fast, the water pressure will reverse and can cause ballooning. Pipe vibration is a typical, visible sign of high back pressure while passage of upstream contaminants on the filter face is a real problem. Further problems arise where there are several vertical drops at use points. During sanitization, it is important to "crack" the terminal valves so that all of the elbows and bends in the piping are full of water and thus get complete exposure to the sanitizing agent.

It should be pointed out that simply because a system is a one-way system, it is not inadequate. With good SOPs, based on validation data, and routine hot flushings of this system, it could be acceptable. Long system (over 200 yards) with numerous outlets (e.g., over 50 outlets) can be acceptable, for example, with daily flushing of all outlets with 80°C water.

In one-way systems that employ a UV light to control microbiological contamination, it turns on only when water is needed. Thus, there are times when water is allowed to remain in the system. Systems containing flexible hose are very difficult to sanitize. UV lights must be properly maintained to work. The glass sleeves around the bulb(s) must be kept clean or their effectiveness will decrease. In multibulb units there must be a system to determine that each bulb is functioning. It must be remembered that, at best, UV light will kill only 90% of the organisms entering the unit.

L. Process Water

Currently, the USP, in the "General Notices" section, allows drug substances to be manufactured from potable water. It comments that any dosage form must be manufactured from purified water, WFI, or one of the forms of sterile water. There is some inconsistency in these two statements, because purified water has to be used for the granulation of tablets, yet potable water can be used for the final purification of the drug substance.

The FDA "Guide to Inspection of Bulk Pharmaceutical Chemicals" comments on the concern for the quality of the water used for the manufacture of drug substances, particularly those used in parenteral manufacture. Excessive levels of microbiological or endotoxin contamination have been found in drug substances, with the source of contamination being the water used in purification. At this time, WFI does not have to be used in the finishing steps of synthesis and purification of drug substances for parenteral use. However, such water systems should be validated to assure minimal endotoxin or microbiological contamination.

In the bulk drug substance industry, particularly for parenteral-grade substances, it is common to see UF and RO systems in use in water systems. Although UF may not be as efficient at reducing pyrogens, it reduces the high–molecular-weight endotoxins that are a contaminant in water systems. As with RO, UF is not absolute, but it reduces numbers. Additionally, as previously discussed with other cold systems, considerable maintenance is required to maintain the system.

For the manufacture of drug substances that are not for parenteral use, there is still a microbiological concern, although not to the degree as for parenteral-grade drug substances. In some areas of the world, potable (chlorinated) water may not present a microbiological problem. However, there may be other issues. For example, chlorinated water will generally increase chloride levels. In some areas, process water can be obtained directly from neutral sources.

M. Evaluation Strategy

Manufacturers should have some way of presenting their water quality data, which should be thoroughly reviewed to contain any investigation reports when values exceed limits.

Because microbiological test results from a water system are not usually obtained until after the drug product is manufactured, results exceeding limits should be reviewed with regard to the drug product formulated from such water. Consideration with regard to the further processing or release of such a product will depend on the specific contaminant, the process, and the end use of the product. Such situations are usually evaluated on a case-by-case basis. It is a good practice in such situations to include an investigation report with the logic for release or rejection. End-product microbiological testing, while providing some information, should not be relied on as the sole justification for the release of the drug product. The limitations of microbiological sampling and testing should be recognized. Manufacturers should also have maintenance records or logs for equipment, such as the still.

RELEVANT GUIDANCE DOCUMENTS (FDA)

1. Guidance for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Product, 1994.
2. Guideline for Validation of Limulus Amebocyte Lysate Test as an End Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices, 1987.
3. Guide to Inspections of Lyophilization of Parenterals, 1993.
4. Guide to Inspections of High-Purity Water Systems, 1993.
5. Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories, 1993.
6. Guide to Inspections of Sterile Drug Substance Manufacturers, 1994.
7. Pyrogens: Still a Danger, 1979 (Inspection Technical Guide); Bacterial Endotoxins/Pyrogens, 1985 (Inspection Technical Guide).
8. Heat Exchangers to Avoid Contamination, 1979 (Inspection Technical Guide).
9. Guidance for Industry: Container and Closure Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products, 1999.
10. Compliance Policy Guide 7132a.13: Parametric Release of Terminally Heat Sterilized Drug Products, 1987.
11. Compliance Policy Guide 7150.16: Status and Responsibilities of Contract Sterilizers Engaged in the Sterilization of Drugs and Devices, 1995.
12. Compliance Program CP7346.832: Pre-Approval Inspections/Investigations, 1994.
13. Compliance Program CP7346.843: Post-Approval Audit Inspections, 1992.
14. Compliance Program CP7346.002A: Sterile Drug Process Inspections, Foreign Inspection Guide, 1992.
15. Laboratory Inspection Guide, 1993.
16. Cleaning Validation Inspection Guide, 1993.

GLOSSARY

Action Limit—An established microbial or particulate level which, when exceeded, should trigger appropriate investigation and corrective action based on the investigation.

AirLock—A small room with interlocked doors, constructed to maintain air pressure control between adjoining rooms (generally with different air cleanliness standards). The intent of an aseptic processing airlock is to preclude ingress of particulate matter and microorganism contamination from a lesser-controlled area.

Alert Limit—An established microbial or particulate level giving early warning of potential drift from normal operating conditions and triggering appropriate scrutiny and follow-up to address the potential problem. Alert limits are always lower than action limits.

Asepsis—State of control attained by using an aseptic work area and performing activities in a manner that

precludes microbiological contamination of the exposed sterile product.

Aseptic Processing Facility—Building containing clean rooms in which air supply, materials, and equipment are regulated to control microbial and particulate contamination.

Aseptic Processing Room—A room in which one or more aseptic activities or processes are performed.

Atmosphere, The Earth's—The envelope of gases surrounding the earth, exerting under gravity a pressure at the earth's surface, which includes by volume 78% nitrogen, 21% oxygen, and small quantities of hydrogen, carbon dioxide, noble gases, water vapor, pollutants, and dust.

Atmospheric Pressure—The pressure exerted at the earth's surface by the atmosphere. For reference purposes a standard atmosphere is defined as 760 torr or mm Hg, or 760,000 mm.

Backstreaming—A process that occurs at low chamber pressures wherein hydrocarbon vapors from the vacuum system can enter the product chamber.

Barrier—Physical partition that affords aseptic manufacturing zone protection by partially separating it from the surrounding area.

Bioburden—Total number of microorganisms associated with a specific item prior to sterilization.

Biological Indicator (BI)—A population of microorganisms inoculated onto a suitable medium (e.g., solution, container/closure) and placed within appropriate sterilizer load locations to determine the sterilization cycle efficacy of a physical or chemical process. The challenged microorganism is selected based on its resistance to the given process. Incoming lot *D*-value and microbiological count define the quality of the BI.

Blank-Off Pressure—The ultimate pressure the pump or system can attain.

Blower—This pump is positioned between the mechanical pump and the chamber. It operates by means of two lobes turning at high speed. It is used to reduce the chamber pressure to less than 20 mm. See Mechanical Booster Pump.

Breaking Vacuum—Admitting air or a selected gas to an evacuated chamber, while isolated from a vacuum pump, to raise the pressure toward, or up to, atmospheric.

Circulation Pump—A pump for conveying the heat transfer fluid.

Clean Area—An area with defined particulate and microbiological cleanliness standards (e.g., Class 100, Class 10,000, or Class 100,000).

Clean Zone—See Clean Area.

Clean Room—A room designed, maintained, and controlled to prevent particulate and microbiological contamination of drug products. Such a room is assigned and must meet an appropriate air cleanliness classification.

Colony-Forming Unit (CFU)—A microbiological term that describes the formation of a single macroscopic colony after the introduction of one or more microorganism(s) into microbiological growth media. One colony-forming unit is expressed as 1 CFU.

Component—Any ingredient intended for use in the manufacture of a drug product, including one that may not appear in the final drug product.

Conax Connection—A device to pass thermocouple wires through and maintain a vacuum-tight vessel.

Condenser (Cold Trap)—In terms of the lyophilization process, the vessel that collects the moisture on plates and holds it in the frozen state. Protects the vacuum pump from water vapor contaminating the vacuum pump oil.

Condenser/Receiver—In terms of refrigeration, the unit that condenses (changes) the hot refrigerant gas into a liquid and stores it under pressure to be reused by the system.

Contamination—In the vacuum system, the introduction of water vapor into the oil in the vacuum pump, which then causes the pump to lose its ability to attain its ultimate pressure.

Cooling—Lowering the temperature in any part of the temperature scale.

Critical Areas—Areas designed to maintain sterility of sterile materials. Sterilized product, container/closures, and equipment may be exposed in critical areas.

Critical Surfaces—Surfaces that may come into contact with or directly impact on sterilized product or containers/closures. Critical surfaces are rendered sterile prior to the start of the manufacturing operation, and sterility is maintained throughout processing.

***D*-Value**—The time (minutes) of exposure to a given temperature that causes a one-log or 90% reduction in the population of a specific microorganism.

Decontamination—A process that eliminates viable bioburden via use of sporicidal chemical agents.

Defrosting—The removal of ice from a condenser by melting or mechanical means.

Degree of Crystallization—The ratio of the energy released during the freezing of a solution to that of an equal volume of water.

Degree of Supercooling—The number of degrees below the equilibrium freezing temperature where ice first starts to form.

Depyrogenation—A process used to destroy or remove pyrogens (e.g., endotoxin).

Desiccant—A drying agent.

Dry—Free from liquid or moisture, or both.

Drying—The removal of moisture and other liquids by evaporation.

Dynamic—Conditions relating to clean-area classification under conditions of normal production.

Endotoxin—A pyrogenic product (e.g., lipopolysaccharide) present in the bacterial cell wall. Endotoxin can lead to reactions ranging from fever to death in patients receiving injections.

Equilibrium Freezing Temperature—The temperature at which ice will form in the absence of supercooling.

Eutectic Temperature—A point of a phase diagram at which all phases are present and the temperature and composition of the liquid phase cannot be altered without one of the phases disappearing.

Expansion Tank—This tank is located in the circulation system and is used as a holding and expansion tank for the transfer liquid.

Filter or Filter/Drier—Two systems have their systems filtered or filter/dried: the circulation and refrigeration systems. In the newer dryers, this filter or filter/dryer is the same and can be replaced with a new core.

Free Water—Water that is absorbed on the surfaces of a product and must be removed to limit further biological and chemical reactions.

Freezing—The absence of heat. A controlled change of the product temperature as a function of time, during the

freezing process, so as to ensure a completely frozen form.

Gas Ballast—Used in the vacuum system on the vacuum pump to decontaminate small amounts of moisture in the vacuum pump oil.

Gas Bleed (Vacuum Control)—To control the pressure in the chamber during the cycle to help the drying process. In freeze-drying, the purpose is to improve heat transfer to the product.

Gowning Qualification—Program that establishes, both initially and on a periodic basis, the capability of an individual to don the complete sterile gown in an aseptic manner.

Heat Exchanger—The exchanger located in circulation and refrigeration systems that transfers heat from the circulation system to the refrigeration system.

Heat Transfer Fluid—A liquid of suitable vapor pressure and viscosity range for transferring heat to or from a component, for example, a shelf or condenser in a freeze-dryer. The choice of such a fluid may depend on safety considerations. Diathermic fluid.

HEPA filter—High-efficiency particulate air filter with minimum 0.3-μm particle-retaining efficiency of 99.97%.

Hot Gas Bypass—A refrigeration system to control the suction pressure of the big four (20–30 hp) compressors during the refrigeration operation.

Hot Gas Defrost—A refrigeration system to defrost the condenser plates after the lyophilization cycle is complete.

HVAC—Heating, ventilation, and air conditioning.

Ice—The solid, crystalline form of water.

Inert Gas—Any gas of a group including helium, radon, and nitrogen, formerly considered chemically inactive.

Interstage—In a two-stage compressor system, the crossover piping on top of the compressor that connects the low side to the high side. One could also think of it as low side, intermediate, and high side.

Interstage Pressure Regulating Valve—Valve that prevents the interstage pressure from exceeding 80 to 90 psi. This valve opens to suction as the interstage pressure rises above 80 to 90 psi.

Intervention—An aseptic manipulation or activity that occurs at the critical zone.

Isolator—A decontaminated unit, supplied with HEPA- or ULPA-filtered air, that provides uncompromised, continuous isolation of its interior from the external environment (e.g., surrounding clean-room air and personnel).

Laminarity—Unidirectional airflow at a velocity sufficient to uniformly sweep particulate matter away from a critical processing or testing area.

Lexsol—A heat transfer fluid (high grade kerosene).

Liquid Subcooler Heat Exchanger—The liquid refrigerant leaving the condenser/receiver at cooling water temperature is subcooled to a temperature of +15°F (–10°C) to –15°F (–25°C); see Subcooled Liquid.

Lyophilization—A process in which the product is first frozen and then, while still in the frozen state, the major portion of the water and solvent system is reduced by sublimation and desorption so as to limit biological and chemical reactions at the designated storage temperature.

Main Vacuum Valve—This valve between the chamber and external condenser to isolate the two vessels after the process is finished. This valve protects the finished product. See Vapor Valve.

Matrix—In terms of the lyophilization process, a system of ice crystals and solids that is distributed throughout the product.

Mechanical Booster Pump—A roots pump with a high displacement for its size but a low compression ratio. When backed by an oil-seal rotary pump, the combination is an economical alternative to a two-stage, oil-sealed rotary pump, with the advantage of obtaining a high vacuum. See Blower.

Mechanical Vacuum Pump—The mechanical pumping system that lowers the pressure in the chamber to below atmospheric pressure so that sublimation can occur.

Melting Temperature (Meltback)—That temperature at which mobile water first becomes evident in a frozen system.

Micron—A unit of pressure used in the lyophilization process. 1 mm = 1 Mtorr or 25,400 mm = 1 in Hg, or 760,000 mm = 1 atm. See Torr.

Noncondensables—A mixture of gases such as nitrogen, hydrogen, chlorine, and hydrocarbons, which may be drawn into the system through leaks when part of the system is under a vacuum. Presence of the gases reduces the operating efficiency of the system by increasing the condensing pressure.

Nucleation—The formation of ice crystals on foreign surfaces or as a result of the growth of water clusters.

Oil-Mist Filter—In vacuum terminology, a filter attached to the discharge (exhaust) of an oil-sealed rotary pump to eliminate most of the "smoke" of suspended fine droplets of oil that would be discharged into the environment.

Oil-Sealed Rotary Pump—A standard type of mechanical vacuum pump used in freeze-drying with a high compression ratio but a relatively low displacement (speed) for its size. A two-stage pump is effectively two such pumps in series and can obtain an ultimate vacuum.

Oil Separator—Separates the oil from the compressor discharge gas and returns the oil through the oil float trap and piping to the compressor crankcase.

Operator—Any individual participating in the aseptic processing operation, including line setup, filler, maintenance, or other personnel associated with aseptic line activities.

Overkill Sterilization Process—A process that is sufficient to provide at least a 12-log reduction of microorganisms having a minimum *D*-value of 1 minute.

Pyrogen—Substance that induces a febrile reaction in a patient.

Real Leak—A source of atmospheric gases resulting from a penetration through the chamber.

Reconstitute—Dissolving of the dried product into a solvent or diluent.

Relief Valve—Used for safety purposes to prevent damage in case excessive pressure is encountered.

Rotary Vane Pump—A mechanical pumping system with sliding vanes as the mechanical seal. Can be single or two stages.

Self-Liquid Heat Exchanger—Transfer of heat from the shelf fluid to the refrigeration system through tubes in the exchanger causing compressor suction gas to warm.

Shelf Compressor (Controlling Compressor)—For controlling shelf temperature, either by cooling or by preventing overheating.

Shelves—In terms of the lyophilization process, a form of heat exchanger within the chamber that has a

serpentine liquid flow through it, entering one side and flowing to the other side. Located in the circulation system.

Silicone Oil—A heat-transfer fluid.

Single-Stage Compressor—A normal type compressor used in refrigeration. In the lyophilization process, used to control the shelf temperature, both for cooling and keeping the shelf temperature from overheating by using a temperature controller.

Sterilization—The use of steam and pressure to kill any bacteria that could contaminate that environment or vessel.

Sterilizing-Grade Filter—A filter which, when appropriately validated, removes all microorganisms from a fluid stream, producing a sterile effluent.

Subcooled Liquid—The liquid refrigerant cooled through an exchanger so that it increases the refrigerating effect as well as reduces the volume of gas flashed from the liquid refrigerant passing through the expansion valve. See Liquid Subcooler Heat Exchanger.

Sublimation—Conversion of a material from a solid phase directly to a vapor phase, without passing through the liquid phase. Referred to as the primary drying stage.

Suction Line Accumulator—To prevent refrigerant liquid slug (droplets of liquid refrigerant) from returning to the compressor and damaging it.

Temperature—The degree of hotness or coldness of a body.

Terminal Sterilization—The application of a lethal agent to sealed, finished drug products to achieve a predetermined sterility assurance level of usually less than 10^6 (i.e., a probability of a nonsterile unit of greater than one in a million).

Thermocouple—A metal-to-metal contact between wires of two dissimilar metals that produces a small voltage across the free ends of the wires.

Thermostatic Expansion Valve—An automatic variable device controlling the flow of liquid refrigerant.

Torr—A unit of measure equivalent to the amount of pressure in 1000 mm. See Micron.

Trichloroethylene (TCE)—A heat-transfer fluid.

Two-Stage Compressor—A specially built compressor that attains low temperatures by being able to operate at low pressures. It is two compressors built into one: a low stage connected internally and a high stage connected externally with piping, called interstage. See Interstage

ULPA Filter—Ultra-low penetration air filter with a minimum 0.3-mm particle-retaining efficiency of 99.999%.

Unloading Valve—The valve that connects the interstage with suction to equalize both pressures during pumpdown.

Vacuum—Strictly speaking, a space in which the total pressure is less than atmospheric.

Vacuum Control (Gas Bleed)—To assist in the rate of sublimation by controlling the pressure in the lyophilizer.

Vacuum Pump—A mechanical way of reducing the pressure in a vessel below atmospheric pressure at which sublimation can occur. There are three types of pumps: rotary vane, rotary piston, and mechanical booster.

Vacuum Valves—Ball- or disk-type valves that can seal without leaking. The ball types are used for services to the chamber and condenser and also for drains and isolation applications. The disk types are used in the vacuum line system and are connected to the vacuum pump, chamber, and condenser.

Validation—Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

Vapor Baffle—A target-shaped object placed in the condenser to direct vapor flow and to promote an even distribution of condensate.

Vapor Valve—The vacuum valve between the chamber and external condenser. When this valve is closed, the chamber is isolated from the external condenser. Also known as the main vapor valve. See Main Vacuum Valve.

Vial—A small glass bottle with a flat bottom, short neck, and flat flange designed for stoppering.

Virtual Leak—In the vacuum system, the passage of gas into the chamber from a source that is located internally in the chamber.

Worst Case—A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, that pose the greatest chance of process or product failure (when compared to ideal conditions). Such conditions do not necessarily induce product or process failure.

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4

New Drug Application for Sterilized Products

I. INTRODUCTION

The efficacy of a given sterilization process for a specific drug product is evaluated on the basis of a series of protocols and scientific experiments designed to demonstrate that the sterilization process and associated control procedures can reproducibly deliver a sterile product. Data derived from experiments and control procedures allow conclusions to be drawn about the probability of nonsterile product units (sterility assurance level). Whether a drug product is sterilized by a terminal sterilization process or by an aseptic filling process, the efficacy of the sterilization process may be validated without the manufacture of three production batches. Sterilization process validation data, however, should be generated by procedures and conditions that are fully representative and descriptive of the procedures and conditions proposed for manufacture of the product in the application.

II. TERMINAL HEAT STERILIZATION

A. Description of the Process and Product

1. *Drug product and container/closure system.* Descriptions of the drug product and the container/closure system(s) to be sterilized (e.g., size(s), fill volume, or secondary packaging) should be provided.
2. *Sterilization process.* The sterilization process used to sterilize the drug product in its final container/closure system, as well as a description of any other sterilization process(es) used to sterilize delivery sets, components, packaging, bulk drug substance or bulk product, and related items, should be described. Information and data in support of the efficacy of these processes should also be submitted.
3. *Autoclave process and performance specifications.* The autoclave process, including pertinent information such as cycle type (e.g., saturated steam, water immersion, and water spray); cycle parameters; and performance specifications, including temperature, pressure, time, and minimum and maximum F_0, should be described. The autoclave(s) to be used for production sterilization, including manufacturer and model, should be identified.
4. *Autoclave loading patterns.* A description of representative autoclave loading patterns should be provided.
5. *Methods and controls to monitor production cycles.* Methods and controls used to monitor routine production cycles (e.g., thermocouples, pilot bottles, and biological indicators) should be described, including the number and location of each as well as acceptance and rejection specifications.
6. *Requalification of production autoclaves.* A description of the program for routine and unscheduled requalification of production autoclaves, including frequency, should be provided.
7. *Reprocessing.* A description and validation summary of any program that provides for reprocessing (e.g., additional thermal processing) of product should be provided.

B. Thermal Qualification of the Cycle

1. *Heat distribution and penetration studies.* Heat distribution and penetration study protocols and data summaries that demonstrate the uniformity, reproducibility, and conformance to specifications of the production sterilization cycle should be provided. Results from a minimum of three consecutive successful cycles should be provided to ensure that the results are consistent and meaningful.
2. *Thermal monitors.* The number of thermal monitors used and their location in the chamber should be described. A diagram is helpful.
3. *Effects of loading on thermal input.* Data should be generated with minimum and maximum load to demonstrate the effects of loading on thermal input to product. Additional studies may be necessary if different fill volumes are used in the same container line. Data summaries are acceptable for these purposes. A summary should consist of, for example, high and low temperatures (range), average temperature during the dwell period, minimum and maximum F_0 values, dwell time, run date and time, and identification of the autoclave(s) used. These data should have been generated from studies carried out in production autoclave(s) that will be used for sterilization of the product that is the subject of the application.
4. *Information included in the batch record.* The batch record supplied with the chemistry, manufacturing, and controls section of the application should identify the validated processes to be used for sterilization and for depyrogenation of any container/closure components. This information can be included in the batch record by reference to the validation protocol or standard operating procedure (SOP). Validation information should be provided as described previously.

C. Microbiological Efficacy of the Cycle

Validation studies that demonstrate the efficacy (lethality) of the production cycle should be provided. A sterility assurance of 10^{-6} or better should be demonstrated for any terminal sterilization process. This level of sterility assurance should be demonstrated for all parts of the drug product (including the container and closure, if applicable), which are claimed to be sterile. The specific type of study and the methods used to carry out the study (or studies) are product and process specific and may vary from manufacturer to manufacturer. In general, the following types of information and data should be provided.

1. *Identification and characterization of bioburden organisms.* The methods and results from studies used to identify and characterize bioburden organisms should be described. The amount and type of information supplied may depend on the validation strategy chosen. For example, more information may be needed for bioburden-based autoclave

processes than for overkill processes. Information concerning the number, type, and resistance of bioburden organisms may be necessary, including those organisms associated with the product solution and the container and closure. It may be necessary to identify the most heat-resistant bioburden organisms.

2. *Specifications for bioburden.* Specifications (alert and action levels) for bioburden should be provided. A description should be included of the program for routinely monitoring bioburden to ensure that validated and established limits are not exceeded (e.g., frequency of analysis and methods used in bioburden screening). The methods provided should be specific.
3. *Identification, resistance, and stability of biological indicators*. Information and data concerning the identification, resistance (D and Z values), and stability of biological indicators used in the biological validation of the cycle should be provided. If biological indicators are purchased from a commercial source, it may be necessary to corroborate the microbial count and resistance, and provide performance specifications.
4. *Resistance of the biological indicator relative to that of bioburden*. Studies characterizing the resistance of the biological indicator relative to that of bioburden may be necessary. Resistance in or on the product (i.e., in the product solution or on the surface of container or closure parts or interfaces) should be determined as necessary. If spore carriers are used (e.g., spore strips), the resistance of spores on the carrier relative to that of directly inoculated product should be determined, if necessary.
5. *Microbiological challenge studies*. Microbiological validation studies should be submitted that demonstrate the efficacy of the minimum cycle to provide a sterility assurance of 10^{-6} or better to the product under the most difficult to sterilize conditions (e.g., the most difficult to sterilize load with biological indicators at microbiological master sites or in master product or both). Use of a microbiological master product or site should be supported by scientific data. Microbiological master sites or solutions are those sites or solutions in which it is most difficult to kill the biological indicator under sterilization cycles that simulate production conditions.

D. Microbiological Monitoring of the Environment

Section 211.160 of the CFR requires, in part, the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to ensure that components, drug product containers, closures, in-process materials, and drug products conform to appropriate quality standards. Therefore, a microbiological monitoring program for production areas along with a bioburden monitoring program for product components and process water should be established. Process water includes autoclaved cooling water. Applicants should provide information concerning this program. Frequency, methods used, action levels, and data summaries should be included. A description of the actions taken when specifications are exceeded should be provided.

E. Container/Closure and Package Integrity

An applicant should provide scientific validation studies (and data) in support of the microbial integrity of the drug packaging components. The following types of information should be included

1. *Simulation of the stresses from processing*. Experimental designs should simulate the stresses of the sterilization process, handling, and storage of the drug and their effects on the container/closure system. Physical, chemical, and microbiological challenge studies may be necessary.
2. *Demonstrate integrity following maximum exposure*. Container-closure integrity should be demonstrated on product units that have been exposed to the maximum sterilization cycle(s). If a product is exposed to more than one process, then exposure to the maximum cycle of all processes should be incorporated into the study design.
3. *Multiple barriers*. Each barrier that separates areas of the drug product claimed to be sterile should be separately evaluated and validated.
4. *Sensitivity of the test.* The sensitivity of the experimental method used for container/closure integrity testing should be specified and provided.
5. *Integrity over product shelf life.* Microbial integrity of the container/closure system should be demonstrated over the shelf life of the product.

F. Bacterial Endotoxins Test and Method

The bacterial endotoxins test used for the product should be described. The description should include qualification of the laboratory, inhibition and enhancement testing and results, determination of noninhibitory concentration, and maximum valid dilution. For further information, see the agency guidance entitled "Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endo-toxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices."

G. Sterility Testing Methods and Release Criteria

Sterility test methods should be described and should include the protocol for selecting representative units during production. When test methods differ significantly from compendial test methods, a demonstration of the equivalency to the compendial method should be provided. Testing performed within barrier systems should be described, and information concerning validation of the barrier system may be necessary.

H. Evidence of Formal Written Procedures

Section 211.113(b) of the CFR requires that written procedures designed to prevent microbiological contamination of drug products purporting to be sterile be established and followed. Such procedures should include validation of any sterilization process. Therefore, evidence should be provided that there are formal written procedures describing the elements listed previously and that these procedures are followed. Such evidence may consist of SOPs, listing of SOPs, and protocols submitted as part of these elements.

III. OTHER TERMINAL STERILIZATION PROCESSES

Although the information provided previously directly addresses moist heat processes, the same type of information will pertain to other terminal sterilization processes used singly or in combination to sterilize a drug product. The types of information outlined are, in general, also applicable to ethylene oxide and radiation (gamma and electron beam). These other processes should be addressed as each applies to the drug product, sterile packaging, and in-process sterilization of components. Examples of such information might include descriptions of loading configurations; qualification

and validation of master load configurations; determination and validation of the efficacy of the minimum cycle to provide sterility assurance at the product master sites; requalification of the cycle; provisions for resterilization, specifications, and monitoring program for product bioburden; and container/closure integrity. Specific examples are provided to demonstrate the application of these concepts to other sterilization processes. Additional information relating to the effects of the sterilization process on the chemical and physical attributes of the drug substance or drug product may be applicable and should be supplied to the chemistry, manufacturing, and controls section of the application.

A. Ethylene Oxide

1. *Description of the sterilizer*. The sterilizer(s) and controlled site(s) for prehumidification and aeration of the product load should be described.
2. *Cycle parameters*. The parameters and limits for all phases of the cycle, such as prehumidification, gas concentration, vacuum and gas pressure cycles, exposure time and temperature, humidity, degassing, aeration, and determination of residuals, should be specified. Specific procedures used to monitor and control routine production cycles to assure that performance is within validated limits should be provided.
3. *Microbiological methods*. The microbiological methods (growth medium, incubation temperature, and time interval) for cultivating spores from inoculated samples during validation experiments should be described as well as the microbiological methods used as part of routine production cycles.
4. *Stability.* The program for monitoring the stability of packaging and the integrity of the container/closure system barrier over the claimed shelf life should be described.

B. Radiation

1. *Facility and process.* The radiation facility should be identified. The radiation source, method of exposure (i.e., movement through the irradiator), and the type and location of dosimeters used to monitor routine production loads should be described. If the low-dose site is not used for routine monitoring, data that show the dose relationship between the two sites should be provided.
2. *Packaging of the product*. The packaging of the drug product within the shipping carton and within the carrier should be described.
3. *Multiple-dose mapping studies*. Multiple-dose mapping studies for identification of low- and high-dose sites and demonstration of uniformity and reproducibility of the process should be described.
4. *Microbiological methods and controls*. The microbiological methods and controls used to establish, validate, and audit the efficacy of the cycle should be described.
5. *Monitoring stability*. The program for monitoring the stability of packaging and the integrity of the container/closure system barrier over the claimed shelf life should be described.

IV. ASEPTIC FILL MANUFACTURING PROCESSES

The following types of information should be submitted in support of sterility assurance for products manufactured by aseptic processing.

A. Buildings and Facilities

A brief description of the manufacturing building and facilities should be provided. The following information should be included

1. *Floor plan*. A floor plan of the areas holding the aseptic filling facilities, including preparation and holding areas, filtering and filling areas, and gowning rooms, should be included. The air cleanliness class of each area should be identified (e.g., class 100, class 10,000, class 100,000). Isolators or barrier systems should be identified.
2. *Location of equipment*. The placement of all critical equipment, including, but not limited to, laminar flow hoods, autoclaves, lyophilizers, and filling heads, should be identified. Equipment within barrier or isolation systems should be noted.

B. Overall Manufacturing Operation

The overall manufacturing operation including, for example, material flow, filling, capping, and aseptic assembly, should be described. The normal flow (movement) of product and components from formulation to finished dosage form should be identified and indicated on the floor plan described above. The following information should be considered when describing the overall manufacturing operation.

1. *Drug product solution filtration.* The specific bulk drug product solution filtration processes, including tandem filter units, prefilters, and bacterial retentive filters, should be described. A summary should be provided containing information and data concerning the validation of the retention of microbes and compatibility of the filter used for the specific product. Any effects of the filter on the product formulation should be described (e.g., adsorption of preservatives or active drug substance, or extractables).
2. *Specifications concerning holding periods.* Section 211.111 of the CFR requires, in part, when appropriate, the establishment of time limits for completing each phase of production to ensure the quality of the drug product. Therefore, specifications concerning any holding periods between the compounding of the bulk drug product and its filling into final containers should be provided. These specifications should include, holding tanks, times, temperatures, and conditions of storage. Procedures used to protect microbiological quality of the bulk drug during these holding periods should be indicated. Maintenance of the microbiological quality during holding periods may need verification.
3. *Critical operations.* The critical operations that expose product or product contact surfaces to the environment (such as transfer of sterilized containers or closures to the aseptic filling areas) should be described. Any barrier or isolation systems should be described.

C. Containers and Closures

The sterilization and depyrogenation processes used for containers, closures, equipment, components, and barrier systems should be described. A description of the validation of these processes should be provided including, where applicable, heat distribution and penetration summaries, biological challenge studies (microbiological indicators and endotoxins), and routine monitoring procedures. Validation information for sterilization processes other than moist heat should also be included. Methods and data (including controls) demonstrating distribution and penetration of the sterilant and microbiological efficacy of each process

should be submitted. The section of this guidance concerning terminal sterilization contains information that may be of further assistance.

1. *Bulk drug solution components sterilized separately.* If the bulk drug solution is aseptically formulated from components that are sterilized separately, information and data concerning the validation of each of these separate sterilization processes should be provided.
2. *Sterilization information in batch records*. The completed batch record supplied with the chemistry, manufacturing, and controls section of the application should identify the validated processes to be used for sterilization and depyrogenation of any container/closure components. This information may be included in the batch record by reference to the validation protocol or SOP.

D. Procedures and Specifications for Media Fills

The procedures and specifications used for media fills and summaries of results for validation using the same container/closure system and filling process that is to be used for the product should be described. The microbiological testing method(s) used should be described. Any procedural differences between the media fill and the production process should be indicated. A summary of recent media fill results, including failures, should be provided. These data should be obtained by the same filling line(s) that is to be used for the drug product. The following are recommended to be included with the data summary for each media fill run described.

1. *The filling room*. The aseptic filling area used should be identified and related to the floor plan.
2. Container-closure type and size.
3. Volume of medium used in each container.
4. Type of medium used.
5. Number of units filled.
6. Number of units incubated.
7. Number of units positive.
8. *Incubation parameters*. The incubation time and temperature for each group of units incubated and specifications for any group of units subjected to two (or more) different temperatures should be specified.
9. Date of each media fill.
10. *Simulations*. The procedures used to simulate any steps of a normal production fill should be described. This might include, for example, slower line speed, personnel shift changes, equipment failure and repair, mock lyophilization, and substitution of vial headspace gas.
11. *Microbiological monitoring*. The microbiological monitoring data obtained during the media fill runs should be provided.
12. *Process parameters*. The parameters used for production filling and for media fills (e.g., line speed, fill volume, number of containers filled, or duration of fill) should be compared.

E. Actions Concerning Product When Media Fills Fail

The disposition of product made before and after a failed media fill should be described. The description should include details of investigations, reviews, and how decisions are made to reject or release product.

F. Microbiological Monitoring of the Environment

The microbiological monitoring program used during routine production and media fills should be described. The frequency of monitoring, type of monitoring, sites monitored, alert and action level specifications, and precise descriptions of the actions taken when specifications are exceeded should be included.

1. *Microbiological methods.* The microbiological materials and methods used in the environmental monitoring program should be described. Methods may include sample collection, transport, neutralization of sanitizers, incubation, and calculation of results. The following are sources of microbial contamination and their monitoring that should be addressed, including specifications:
   - Airborne microorganisms
   - Microorganisms on inanimate surfaces
   - Microorganisms on personnel
   - Water systems
   - Product component bioburden
2. *Yeasts, molds, and anaerobic microorganisms.* A description of periodic or routine monitoring methods used for yeasts, molds, and anaerobes should be provided.
3. *Exceeded limits*. A description of the actions taken when specifications are exceeded should be provided.

G. Container/Closure and Package Integrity

The methods and results demonstrating the integrity of the microbiological barrier of the container/closure system should be summarized. This should include testing for initial validation. The procedures used for the stability protocol also should be described. For initial validation of microbiological integrity of container/closure systems, product sterility testing is not normally considered sufficient. The sensitivity of the experimental method used for container/closure integrity testing should be specified and provided.

H. Sterility Testing Methods and Release Criteria

Sterility test methods should be described and should include the protocol for selecting representative units during production. For a drug product represented to be a drug recognized in an official compendium, when test methods differ significantly from official compendial test methods, a demonstration of the equivalency to the official compendial method should be provided. Testing performed within barrier systems should be discussed, and information concerning validation of the barrier system may be necessary.

I. Bacterial Endotoxins Test and Method

The bacterial endotoxins test used for the product should be described, if applicable. This description should include qualification of the laboratory, inhibition and enhancement testing and results, determination of noninhibitory concentration, and maximum valid dilution. For further information see the agency guidance entitled "Guidance on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices."

J. Evidence of Formal Written Procedures

Evidence should be provided that there are formal written procedures describing the elements listed previously and that these procedures are followed. Such evidence may consist of SOPs or a listing of SOPs or protocols submitted as part of the elements listed previously.

V. MAINTENANCE OF MICROBIOLOGICAL CONTROL AND QUALITY: STABILITY CONSIDERATIONS

A. Container/Closure Integrity

The ability of the container/closure system to maintain the integrity of its microbial barrier and hence the sterility of a drug product throughout its shelf life should be demonstrated. As previously stated, sterility testing at the initial time point is not considered sufficient to demonstrate the microbial integrity of a container/closure system. Documentation of the sensitivity of the container/closure integrity test should be provided.

B. Preservative Effectiveness

The efficacy of preservative systems to control bacteria and fungi inadvertently introduced during drug product use should be demonstrated at the minimum concentration specified for drug product release or at the minimum concentration specified for the end of the expiration dating period, whichever is less. Because the efficacy of preservative systems is judged by their effect on microorganisms, microbial challenge assays should be performed. The United States Pharmacopoeia (USP) provides a microbial challenge assay under the title "Antimicrobial Preservatives—Effectiveness." For purposes of the stability protocol, the first three production lots should be tested with a microbial challenge assay at the beginning and end of the stability period. Chemical assays to monitor the concentration of preservatives should be performed at all test intervals. For subsequent lots placed on stability, chemical assays may be adequate to demonstrate the presence of specified concentrations of preservatives, and such testing should be carried out according to the approved stability study protocol.

C. Pyrogen or Endotoxin Testing

For drug products purporting to be pyrogen-free, it is recommended that pyrogen or endotoxin tests be carried out at the beginning and end of the stability period as part of the approved stability study protocol.

5

Validation of Cleaning Process

I. INTRODUCTION

Validation of cleaning procedures has generated considerable discussion since FDA documents, including the *Inspection Guide for Bulk Pharmaceutical Chemicals* and *Biotechnology Inspection Guide*, have briefly addressed this issue. These FDA documents clearly establish the expectation that cleaning procedures (processes) must be validated. It is recognized that for cleaning validation, as with validation of other processes, more than one way might exist to validate a process. In the end, the test of any validation process is whether or not scientific data show that the system consistently does as expected and produces a result that consistently meets predetermined specifications. The discussion in this chapter is intended to cover equipment cleaning for chemical residues only. While cleaning validation in the manufacture of over-the-counter (OTC) products may not be as great a concern as for the manufacture of other drugs, it is an important component of current good manufacturing practices (cGMPs) that requires reiteration, which is why this chapter has been included in a book dealing with OTC drugs.

II. BACKGROUND

For the FDA to require that equipment be clean prior to use is nothing new. The 1963 GMP Regulations (part 133.4) stated as follows: "Equipment shall be maintained in a clean and orderly manner." A similar section on equipment cleaning (211.67) was included in the 1978 cGMP regulations. Of course, the main rationale for requiring clean equipment is to prevent contamination or adulteration of drug products. Historically, FDA investigators have looked for gross insanitation due to inadequate cleaning and maintenance of equipment and/or poor dust-control systems. Also, historically speaking, the FDA was more concerned about contamination of nonpenicillin drug products with penicillins or cross-contamination of drug products with potent steroids or hormones. A number of products have been recalled over the past decade due to actual or potential penicillin cross-contamination.

One event that increased FDA awareness of the potential for cross-contamination due to inadequate procedures was the 1988 recall of a finished drug product, cholestyramine resin USP. The bulk pharmaceutical chemical used to produce the product had become contaminated with low levels of intermediates and degradants from the production of agricultural pesticides. The FDA instituted an import alert in 1992 on a foreign bulk pharmaceutical manufacturer that manufactured potent steroid products as well as nonsteroidal products using common equipment. This firm was a multiuse bulk pharmaceutical facility. The FDA considered the potential for cross-contamination to be significant and to pose a serious health risk to the public. The firm had only recently started a cleaning validation program at the time of the inspection, and it was considered inadequate by the FDA. One of the reasons why it was considered inadequate was that the firm was only looking for evidence of the absence of the previous compound. The firm had evidence, from TLC tests on the rinse water, of the presence of residues of reaction byproducts and degradants from the previous process.

III. GENERAL REQUIREMENTS

- The FDA expects firms to have written SOPs detailing the cleaning processes used for various pieces of equipment. If firms have one cleaning process for cleaning between different batches of the same product and use a different process for cleaning between product changes, the FDA expects the written procedures to address these different scenarios. Similarly, if firms have one process for removing water-soluble residues and another process for non-water-soluble residues, the written procedure should address both scenarios and make it clear when a given procedure is to be followed. Bulk pharmaceutical firms may decide to dedicate certain equipment for particular chemical manufacturing process steps that produce tarry or gummy residues that are difficult to remove from the equipment. Fluid-bed dryer bags are another example of equipment that is difficult to clean and is often dedicated to a specific product. Any residues from the cleaning process itself (detergents, solvents, and so on) also have to be removed from the equipment.
- The FDA expects firms to have written general procedures on how cleaning processes will be validated.
- The FDA expects the general validation procedures to address who is responsible for performing and approving the validation study, the acceptance criteria, and when revalidation will be required.
- The FDA expects firms to prepare specific written validation protocols in advance for the studies to be performed on each manufacturing system or piece of equipment, which should address such issues as sampling procedures and analytical methods to be used, including the sensitivity of those methods.
- The FDA expects firms to conduct the validation studies in accordance with the protocols and to document the results of studies.
- The FDA expects a final validation report that is approved by management and states whether or not the cleaning process is valid. The data should support a conclusion that residues have been reduced to an "acceptable level."

IV. EVALUATION OF CLEANING VALIDATION

The first step is to focus on the objective of the validation process; some companies fail to develop such objectives prior to establishing all sorts of protocols and detailed investigations.

It is not unusual to see manufacturers use extensive sampling and testing programs following the cleaning process without ever really evaluating the effectiveness of the steps used to clean the equipment. Several questions need to be addressed when evaluating the cleaning process. For example, at what point does a piece of equipment or system become clean? Does it have to be scrubbed by hand? What is accomplished by hand scrubbing rather than just a solvent wash? How variable are manual cleaning processes from batch to batch and product to product? The answers to these questions are obviously important to the evaluation of the cleaning process because one must determine the overall effectiveness of the process. Answers to these questions may also identify steps that can be eliminated for more effective measures and result in resource savings for the company.

Ideally, a piece of equipment or system will have one process for cleaning; however, this will depend on the products being produced and whether the cleanup occurs between batches of the same product (as in a large campaign) or between batches of different products. When the cleaning process is used only between batches of the same product (or different lots of the same intermediate in a bulk process), the manufacturer must only meet a criterion of "visibly clean" for the equipment; such between-batch cleaning processes do not require validation.

A. Equipment Design

The design of equipment, particularly in large systems that may employ semiautomatic or fully automatic clean-in-place (CIP) systems, is important. For example, a sanitary type of piping without ball valves should be used. When such ball valves are used, as is common in the bulk drug industry, the cleaning process is more difficult. When such systems are identified, it is important that operators performing cleaning operations be aware of problems and have special training in cleaning these systems and valves. The cleaning operators must have knowledge of these systems and the level of training and experience required for cleaning these systems. Also, the written and validated cleaning process must be properly identified and validated.

In larger systems, such as those employing long transfer lines or piping, flow charts and piping diagrams must be available for the identification of valves, as well as written cleaning procedures. Piping and valves should be tagged and easily identifiable by the operator performing the cleaning function. Sometimes, inadequately identified valves, both on prints and physically, have led to incorrect cleaning practices.

The documentation should be complete in regard to the cleaning processes of critical steps and should identify and control the length of time between the end of processing and each cleaning step. This is especially important for topicals, suspensions, and bulk drug operations. In such operations, the drying of residues will directly affect the efficiency of a cleaning process.

Whether or not CIP systems are used for cleaning of processing equipment, the microbiological aspects of equipment cleaning should be considered, largely through taking preventive measures rather than removing contamination once it has occurred. Manufacturers should maintain some evidence that routine cleaning and storage of equipment do not allow microbial proliferation. For example, equipment should be dried before storage, and under no circumstances should stagnant water be allowed to remain in equipment subsequent to cleaning operations.

Subsequent to the cleaning process, equipment may be subjected to sterilization or sanitization procedures when such equipment is used for sterile processing or to nonsterile processing when products may support microbial growth. While such sterilization or sanitization procedures are beyond the scope of this guide, it is important to note that control of the bioburden through adequate cleaning and storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary level of sterility. This is also particularly important from the standpoint of the control of pyrogens in sterile processing, as equipment sterilization processes may not be adequate to achieve significant inactivation or removal of pyrogens.

B. Cleaning Process, Written Procedure, and Documentation

The detail and specificity of the procedure for the (cleaning) process being validated and the amount of documentation required to establish it are critical. Some manufacturers use general SOPs, while others use a batch record or log sheet system that requires some type of specific documentation for performing each step. Depending on the complexity of the system and cleaning process and the ability and training of the operators, the amount of documentation necessary for executing various cleaning steps or procedures will vary.

When more complex cleaning procedures are required, it is important to document the critical cleaning steps (e.g., certain bulk drug synthesis processes). In this regard, it is valuable to have specific documentation on the equipment itself that includes information about who cleaned it and when; however, for relatively simple cleaning operations, merely documenting that the overall cleaning process was performed might be sufficient.

Other factors, such as history of cleaning, residue levels found after cleaning, and variability of test results, may also dictate the amount of documentation required. For example, when variable residue levels are detected following cleaning, particularly for a process that is believed to be acceptable, one must establish the effectiveness of the process and operator performance. Appropriate evaluations must be made, and when operator performance is deemed a problem more extensive documentation (guidance) and training may be required.

C. Analytical Methods

The specificity and sensitivity of the analytical method used to detect residuals or contaminants should be well established. With advances in analytical technology, residues from the manufacturing and cleaning processes can be detected at very low levels. If levels of contamination or residual are not detected, it does not mean that no residual contaminant is present after cleaning. It only means that levels of contaminant greater than the sensitivity or detection limit of the analytical method are not present in the sample. The firm should challenge the analytical method in combination with the sampling methods used to show that contaminants can be recovered from the equipment surface and at what level (e.g., 50% or 90% recovery). This is necessary before any conclusions can be made based on the sample results. A negative test may also be the result of poor sampling technique (see below).

D. Sampling

Two general types of sampling have been found to be acceptable. The most desirable is the direct method of sampling the surface of the equipment, and the other method is the use of rinse solutions.

1. Direct Surface Sampling

The type of sampling material used and its impact on the test data must be identified, as the sampling material may interfere with the test; for example, the adhesive used in swabs has been found to interfere with analysis of samples. Therefore, early in the validation program, it is important to ensure that the sampling medium and solvent (used for extraction from the medium) are satisfactory and can be readily used. Advantages of direct sampling are that areas that are the most difficult to clean and which are reasonably accessible can be evaluated, leading to establishment of a level of contamination or residue per given surface area. Additionally, residues that are dried out or are insoluble can be sampled by physical removal.

2. Rinse Samples

Two advantages of using rinse samples are that a larger surface area may be sampled and inaccessible systems or ones that cannot be routinely disassembled can be sampled and evaluated. A disadvantage of rinse samples is that the residue or contaminant may not be soluble or may be physically occluded in the equipment. An analogy that can be used is a dirty pot. When evaluating the cleaning of a dirty pot, particularly one with dried-out residue, one does not look at the rinse water to see that it is clean; one looks at the pot. It is important to ensure that a direct measurement of the residue or contaminant is made for the rinse water when it is used to validate the cleaning process. For example, it is not acceptable to simply test rinse water for water quality (does it meet the compendia tests?) rather than test it for potential contaminates.

3. Routine Production In-Process Control Monitoring

Indirect testing, such as conductivity testing, may be of some value for routine monitoring once a cleaning process has been validated. This would be particularly true for bulk drug substance manufacturers whose reactors, centrifuges, and piping between such large equipment can be sampled only using rinse solution samples. Any indirect test method must have been shown to correlate with the condition of the equipment. During validation, a manufacturer should be able to provide documentation that testing the uncleaned equipment gives a not acceptable result for the indirect test.

V. ESTABLISHMENT OF LIMITS

The FDA does not generally set acceptance specifications or methods for determining whether a cleaning process is validated. It is impractical for the FDA to do so due to the wide variation in equipment and products used throughout the bulk and finished dosage form industries. A manufacturer's rationale for the residue limits established should be logical based on the manufacturer's knowledge of the materials involved and should be practical, achievable, and verifiable. It is important to define the sensitivity of the analytical methods in order to set reasonable limits. Some limits that have been mentioned by industry representatives in the literature or in presentations include analytical detection levels (such as 10 ppm), biological activity levels (such as 1/1000 of the normal therapeutic dose), and organoleptic levels such as no visible residue.

The manner in which limits are established should be documented. Unlike finished pharmaceuticals, where the chemical identities of residuals are known (e.g., from actives, inactives, detergents), bulk processes may have partial reactants and unwanted byproducts that may never have been chemically identified. In establishing residual limits, it may not be adequate to focus only on the principal reactant, as other chemical variations may be more difficult to remove. In some circumstances, TLC screening, in addition to chemical analyses, may be needed. In a bulk process, particularly for very potent chemicals such as some steroids, the issue of by products must be considered if equipment is not dedicated.

VI. OTHER ISSUES

A. Placebo Product

In order to evaluate and validate cleaning processes, some manufacturers have processed a placebo batch in the equipment under essentially the same operating parameters used for processing product. A sample of the placebo batch is then tested for residual contamination. One cannot be sure that a contaminant is uniformly distributed throughout the system. For example, if the discharge valve or chute of a blender is contaminated, the contaminant would probably not be uniformly dispersed in the placebo; it would most likely be concentrated in the initial discharge portion of the batch. Additionally, if the contaminant or residue is of a larger particle size, it may not be uniformly dispersed in the placebo. Some firms have made the assumption that a residual contaminant would wear off the equipment surface uniformly, but this is an invalid conclusion. Finally, the analytical power may be greatly reduced by dilution of the contaminate. Because of such problems, rinse and/or swab samples should be used in conjunction with the placebo method.

B. Detergent

If a detergent or soap is used for cleaning, evaluate the difficulty that may arise when attempting to test for residues. A common problem associated with detergent use is its composition. Many detergent suppliers will not provide a specific composition, which makes it difficult for the user to evaluate residues. As with product residues, it is important and it is expected that the manufacturer evaluate the efficiency of the cleaning process for the removal of residues. However, unlike product residues, it is expected that no (or, for ultrasensitive analytical tests, very little) detergent remains after cleaning. Detergents are not part of the manufacturing process and are only added to facilitate cleaning during the cleaning process. Thus, they should be easily removable; otherwise, a different detergent should be selected.

C. Test Until Clean

Evaluate the level of testing and the retest results when using this concept. Test, resample, and retest equipment or systems until an acceptable residue level is attained. For a system or equipment with a validated cleaning process, this practice of resampling should not be utilized and is acceptable only in rare cases. Constant retesting and resampling can show that the cleaning process is not validated, as these retests actually document the presence of unacceptable residue and contaminants from an ineffective cleaning process.

Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

I. INTRODUCTION

This document is concerned with testing and evaluation of the viral safety of biotechnology products derived from characterized cell lines of human or animal origin (i.e., mammalian, avian, insect) and outlines data that should be submitted in the marketing application/registration package. For the purposes of this document, the term virus excludes nonconventional transmissible agents like those associated with bovine spongiform encephalopathy and scrapie. Applicants are encouraged to discuss issues associated with bovine spongiform encephalopathy with the regulatory authorities.

The scope of the document covers products derived from cell cultures initiated from characterized cell banks. It covers products derived from in vitro cell culture, such as interferons, monoclonal antibodies, and recombinant DNA-derived products including recombinant subunit vaccines, and also includes products derived from hybridoma cells grown in vivo as ascites. In the latter case, special considerations apply and additional information on testing cells propagated in vivo is contained in Appendix 1. Inactivated vaccines, all live vaccines containing self-replicating agents, and genetically engineered live vectors are excluded from the scope of this document.

The risk of viral contamination is a feature common to all biotechnology products derived from cell lines. Such contamination could have serious clinical consequences and can arise from the contamination of the source cell lines themselves (cell substrates) or from adventitious introduction of virus during production. To date, however, biotechnology products derived from cell lines have not been implicated in the transmission of viruses. Nevertheless, it is expected that the safety of these products with regard to viral contamination can be reasonably assured only by the application of a virus testing program and assessment of virus removal and inactivation achieved by the manufacturing process, as outlined below.

Three principal, complementary approaches have evolved to control the potential viral contamination of biotechnology products:

(a) selecting and testing cell lines and other raw materials, including media components, for the absence of undesirable viruses which may be infectious and/or pathogenic for humans,
(b) assessing the capacity of the production processes to clear infectious viruses, and
(c) testing the product at appropriate steps of production for absence of contaminating infectious viruses.

All testing suffers from the inherent limitation of quantitative virus assays, that is, that the ability to detect low viral concentrations depends for statistical reasons on the size of the sample. Therefore, no single approach will necessarily establish the safety of a product. Confidence that infectious virus is absent from the final product will in many instances not be derived solely from direct testing for its presence but also from a demonstration that the purification regimen is capable of removing and/or inactivating the viruses.

The type and extent of viral tests and viral clearance studies required at different steps of production will depend on various factors and should be considered on a case-by-case and step-by-step basis. The factors that should be taken into account include the extent of cell bank characterization and qualification, the nature of any viruses detected, culture medium constituents, culture methods, facility and equipment design, the results of viral tests after cell culture, the ability of the process to clear viruses, and the type of product and its intended clinical use.

The purpose of this document is to provide a general framework for virus testing, experiments for the assessment of viral clearance, and a recommended approach for the design of viral tests and viral clearance studies. Related information is described in the appendices and selected definitions are provided in the glossary.

The manufacturers should adjust the recommendations presented here to their specific product and its production process. The approach used by manufacturers in their overall strategy for ensuring viral safety should be explained and justified. In addition to the detailed data which is provided, an overall summary of the viral safety assessment would be useful in facilitating the review by regulatory authorities. This summary should contain a brief description of all aspects of the viral safety studies and strategies used to prevent virus contamination as they pertain to this document.

II. POTENTIAL SOURCES OF VIRUS CONTAMINATION

Viral contamination of biotechnology products may arise from the original source of the cell lines or from adventitious introduction of virus during production processes.

A. Viruses That Could Occur in the Master Cell Bank

Cells may have latent or persistent virus infection (e.g., herpesvirus) or endogenous retrovirus which may be transmitted vertically from one cell generation to the next, since the viral genome persists within the cell. Such viruses may be constitutively expressed or may unexpectedly become expressed as an infectious virus.

Viruses can be introduced into the master cell bank (MCB) by several routes such as (1) derivation of cell lines from infected animals, (2) use of virus to establish the cell line, (3) use of contaminated biological reagents such as animal serum components, and (4) contamination during cell handling.

B. Adventitious Viruses That Could Be Introduced during Production

Adventitious viruses can be introduced into the final product by several routes including, but not limited to, the following: (1) the use of contaminated biological reagents such as animal serum components; (2) the use of a virus for the induction of expression of specific genes encoding a desired protein; (3) the use of a contaminated reagent, such as a monoclonal antibody affinity column; (4) the use of a contaminated excipient during formulation; and (5) contamination during cell and medium handling. Monitoring of cell culture parameters can be helpful in the early detection of potential adventitious viral contamination.

III. CELL LINE QUALIFICATION: TESTING FOR VIRUSES

An important part of qualifying a cell line for use in the production of a biotechnology product is the appropriate testing for the presence of virus.

A. Suggested Virus Tests for MCB, Working Cell Bank, and Cells at the Limit of In Vitro Cell Age Used for Production

Table 1 shows an example of virus tests to be performed once only at various cell levels, including MCB, WCB, and cells at the limit of in vitro cell age used for production.

1. Master Cell Bank

Extensive screening for both endogenous and nonendogenous viral contamination should be performed on the MCB. For heterohybrid cell lines in which one or more partners are human or nonhuman primate in origin, tests should be performed in order to detect viruses of human or nonhuman primate origin as viral contamination arising from these cells may pose a particular hazard.

Table 1 Virus Tests to Be Performed Once at Various Cell Levels

	MCB	WCB[a]	Cells at the Limit[b]
Tests for retroviruses and other endogenous viruses			
Infectivity	+	−	+
Electron microscopy[c]	+[c]	−	+[c]
Reverse transcriptase[d]	+[d]	−	+[d]
Other virus-specific tests[e]	As appropriate[e]	−	As appropriate[e]
Tests for nonendogenous or adventitious viruses			
In vitro assays	+	−[f]	+
In vivo assays	+	−[f]	+
Antibody production tests[g]	+[g]	−	−
Other virus-specific tests[h]	+[h]	−	−

[a] See text—Section III.A.2.
[b] Cells at the limit: cells at the limit of in vitro cell age used for production (see text—Section III.A.3).
[c] May also detect other agents.
[d] Not necessary if positive by retrovirus infectivity test.
[e] As appropriate for cell lines which are known to have been infected by such agents.
[f] For the first WCB, this test should be performed on cells at the limit of in vitro cell age, generated from that WCB; for WCBs subsequent to the first WCB, a single in vitro and in vivo test can be done either directly on the WCB or on cells at the limit of in vitro cell age.
[g] e.g., MAP, RAP, HAP—Usually applicable for rodent cell lines.
[h] e.g., tests for cell lines derived from human, nonhuman primate, or other cell lines as appropriate.

Testing for nonendogenous viruses should include in vitro and in vivo inoculation tests and any other specific tests, including species-specific tests such as the mouse antibody production (MAP) test, that are appropriate, based on the passage history of the cell line, to detect possible contaminating viruses.

2. Working Cell Bank

Each WCB as a starting cell substrate for drug production should be tested for adventitious virus either by direct testing or by analysis of cells at the limit of in vitro cell age, initiated from the WCB. When appropriate nonendogenous virus tests have been performed on the MCB and cells cultured up to or beyond the limit of in vitro cell age have been derived from the WCB and used for testing for the presence of adventitious viruses, similar tests need not be performed on the initial WCB. Antibody production tests are usually not necessary for the WCB. An alternative approach in which full tests are carried out on the WCB rather than on the MCB would also be acceptable.

3. Cells at the Limit of In Vitro Cell Age Used for Production

The limit of in vitro cell age used for production should be based on data derived from production cells expanded under pilot-plant scale or commercial-scale conditions to the proposed in vitro cell age or beyond. Generally, the production cells are obtained by expansion of the WCB; the MCB could also be used to prepare the production cells. Cells at the limit of in vitro cell age should be evaluated once for those endogenous viruses that may have been undetected in the MCB and WCB. The performance of suitable tests (e.g., in vitro and in vivo) at least once on cells at the limit of in vitro cell age used for production would provide further assurance that the production process is not prone to contamination by adventitious virus. If any adventitious viruses are detected at this level, the process should be carefully checked in order to determine the cause of the contamination, and completely redesigned if necessary.

B. Recommended Viral Detection and Identification Assays

Numerous assays can be used for the detection of endogenous and adventitious viruses. Table 2 outlines examples for these assays. They should be regarded as assay protocols recommended for the present, but the list is not all-inclusive or definitive. Since the most appropriate techniques may change with scientific progress, proposals for alternative techniques, when accompanied by adequate supporting data, may be acceptable. Manufacturers are encouraged to discuss these alternatives with the regulatory authorities. Other tests may be necessary depending on the individual case. Assays should include appropriate controls to ensure adequate sensitivity and specificity. Wherever a relatively high possibility of the presence of a specific virus can be predicted from the species of origin of the cell substrate, specific tests and/or approaches may be necessary. If the cell line used for production is of human or nonhuman primate origin, additional tests for human viruses, such as those causing immunodeficiency diseases and hepatitis, should be performed unless otherwise justified. The polymerase chain reaction (PCR) may be appropriate for detection of sequences of these human viruses as well as for other specific viruses. The following is a brief description of a general framework and philosophical

Table 2 Examples of the Use and Limitations of Assays Which May Be Used to Test for Virus

Test	Test Article	Detection Capability	Detection Limitation
Antibody production	Lysate of cells and their culture medium	Specific viral antigens	Antigens not infectious for animal test system
In vivo virus screen	Lysate of cells and their culture medium	Broad range of viruses pathogenic for humans	Agents failing to replicate or produce diseases in the test system
In vitro virus screen for 1. Cell bank characterization 2. Production screen	1. Lysate of cells and their culture medium (for cocultivation, intact cells should be in the test article) 2. Unprocessed bulk harvest or lysate of cells and their cell culture medium from the production reactor	Broad range of viruses pathogenic for humans	Agents failing to replicate or produce diseases in the test system
TEM on 1. Cell substrate 2. Cell culture supernatant	 1. Viable cells 2. Cell-free culture supernatant	Virus and virus-like particles	Qualitative assay with assessment of identity
Reverse transcriptase (RT)	Cell-free culture supernatant	Retroviruses and expressed retroviral RT	Only detects enzymes with optimal activity under preferred conditions. Interpretation may be difficult due to presence of cellular enzymes; background with some concentrated samples
Retrovirus (RV) infectivity	Cell-free culture supernatant	Infectious retroviruses	RV failing to replicate or form discrete foci or plaques in the chosen test system
Cocultivation 1. Infectivity endpoint 2. TEM endpoint 3. RT endpoint	Viable cells	Infectious retroviruses	RV failing to replicate 1. See above under RV infectivity 2. See above under TEM[a] 3. See above under RT
PCR (Polymerase chain reaction)	Cells, culture fluid, and other materials	Specific virus sequences	Primer sequences must be present. Does not indicate whether virus is infectious

[a] In addition, difficult to distinguish test article from indicator cells.

background within which the manufacturer should justify what was done.

1. Tests for Retroviruses

For the MCB and for cells cultured up to or beyond the limit of in vitro cell age used for production, tests for retroviruses, including infectivity assays in sensitive cell cultures and electron microscopy studies, should be carried out. If infectivity is not detected and no retrovirus or retrovirus-like particles have been observed by electron microscopy, reverse transcriptase (RT) or other appropriate assays should be performed to detect retroviruses which may be noninfectious. Induction studies have not been found to be useful.

2. In Vitro Assays

In vitro tests are carried out by the inoculation of a test article (Table 2) into various susceptible indicator cell cultures capable of detecting a wide range of human and relevant animal viruses. The choice of cells used in the test is governed by the species of origin of the cell bank to be tested, but should include a human and/or a nonhuman primate cell line susceptible to human viruses. The nature of the assay and the sample to be tested are governed by the type of virus which may possibly be present based on the origin or handling of the cells. Both cytopathic and hemadsorbing viruses should be sought.

3. In Vivo Assays

A test article (Table 2) should be inoculated into animals, including suckling and adult mice, and in embryonated eggs to reveal viruses that cannot grow in cell cultures. Additional animal species may be used depending on the nature and source of the cell lines being tested. The health of the animals should be monitored and any abnormality should be investigated to establish the cause of the illness.

4. Antibody Production Tests

Species-specific viruses present in rodent cell lines may be detected by inoculating test article (Table 2) into virus-free animals, and by examining the serum antibody level or enzyme activity after a specified period. Examples of such tests are the mouse antibody production (MAP) test, rat antibody production (RAP) test, and hamster antibody production (HAP) test. The viruses currently screened for in the antibody production assays are discussed in Table 3.

C. Acceptability of Cell Lines

It is recognized that some cell lines used for the manufacture of product will contain endogenous retroviruses, other viruses, or viral sequences. In such circumstances, the action plan recommended for manufacture is described in section V of this document. The acceptability of cell lines containing viruses other than endogenous retroviruses will be considered on an individual basis by the regulatory authorities, by taking into account a risk/benefit analysis based on the benefit of the product and its intended clinical use, the nature of the contaminating viruses, their potential for infecting humans or for causing disease in humans, the purification process for the product (e.g., viral clearance evaluation data), and the extent of the virus tests conducted on the purified bulk.

Table 3 Virus Detected in Antibody Production Tests

MAP	HAP	RAP
Ectromelia virus[b,c]	Lymphocytic choriomeningitis virus (LCM)[a,c]	Hantaan virus[a,c]
Hantaan virus[a,c]	Pneumonia virus of mice (PVM)[b,c]	Kilham rat virus (KRV)[b,c]
K virus[b]	Reovirus type 3 (Reo3)[a,c]	Mouse encephalomyelitis virus (Theilers, GDVII)[b]
Lactic dehydrogenase virus (LDM)[a,c]	Sendai virus[a,c]	Pneumonia virus of mice (PVM)[b,c]
	SV5	Rat coronavirus (RCV)[b]
Lymphocytic choriomeningitis virus (LCM)[a,c]		Reovirus type 3 (Reo3)[a,c]
Minute virus of mice [b,c]		Sendai virus[a,c]
Mouse adenovirus (MAV)[b,c]		Sialoacryoadenitis virus (SDAV)[b]
Mouse cytomegalovirus (MCMV)[b,c]		
Mouse encephalomyelitis virus (Theilers, GDVII)[b]		Toolan virus (HI)[b,c]
Mouse hepatitis virus (MHV)[b]		
Mouse rotavirus (EDIM)[b,c]		
Pneumonia virus of mice (PVM)[b,c]		
Polyoma virus[b]		
Reovirus type 3 (Reo3)[a,c]		
Sendai virus[a,c]		
Thymic virus[b]		

[a] Viruses for which there is evidence of capacity for infecting humans or primates.
[b] Viruses for which there is no evidence of capacity for infecting humans.
[c] Virus capable of replicating in vitro in cells of human or primate origin.

IV. TESTING FOR VIRUSES IN UNPROCESSED BULK

The unprocessed bulk constitutes one or multiple pooled harvests of cells and culture media. When cells are not readily accessible (e.g., hollow fiber or similar systems), the unprocessed bulk would constitute fluids harvested from the fermenter. A representative sample of the unprocessed bulk, removed from the production reactor prior to further processing, represents one of the most suitable levels at which the possibility of adventitious virus contamination can be determined with a high probability of detection. Appropriate testing for viruses should be performed at the unprocessed bulk level unless virus testing is made more sensitive by initial partial processing (e.g., unprocessed bulk may be toxic in test cell cultures, whereas partially processed bulk may not be toxic).

In certain instances, it may be more appropriate to test a mixture consisting of both intact and disrupted cells and their cell culture supernatants removed from the production reactor prior to further processing. Data from at least 3 lots of unprocessed bulk at pilot-plant scale or commercial scale should be submitted as part of the marketing application/registration package.

It is recommended that manufacturers develop programs for the ongoing assessment of adventitious viruses in production batches. The scope, extent, and frequency of virus testing on the unprocessed bulk should be determined by taking several points into consideration including the nature of the cell lines used to produce the desired products, the results and extent of virus tests performed during the qualification of the cell lines, and the cultivation method, raw material sources, and results of viral clearance studies. In vitro screening tests, using one or several cell lines, are generally employed to test unprocessed bulk. If appropriate, a PCR test or other suitable methods may be used.

Generally, harvest material in which adventitious virus has been detected should not be used to manufacture the product. If any adventitious viruses are detected at this level, the process should be carefully checked to determine the cause of the contamination, and appropriate actions taken.

V. RATIONALE AND ACTION PLAN FOR VIRAL CLEARANCE STUDIES AND VIRUS TESTS ON PURIFIED BULK

It is important to design the most relevant and rational protocol for virus tests from the MCB level, through the various steps of drug production, to the final product including evaluation and characterization of viral clearance from unprocessed bulk. The evaluation and characterization of viral clearance plays a critical role in this scheme. The goal should be to obtain the best reasonable assurance that the product is free of virus contamination.

In selecting viruses to use for a clearance study, it is useful to distinguish between the need to evaluate processes for their ability to clear viruses that are known to be present and the desire to estimate the robustness of the process by characterizing the clearance of nonspecific "model" viruses (described later). Definitions of "relevant," specific, and nonspecific "model" viruses are given in the glossary. Process evaluation requires knowledge of how much virus may be present in the process, such as the unprocessed bulk, and how much can be cleared in order to assess product safety. Knowledge of the time dependence for inactivation procedures is helpful in assuring the effectiveness of the inactivation process. When evaluating clearance of known contaminants, in-depth time-dependent inactivation studies, demonstration of reproducibility of inactivation/removal, and evaluation of process parameters will be needed. When a manufacturing process is characterized for robustness of clearance using nonspecific "model" viruses, particular attention should be paid to nonenveloped viruses in the study design. The extent of viral clearance characterization studies may be influenced by the results of tests on cell lines and unprocessed bulk. These studies should be performed as described below (section VI).

Table 4 presents an example of an action plan, in terms of process evaluation and characterization of viral clearance as well as virus tests on purified bulk, in response to the results of virus tests on cells and/or the unprocessed bulk. Various cases are considered. In all cases, characterization of clearance using nonspecific "model" viruses should be performed. The most common situations are Cases A and B. Production systems contaminated with a virus other than a

Table 4 Action Plan for Process Assessment of Viral Clearance and Virus Tests on Purified Bulk

	Case A	Case B	Case C[b]	Case D[b]	Case E[b]
Status					
Presence of virus[a]	−	−	+	+	(+)[c]
Virus-like particles[a]	−	−	−	−	(+)[c]
Retrovirus-like particles[a]	−	+	−	−	(+)[c]
Virus identified	Not applicable	+	+	+	−
Virus pathogenic for humans	Not applicable	−[d]	−[d]	+	Unknown
Action					
Process characterization of viral clearance using nonspecific "model" viruses	Yes[e]	Yes[e]	Yes[e]	Yes[e]	Yes[g]
Process evaluation of viral clearance using "relevant" or specific "model" viruses	No	Yes[f]	Yes[f]	Yes[f]	Yes[g]
Test for virus in purified bulk	Not applicable	Yes[h]	Yes[h]	Yes[h]	Yes[h]

[a] Results of virus tests for the cell substrate and/or at the unprocessed bulk level. Cell cultures used for production which are contaminated with viruses will generally be not acceptable. Endogenous viruses (such as retroviruses) or viruses that are an integral part of the MCB may be acceptable if appropriate viral clearance evaluation procedures are followed.

[b] The use of source material which is contaminated with viruses, whether or not they are known to be infectious and/or pathogenic in humans, will only be permitted under very exceptional circumstances.

[c] Virus has been observed by either direct or indirect methods.

[d] Believed to be nonpathogenic.

[e] Characterization of clearance using nonspecific "model" viruses should be performed.

[f] Process evaluation for "relevant" viruses or specific "model" viruses should be performed.

[g] See text under Case E.

[h] The absence of detectable virus should be confirmed for purified bulk by means of suitable methods having high specificity and sensitivity for the detection of the virus in question. For the purpose of marketing authorization, data from at least 3 lots of purified bulk manufactured at pilot-plant scale or commercial scale should be provided. However, for cell lines such as CHO cells for which the endogenous particles have been extensively characterized and adequate clearance has been demonstrated, it is not usually necessary to assay for the presence of the noninfectious particles in purified bulk.

rodent retrovirus are normally not used. Where there are convincing and well-justified reasons for drug production using a cell line from Cases C, D, or E, these should be discussed with the regulatory authorities. With Cases C, D, and E it is important to have validated effective steps to inactivate/remove the virus in question from the manufacturing process.

Case A: Where no virus, virus-like particle, or retrovirus-like particle has been demonstrated in the cells or the unprocessed bulk, virus removal and inactivation studies should be performed with nonspecific "model" viruses as previously stated.

Case B: Where only a rodent retrovirus (or a retrovirus-like particle which is believed to be nonpathogenic, such as rodent A- and R-type particles) is present, process evaluation using a specific "model" virus, such as a murine leukemia virus, should be performed. Purified bulk should be tested using suitable methods having high specificity and sensitivity for the detection of the virus in question. For marketing authorization, data from at least 3 lots of purified bulk at pilot-plant scale or commercial scale should be provided. Cell lines such as CHO, C127, BHK, and murine hybridoma cell lines have frequently been used as substrates for drug production with no reported safety problems related to viral contamination of the products. For these cell lines in which the endogenous particles have been extensively characterized and clearance has been demonstrated, it is not usually necessary to assay for the presence of the noninfectious particles in purified bulk. Studies with nonspecific "model" viruses, as in Case A, are appropriate.

Case C: When the cells or unprocessed bulk are known to contain a virus, other than a rodent retrovirus, for which there is no evidence of capacity for infecting humans, [such as those identified by footnote 2 in Table 3, except rodent retroviruses (Case B)], virus removal and inactivation evaluation studies should use the identified virus. If it is not possible to use the identified virus, "relevant" or specific "model" viruses should be used to demonstrate acceptable clearance. Time-dependent inactivation for identified (or "relevant" or specific "model") viruses at the critical inactivation step(s) should be obtained as part of process evaluation for these viruses. Purified bulk should be tested using suitable methods having high specificity and sensitivity for the detection of the virus in question. For the purpose of marketing authorization, data from at least 3 lots of purified bulk manufactured at pilot-plant scale or commercial scale should be provided.

Case D: Where a known human pathogen, such as those indicated by footnote 1 in Table 3, is identified, the product may be acceptable only under exceptional circumstances. In this instance, it is recommended that the identified virus be used for virus removal and inactivation evaluation studies and specific methods with high specificity and sensitivity for the detection of the virus in question be employed. If it is not possible to use the identified virus, "relevant" and/or specific "model" viruses (described later) should be used. The process should be shown to achieve the removal and inactivation of the selected viruses during the purification and inactivation processes. Time-dependent inactivation data for the critical inactivation step(s) should be obtained as part of process evaluation. Purified bulk should be tested using suitable methods having high specificity and sensitivity for the detection of the virus in question. For the purpose of marketing authorization, data from at least 3 lots of purified bulk manufactured at pilot-plant scale or commercial scale should be provided.

Case E: When a virus, which cannot be classified by currently available methodologies, is detected in the cells or unprocessed bulk, the product is usually considered unacceptable since the virus may prove to be pathogenic. In the very rare case where there are convincing and well-justified reasons for drug production using such a cell line, this should be discussed with the regulatory authorities before proceeding further.

VI. EVALUATION AND CHARACTERIZATION OF VIRAL CLEARANCE PROCEDURES

Evaluation and characterization of the virus removal and/or inactivation procedures play an important role in establishing the safety of biotechnology products. Many instances of contamination in the past have occurred with agents whose presence was not known or even suspected, and though this happened to biological products derived from various source materials other than fully characterized cell lines, assessment of viral clearance will provide a measure of confidence that any unknown, unsuspected, and harmful viruses may be removed. Studies should be carried out in a manner that is well documented and controlled.

The objective of viral clearance studies is to assess process step(s) that can be considered to be effective in inactivating/removing viruses and to estimate quantitatively the overall level of virus reduction obtained by the process. This should be achieved by the deliberate addition ("spiking") of significant amounts of a virus to the crude material and/or to different fractions obtained during the various process steps and demonstrating its removal or inactivation during the subsequent steps. It is not necessary to evaluate or characterize every step of a manufacturing process if adequate clearance is demonstrated by the use of fewer steps. It should be borne in mind that other steps in the process may have an indirect effect on the viral inactivation/removal achieved. Manufacturers should explain and justify the approach used in studies for evaluating virus clearance.

The reduction of virus infectivity may be achieved by removal of virus particles or by inactivation of viral infectivity. For each production step assessed, the possible mechanism of loss of viral infectivity should be described with regard to whether it is due to inactivation or removal. For inactivation steps, the study should be planned in such a way that samples are taken at different times and an inactivation curve constructed (see section VI.B.5).

Viral clearance evaluation studies are performed to demonstrate the clearance of a virus known to be present in the MCB and/or to provide some level of assurance that adventitious virus which could not be detected, or might gain access to the production process, would be cleared. Reduction factors are normally expressed on a logarithmic scale which implies that, while residual virus infectivity will never be reduced to zero, it may be greatly reduced mathematically.

In addition to clearance studies for viruses known to be present, studies to characterize the ability to remove and/or inactivate other viruses should be conducted. The purpose of studies with viruses, exhibiting a range of biochemical and biophysical properties that are not known or expected to be present, is to characterize the robustness of the procedure rather than to achieve a specific inactivation or removal goal. A demonstration of the capacity of the production process to inactivate or remove viruses is desirable (see section VI.C). Such studies are not performed to evaluate a specific safety risk. Therefore, a specific clearance value need not be achieved.

A. The Choice of Viruses for the Evaluation and Characterization of Viral Clearance

Viruses for clearance evaluation and process characterization studies should be chosen to resemble viruses which may contaminate the product and to represent a wide range of physicochemical properties in order to test the ability of the system to eliminate viruses in general. The manufacturer should justify the choice of viruses in accordance with the aims of the evaluation and characterization study and the guidance provided in this guideline.

1. "Relevant" Viruses and "Model" Viruses

A major issue in performing a viral clearance study is to determine which viruses should be used. Such viruses fall into three categories: "relevant" viruses, specific "model" viruses, and nonspecific "model" viruses.

"Relevant" viruses are viruses used in process evaluation of viral clearance studies which are either the identified viruses, or of the same species as the viruses that are known, or likely to contaminate the cell substrate or any other reagents or materials used in the production process. The purification and/or inactivation process should demonstrate the capability to remove and/or inactivate such viruses. When a "relevant" virus is not available or when it is not well adapted to process evaluation of viral clearance studies (e.g., it cannot be grown in vitro to sufficiently high titers), a specific "model" virus should be used as a substitute. An appropriate specific "model" virus may be a virus which is closely related to the known or suspected virus (same genus or family), having similar physical and chemical properties to the observed or suspected virus.

Cell lines derived from rodents usually contain endogenous retrovirus particles or retrovirus-like particles, which may be infectious (C-type particles) or noninfectious (cytoplasmic A- and R-type particles). The capacity of the manufacturing process to remove and/or inactivate rodent retroviruses from products obtained from such cells should be determined. This may be accomplished by using a murine leukemia virus, a specific "model" virus in the case of cells of murine origin. When human cell lines secreting monoclonal antibodies have been obtained by the immortalization of B lymphocytes by Epstein-Barr Virus (EBV), the ability of the manufacturing process to remove and/or inactivate a herpes virus should be determined. Pseudorabies virus may also be used as a specific "model" virus.

When the purpose is to characterize the capacity of the manufacturing process to remove and/or inactivate viruses in general, that is, to characterize the robustness of the clearance process, viral clearance characterization studies should be performed with nonspecific "model" viruses with differing properties. Data obtained from studies with "relevant" and/or specific "model" viruses may also contribute to this assessment. It is not necessary to test all types of viruses. Preference should be given to viruses that display a significant resistance to physical and/or chemical treatments. The results obtained for such viruses provide useful information about the ability of the production process to remove and/or inactivate viruses in general. The choice and number of viruses used will be influenced by the quality and characterization of the cell lines and the production process.

Examples of useful "model" viruses representing a range of physicochemical structures and examples of viruses which have been used in viral clearance studies are given in Appendix 2 and Table A.1.

2. Other Considerations

Additional points to be considered are as follows:

(a) Viruses which can be grown to high titer are desirable, although this may not always be possible.
(b) There should be an efficient and reliable assay for the detection of each virus used, for every stage of manufacturing that is tested.

(c) Consideration should be given to the health hazard which certain viruses may pose to the personnel performing the clearance studies.

B. Design and Implications of Viral Clearance Evaluation and Characterization Studies

1. Facility and Staff

It is inappropriate to introduce any virus into a production facility because of GMP constraints. Therefore, viral clearance studies should be conducted in a separate laboratory equipped for virological work and performed by staff with virological expertise in conjunction with production personnel involved in designing and preparing a scaled-down version of the purification process.

2. Scaled-Down Production System

The validity of the scaling down should be demonstrated. The level of purification of the scaled-down version should represent the production procedure as closely as possible. For chromatographic equipment, column bed-height, linear flow-rate, flow-rate-to-bed-volume ratio (i.e., contact time), buffer and gel types, pH, temperature, and concentration of protein, salt, and product should all be shown to be representative of commercial-scale manufacturing. A similar elution profile should result. For other procedures, similar considerations apply. Deviations which cannot be avoided should be discussed with regard to their influence on the results.

3. Analysis of StepWise Elimination of Virus

When viral clearance studies are being performed, it is desirable to assess the contribution of more than one production step to virus elimination. Steps which are likely to clear virus should be individually assessed for their ability to remove and inactivate virus and careful consideration should be given to the exact definition of an individual step. Sufficient virus should be present in the material of each step to be tested so that an adequate assessment of the effectiveness of each step is obtained. Generally, virus should be added to in-process material of each step to be tested. In some cases, simply adding high titer virus to unpurified bulk and testing its concentration between steps will be sufficient. Where virus removal results from separation procedures, it is recommended that, if appropriate and if possible, the distribution of the virus load in the different fractions be investigated. When virucidal buffers are used in multiple steps within the manufacturing process, alternative strategies such as parallel spiking in less virucidal buffers may be carried out as part of the overall process assessment. The virus titer before and after each step being tested should be determined. Quantitative infectivity assays should have adequate sensitivity and reproducibility and should be performed with sufficient replicates to ensure adequate statistical validity of the result. Quantitative assays not associated with infectivity may be used if justified. Appropriate virus controls should be included in all infectivity assays to ensure the sensitivity of the method. Also, the statistics of sampling virus when at low concentrations should be considered (Appendix 3).

4. Determining Physical Removal Vs. Inactivation

Reduction in virus infectivity may be achieved by the removal or inactivation of virus. For each production step assessed, the possible mechanism of loss of viral infectivity should be described with regard to whether it is due to inactivation or removal. If little clearance of infectivity is achieved by the production process, and the clearance of virus is considered to be a major factor in the safety of the product, specific or additional inactivation/removal steps should be introduced. It may be necessary to distinguish between removal and inactivation for a particular step, for example, when there is a possibility that a buffer used in more than one clearance step may contribute to inactivation during each step; that is, the contribution to inactivation by a buffer shared by several chromatographic steps and the removal achieved by each of these chromatographic steps should be distinguished.

5. Inactivation Assessment

For assessment of viral inactivation, unprocessed crude material or intermediate material should be spiked with infectious virus and the reduction factor calculated. It should be recognized that virus inactivation is not a simple, first-order reaction and is usually more complex, with a fast "phase 1" and a slow "phase 2." The study should, therefore, be planned in such a way that samples are taken at different times and an inactivation curve constructed. It is recommended that studies for inactivation include at least one time point less than the minimum exposure time and greater than zero, in addition to the minimum exposure time. Additional data are particularly important where the virus is a "relevant" virus known to be a human pathogen and an effective inactivation process is being designed. However, for inactivation studies in which nonspecific "model" viruses are used or when specific "model" viruses are used as surrogates for virus particles such as the CHO intracytoplasmic retrovirus-like particles, reproducible clearance should be demonstrated in at least two independent studies. Whenever possible, the initial virus load should be determined from the virus which can be detected in the spiked starting material. If this is not possible, the initial virus load may be calculated from the titer of the spiking virus preparation. Where inactivation is too rapid to plot an inactivation curve using process conditions, appropriate controls should be performed to demonstrate that infectivity is indeed lost by inactivation.

6. Function and Regeneration of Columns

Over time and after repeated use, the ability of chromatography columns and other devices used in the purification scheme to clear virus may vary. Some estimate of the stability of the viral clearance after several uses may provide support for repeated use of such columns. Assurance should be provided that any virus potentially retained by the production system would be adequately destroyed or removed prior to reuse of the system. For example, such evidence may be provided by demonstrating that the cleaning and regeneration procedures do inactivate or remove virus.

7. Specific Precautions

(a) Care should be taken in preparing the high-titer virus to avoid aggregation which may enhance physical removal and decrease inactivation, thus distorting the correlation with actual production.
(b) Consideration should be given to the minimum quantity of virus which can be reliably assayed.
(c) The study should include parallel control assays to assess the loss of infectivity of the virus due to such reasons as the dilution, concentration, filtration, or storage of samples before titration.
(d) The virus "spike" should be added to the product in a small volume so as not to dilute or change the

characteristics of the product. Diluted, test-protein sample is no longer identical to the product obtained at commercial scale.

(e) Small differences in, for example, buffers, media, or reagents can substantially affect viral clearance.

(f) Virus inactivation is time dependent; therefore, the amount of time a spiked product remains in a particular buffer solution or on a particular chromatography column should reflect the conditions of the commercial-scale process.

(g) Buffers and product should be evaluated independently for toxicity or interference in assays used to determine the virus titer, as these components may adversely affect the indicator cells. If the solutions are toxic to the indicator cells, dilution, adjustment of the pH, or dialysis of the buffer-containing spiked virus might be necessary. If the product itself has antiviral activity, the clearance study may need to be performed without the product in a "mock" run, although omitting the product or substituting a similar protein that does not have antiviral activity could affect the behavior of the virus in some production steps. Sufficient controls to demonstrate the effect of procedures used solely to prepare the sample for assay (e.g., dialysis, storage) on the removal/inactivation of the spiking virus should be included.

(h) Many purification schemes use the same or similar buffers or columns repetitively. The effects of this approach should be taken into account when analyzing the data. The effectiveness of virus elimination by a particular process may vary with the stage in manufacture at which it is used.

(i) Overall reduction factors may be underestimated where production conditions or buffers are too cytotoxic or virucidal and should be discussed on a case-by-case basis. Overall reduction factors may also be overestimated due to inherent limitations or inadequate design of viral clearance studies.

C. Interpretation of Viral Clearance Studies

1. Acceptability

The object of assessing virus inactivation/removal is to evaluate and characterize process steps that can be considered to be effective in inactivating/removing viruses and to estimate quantitatively the overall level of virus reduction obtained by the manufacturing process. For virus contaminants, as in Cases B–E, it is important to show that not only is the virus eliminated or inactivated, but that there is excess capacity for viral clearance built into the purification process to assure an appropriate level of safety for the final product. The amount of virus eliminated or inactivated by the production process should be compared to the amount of virus which may be present in unprocessed bulk.

To carry out this comparison, it is important to estimate the amount of virus in the unprocessed bulk. This estimate should be obtained using assays for infectivity or other methods such as transmission electron microscopy (TEM). The entire purification process should be able to eliminate substantially more virus than is estimated to be present in a single-dose-equivalent of unprocessed bulk. See Appendix 4 for calculation of virus reduction factors and Appendix 5 for calculation of estimated particles per dose.

Manufacturers should recognize that clearance mechanisms may differ between virus classes. A combination of factors must be considered when judging the data supporting the effectiveness of virus inactivation/removal procedures. These include

(i) the appropriateness of the test viruses used,
(ii) the design of the clearance studies,
(iii) the log reduction achieved,
(iv) the time dependence of inactivation,
(v) the potential effects of variation in process parameters on virus inactivation/removal,
(vi) the limits of assay sensitivities, and
(vii) the possible selectivity of inactivation/removal procedure(s) for certain classes of viruses.

Effective clearance may be achieved by any of the following: multiple inactivation steps, multiple complementary separation steps, or combinations of inactivation and separation steps. Since separation methods may be dependent on the extremely specific physicochemical properties of a virus which influence its interaction with gel matrices and precipitation properties, "model" viruses may be separated in a different manner from a target virus. Manufacturing parameters influencing separation should be properly defined and controlled. Differences may originate from changes in surface properties such as glycosylation. However, despite these potential variables, effective removal can be obtained by a combination of complementary separation steps or combinations of inactivation and separation steps. Therefore, well-designed separation steps, such as chromatographic procedures, filtration steps, and extractions, can be effective virus removal steps provided that they are performed under appropriately controlled conditions. An effective virus removal step should give reproducible reduction of virus load shown by at least two independent studies.

An overall reduction factor is generally expressed as the sum of the individual factors. However, reduction in virus titer of the order of 1 $\log_{10}$ or less would be considered negligible and would be ignored unless justified.

If little reduction of infectivity is achieved by the production process, and the removal of virus is considered to be a major factor in the safety of the product, a specific, additional inactivation/removal step or steps should be introduced. For all viruses, manufacturers should justify the acceptability of the reduction factors obtained. Results will be evaluated on the basis of the factors listed above.

D. Limitations of Viral Clearance Studies

Viral clearance studies are useful for contributing to the assurance that an acceptable level of safety in the final product is achieved but do not establish safety by themselves. However, a number of factors in the design and execution of viral clearance studies may lead to an incorrect estimate of the ability of the process to remove virus infectivity. These factors include the following:

1. Virus preparations used in clearance studies for a production process are likely to be produced in tissue culture. The behavior of a tissue culture virus in a production step may be different from that of the native virus; for example, if native and cultured viruses differ in purity or degree of aggregation.
2. Inactivation of virus infectivity frequently follows a biphasic curve in which a rapid initial phase is followed by a slower phase. It is possible that virus escaping a first inactivation step may be more resistant to subsequent steps. For example, if the resistant fraction takes the form of virus aggregates, infectivity may be resistant to a range of different chemical treatments and to heating.

3. The ability of the overall process to remove infectivity is expressed as the sum of the logarithm of the reductions at each step. The summation of the reduction factors of multiple steps, particularly of steps with little reduction (e.g., below 1 $\log_{10}$), may overestimate the true potential for virus elimination. Furthermore, reduction values achieved by repetition of identical or near identical procedures should not be included unless justified.
4. The expression of reduction factors as logarithmic reductions in titer implies that, while residual virus infectivity may be greatly reduced, it will never be reduced to zero. For example, a reduction in the infectivity of a preparation containing 8 $\log_{10}$ infectious units per milliliter by a factor of 8 $\log_{10}$ leaves 0 $\log_{10}$ per milliliter or one infectious unit per milliliter, taking into consideration the limit of detection of the assay.
5. Pilot-plant scale processing may differ from commercial-scale processing despite care taken to design the scaled-down process.
6. Addition of individual virus reduction factors resulting from similar inactivation mechanisms along the manufacturing process may overestimate overall viral clearance.

E. Statistics

The viral clearance studies should include the use of statistical analysis of the data to evaluate the results. The study results should be statistically valid to support the conclusions reached (refer to Appendix 3).

F. Reevaluation of Viral Clearance

Whenever significant changes in the production or purification process are made, the effect of that change, both direct and indirect, on viral clearance should be considered and the system reevaluated as needed. For example, changes in production processes may cause significant changes in the amount of virus produced by the cell line; changes in process steps may change the extent of viral clearance.

VII. SUMMARY

This document suggests approaches for the evaluation of the risk of viral contamination and for the removal of virus from product, thus contributing to the production of safe biotechnology products derived from animal or human cell lines and emphasizes the value of many strategies, including

A. thorough characterization/screening of cell substrate starting material in order to identify which, if any, viral contaminants are present,
B. assessment of risk by determination of the human tropism of the contaminants,
C. establishment of an appropriate program of testing for adventitious viruses in unprocessed bulk,
D. careful design of viral clearance studies using different methods of virus inactivation or removal in the same production process in order to achieve maximum viral clearance, and
E. performance of studies which assess virus inactivation and removal.

GLOSSARY

Adventitious Virus—See Virus.
Cell Substrate—Cells used to manufacture product.
Endogenous Virus—See Virus.
Inactivation—Reduction of virus infectivity caused by chemical or physical modification.
In Vitro Cell Age—A measure of the period between thawing of the MCB vial(s) and harvest of the production vessel measured by elapsed chronological time in culture, population doubling level of the cells, or passage level of the cells when subcultivated by a defined procedure for dilution of the culture.
Master Cell Bank (MCB)—An aliquot of a single pool of cells which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers, and stored under defined conditions. The MCB is used to derive all working cell banks. The testing performed on a new MCB (from a previous initial cell clone, MCB, or WCB) should be the same as for the MCB, unless justified.
Minimum Exposure Time—The shortest period for which a treatment step will be maintained.
Nonendogenous Virus—See Virus.
Process Characterization of Viral Clearance—Viral clearance studies in which nonspecific "model" viruses are used to assess the robustness of the manufacturing process to remove and/or inactivate viruses.
Process Evaluation Studies of Viral Clearance—Viral clearance studies in which "relevant" and/or specific "model" viruses are used to determine the ability of the manufacturing process to remove and/or inactivate these viruses.
Production Cells—Cell substrate used to manufacture product.
Unprocessed Bulk—One or multiple pooled harvests of cells and culture media. When cells are not readily accessible, the unprocessed bulk would constitute fluid harvested from the fermenter.
Virus—Intracellularly replicating infectious agents that are potentially pathogenic, possessing only a single type of nucleic acid (either RNA or DNA), are unable to grow and undergo binary fission, and multiply in the form of their genetic material.
Adventitious Virus—Unintentionally introduced contaminant viruses.
Endogenous Virus—Viral entity whose genome is part of the germ line of the species of origin of the cell line and is covalently integrated into the genome of animal from which the parental cell line was derived. For the purposes of this document, intentionally introduced, nonintegrated viruses such as EBV used to immortalize cell substrates or Bovine Papilloma Virus fit in this category.
Nonendogenous Virus—Viruses from external sources present in the Master Cell Bank.
Nonspecific Model Virus—A virus used for characterization of viral clearance of the process when the purpose is to characterize the capacity of the manufacturing process to remove and/or inactivate viruses in general, that is, to characterize the robustness of the purification process.
Relevant Virus—Virus used in process evaluation studies, which is either the identified virus, or of the same species as the virus that is known, or likely to

contaminate the cell substrate or any other reagents or materials used in the production process.

Specific Model Virus—Virus which is closely related to the known or suspected virus (same genus or family), having similar physical and chemical properties to those of the observed or suspected virus.

Viral Clearance—Elimination of target virus by removal of viral particles or inactivation of viral infectivity.

Virus-Like Particles—Structures visible by electron microscopy which morphologically appear to be related to known viruses.

Virus Removal—Physical separation of virus particles from the intended product.

Working Cell Bank (WCB)—The WCB is prepared from aliquots of a homogeneous suspension of cells obtained from culturing the MCB under defined culture conditions.

Appendix 1: Products Derived from Characterized Cell Banks which Were Subsequently Grown In Vivo

For products manufactured from fluids harvested from animals inoculated with cells from characterized banks, additional information regarding the animals should be provided.

Whenever possible, animals used in the manufacture of biotechnological/biological products should be obtained from well-defined, specific pathogen-free colonies. Adequate testing for appropriate viruses, such as those listed in Table 3, should be performed. Quarantine procedures for newly arrived as well as diseased animals should be described, and assurance provided that all containment, cleaning, and decontamination methodologies employed within the facility are adequate to contain the spread of adventitious agents. This may be accomplished through the use of a sentinel program. A listing of agents for which testing is performed should also be included. Veterinary support services should be available on-site or within easy access. The degree to which the vivarium is segregated from other areas of the manufacturing facility should be described. Personnel practices should be adequate to ensure safety.

Procedures for the maintenance of the animals should be fully described. These would include diet, cleaning and feeding schedules, provisions for periodic veterinary care if applicable, and details of special handling that the animals may require once inoculated. A description of the priming regimen(s) for the animals, the preparation of the inoculum and the site and route of inoculation should also be included.

The primary harvest material from animals may be considered an equivalent stage of manufacture to unprocessed bulk harvest from a bioreactor. Therefore, all testing considerations previously outlined in section IV of this document should apply. In addition, the manufacturer should assess the bioburden of the unprocessed bulk, determine whether the material is free of mycoplasma, and perform species-specific assay(s) as well as in vivo testing in adult and suckling mice.

Appendix 2: The Choice of Viruses for Viral Clearance Studies

A. Examples of useful "model" viruses
   1. Nonspecific "model" viruses representing a range of physicochemical structures:
      – SV40 (Polyomavirus maccacae 1), human polio virus 1 (Sabin), animal parvovirus, or some other small, nonenveloped viruses;
      – a parainfluenza virus or influenza virus, Sindbis virus or some other medium-to-large, enveloped, RNA viruses;
      – a herpes virus (e.g., HSV-1 or a pseudorabies virus), or some other medium-to-large, DNA viruses.

   These viruses are examples only and their use is not mandatory.
   2. For rodent cell substrates murine retroviruses are commonly used as specific "model" viruses.

B. Examples of viruses which have been used in viral clearance studies

   Several viruses which have been used in viral clearance studies are listed in Table A.1 However, since these are merely examples, the use of any of the viruses in the table is not mandatory and manufacturers are invited to consider other viruses, especially those which may be more appropriate for their individual production processes. Generally, the process should be assessed for its ability to clear at least three different viruses with differing characteristics.

These viruses are examples only and their use is not mandatory.

Table A.1 Examples of Viruses Which Have Been Used in Viral Clearance Studies

Virus	Family	Genus	Natural host	Genome	Env	Size (nm)	Shape	Resistance[a]
Vesicular stomatitis virus	Rhabdo	*Vesiculovirus*	Equine Bovine	RNA	Yes	70 × 150	Bullet	Low
Parainfluenza virus	Paramyxo	*Paramyxovirus*	Various	RNA	Yes	100–200+	Pleo/Spher	Low
MuLV	Retro	*Type C oncovirus*	Mouse	RNA	Yes	80–110	Spherical	Low
Sindbis virus	Toga	*Alphavirus*	Human	RNA	Yes	60–70	Spherical	Low
BVDV	Flavi	*Pestivirus*	Bovine	RNA	Yes	50–70	Pleo-Spher	Low
Pseudorabies virus	Herpes		Swine	DNA	Yes	120–200	Spherical	Med
Poliovirus Sabin type 1	Picorna	*Enterovirus*	Human	RNA	No	25–30	Icosahedral	Med
Encephalomyo-carditis virus (EMC)	Picorna	*Cardiovirus*	Mouse	RNA	No	25–30	Icosahedral	Med
Reovirus 3	Reo	*Orthoreovirus*	Various	RNA	No	60–80	Spherical	Med
SV40	Papova	*Polyomavirus*	Monkey	DNA	No	40–50	Icosahedral	Very high
Parvoviruses (canine, porcine)	Parvo	*Parvovirus*	Canine Porcine	DNA	No	18–24	Icosahedral	Very high

[a] Resistance to physicochemical treatments based on studies of production processes. Resistance is relative to the specific treatment and it is used in the context of the understanding of the biology of the virus and the nature of the manufacturing process. Actual results will vary according to the treatment.

Appendix 3: Statistical Considerations for Assessing Virus Assays

Virus titrations suffer the problems of variation common to all biological assay systems. Assessment of the accuracy of the virus titrations and reduction factors derived from them and the validity of the assays should be performed to define the reliability of a study. The objective of statistical evaluation is to establish that the study has been carried out to an acceptable level of virological competence.

1. Assay methods may be either quantal or quantitative. Quantal methods include infectivity assays in animals or in tissue-culture-infectious-dose assays, in which the animal or cell culture is scored as either infected or not. Infectivity titers are then measured by the proportion of animals or culture infected. In quantitative methods, the infectivity measured varies continuously with the virus input. Quantitative methods include plaque assays where each plaque counted corresponds to a single infectious unit. Both quantal and quantitative assays are amenable to statistical evaluation.
2. Variation can arise within an assay as a result of dilution errors, statistical effects, and differences within the assay system which are either unknown or difficult to control. These effects are likely to be greater when different assay runs are compared (between-assay variation) than when results within a single assay run are compared (within-assay variation).
3. The 95% confidence limits for results of within-assay variation normally should be on the order of ± 0.5 $\log_{10}$ of the mean. Within-assay variation can be assessed by standard textbook methods. Between-assay variation can be monitored by the inclusion of a reference preparation, the estimate of whose potency should be within approximately 0.5 $\log_{10}$ of the mean estimate established in the laboratory for the assay to be acceptable. Assays with lower precision may be acceptable with appropriate justification.
4. The 95% confidence limits for the reduction factor observed should be calculated wherever possible in studies of clearance of "relevant" and specific "model" viruses. If the 95% confidence limits for the viral assays of the starting material are $+s$, and for the viral assays of the material after the step are $+a$, the 95% confidence limits for the reduction factor are

$$\pm\sqrt{S^2 + a^2} \quad 1$$

Probability of Detection of Viruses at Low Concentrations

At low virus concentrations (e.g., in the range of 10 to 1000 infectious particles per liter), it is evident that a sample of a few milliliters may or may not contain infectious particles. The probability, p, that this sample does not contain infectious viruses is

$$p = \left(\frac{(V - v)}{V}\right)^n$$

where V (liter) is the overall volume of the material to be tested, v (liter) is the volume of the sample and n is the absolute number of infectious particles statistically distributed in V.

If $V \gg v$, this equation can be approximated by the Poisson distribution:

$$p = \mathrm{e}^{-cv}$$

where c is the concentration of infectious particles per liter

$$or, c = \ln \frac{p}{-v}$$

As an example, if a sample volume of 1 mL is tested, the probabilities p at virus concentrations ranging from 10 to 1000 infectious particles per liter are

c	10	100	1000
p	0.99	0.90	0.37

This indicates that for a concentration of 1000 viruses per liter, in 37% of sampling, 1 mL will not contain a virus particle.

If only a portion of a sample is tested for virus and the test is negative, the amount of virus which would have to be present in the total sample in order to achieve a positive result should be calculated and this value taken into account when calculating a reduction factor. Confidence limits at 95% are desirable. However, in some instances, this may not be practical due to material limitations.

Appendix 4: Calculation of Reduction Factors in Studies to Determine Viral Clearance

The virus reduction factor of an individual purification or inactivation step is defined as the $\log_{10}$ of the ratio of the virus load in the prepurification material and the virus load in the postpurification material which is ready for use in the next step of the process. If the following abbreviations are used:

Starting material:

vol v'; titer $10^{a'}$;
virus load: $(v')(10^{a'})$,

Final material:

vol v''; titer $10^{a''}$;
virus load: $(v'')(10^{a''})$,

the individual reduction factors Ri are calculated according to

$$10^{Ri} = \frac{(v')(10^{a'})}{(v'')(10^{a''})}$$

This formula takes into account both the titers and volumes of the materials before and after the purification step.

Because of the inherent imprecision of some virus titrations, an individual reduction factor used for the calculation of an overall reduction factor should be greater than 1.

The overall reduction factor for a complete production process is the sum logarithm of the reduction factors of the individual steps. It represents the logarithm of the ratio of the virus load at the beginning of the first process clearance step and at the end of the last process clearance step. Reduction factors are normally expressed on a logarithmic scale which implies that, while residual virus infectivity will never be reduced to zero, it may be greatly reduced mathematically.

Appendix 5: Calculation of Estimated Particles per Dose

This is applicable to those viruses for which an estimate of starting numbers can be made, such as endogenous retroviruses.

Example:

I. Assumptions

Measured or estimated concentration of virus in cell culture harvest $= 10^6/\text{mL}$
Calculated viral clearance factor $= >10^{15}$
Volume of culture harvest needed to make a dose of product $= 1$ L ($l0^3$ mL)

II. Calculation of Estimated Particles/Dose

$$\frac{(10^6 \text{ virus units/ml}) \times (10^3 \text{ ml/dose})}{\text{Clearance factor} > 10^{15}}$$

$$= \frac{10^9 \text{particles/dose}}{\text{Clearance factor} > 10^{15}}$$

$$= < 10^{-6} \text{ particles/dose}$$

Therefore, less than one particle per million doses would be expected.

7

Analysis of the Expression Construct in Cells Used for Production of rDNA-Derived Protein Products

I. INTRODUCTION

This document presents guidance regarding the characterization of the expression construct for the production of recombinant DNA protein products in eukaryotic and prokaryotic cells. This document is intended to describe the types of information that are considered valuable in assessing the structure of the expression construct used to produce recombinant DNA-derived proteins. This document is not intended to cover the whole quality aspect of rDNA-derived medicinal products.

The expression construct is defined as the expression vector containing the coding sequence of the recombinant protein. Segments of the expression construct should be analyzed using nucleic acid techniques in conjunction with other tests performed on the purified recombinant protein for assuring the quality and consistency of the final product. Analysis of the expression construct at the nucleic acid level should be considered as part of the overall evaluation of quality, taking into account that this testing only evaluates the coding sequence of a recombinant gene and not the translational fidelity nor other characteristics of the recombinant protein, such as secondary structure, tertiary structure, and posttranslational modifications.

II. RATIONALE FOR ANALYSIS OF THE EXPRESSION CONSTRUCT

The purpose of analyzing the expression construct is to establish that the correct coding sequence of the product has been incorporated into the host cell and is maintained during culture to the end of production. The genetic sequence of recombinant proteins produced in living cells can undergo mutations that could alter the properties of the protein with potential adverse consequences to patients. No single experimental approach can be expected to detect all possible modifications to a protein. Protein analytical techniques can be used to assess the amino acid sequence of the protein and structural features of the expressed protein due to posttranslational modifications such as proteolytic processing, glycosylation, phosphorylation, and acetylation. Data from nucleic acid analysis may be useful since protein analytical methods may not detect all changes in protein structure resulting from mutations in the sequence coding for the recombinant protein. The relative importance of nucleic acid analysis and protein analysis will vary from product to product.

Nucleic acid analysis can be used to verify the coding sequence and the physical state of the expression construct. The nucleic acid analysis is performed to ensure that the expressed protein will have the correct amino acid sequence but is not intended to detect low levels of variant sequences. Where the production cells have multiple integrated copies of the expression construct, not all of which may be transcriptionally active, examination of the transcription product itself by analysis of mRNA or cDNA may be more appropriate than analysis of genomic DNA. Analytical approaches that examine a bulk population of nucleic acids, such as those performed on pooled clones or material amplified by the polymerase chain reaction, may be considered as an alternative to approaches that depend on selection of individual DNA clones. Other techniques could be considered that allow for rapid and sensitive confirmation of the sequence coding for the recombinant protein in the expression construct.

The following sections describe information that should be supplied regarding the characterization of the expression construct during the development and validation of the production system. Analytical methodologies should be validated for the intended purpose of confirmation of sequence. The validation documentation should at a minimum include estimates of the limits of detection for variant sequences. This should be performed for either nucleic acid or protein sequencing methods. The philosophy and recommendations for analysis expressed in this document should be periodically reviewed to take advantage of new advances in technology and scientific information.

III. CHARACTERIZATION OF THE EXPRESSION SYSTEM

A. Expression Construct and Cell Clone Used to Develop the Master Cell Bank

The manufacturer should describe the origin of the nucleotide sequence coding for the protein. This should include identification and source of the cell from which the nucleotide sequence was originally obtained. Methods used to prepare the DNA coding for the protein should be described.

The steps in the assembly of the expression construct should be described in detail. This description should include the source and function of the component parts of the expression construct, for example, origins of replication, antibiotic resistance genes, promoters, enhancers, whether or not the protein is being synthesized as a fusion protein. A detailed component map and a complete annotated sequence of the plasmid should be given, indicating those regions that have been sequenced during the construction and those taken from the literature. Other expressed proteins encoded by the plasmid should be indicated. The nucleotide sequence of the coding region of the gene of interest and associated flanking regions that are inserted into the vector, up to and including the junctions of insertion, should be determined by DNA sequencing of the construct.

A description of the method of transfer of the expression construct into the host cell should be provided. In addition, methods used to amplify the expression construct and criteria used to select the cell clone for production should be described in detail.

B. Cell Bank System

Production of the recombinant protein should be based on well-defined Master and Working Cell Banks. A cell bank is a collection of ampoules of uniform composition stored under defined conditions each containing an aliquot of a single pool of cells. The Master Cell Bank (MCB) is generally derived from the selected cell clone containing the expression construct. The Working Cell Bank (WCB) is derived by expansion of one or more ampoules of the MCB. The cell line history and production of the cell banks should be described in detail, including methods and reagents used during culture, in vitro cell age, and storage conditions. All cell banks should be characterized for relevant phenotypic and genotypic markers which could include the expression of the recombinant protein or presence of the expression construct.

The expression construct in the MCB should be analyzed as described below. If the testing cannot be carried out on the MCB, it should be carried out on each WCB.

Restriction endonuclease mapping or other suitable techniques should be used to analyze the expression construct for copy number, for insertions or deletions, and for the number of integration sites. For extrachromosomal expression systems, the percent of host cells retaining the expression construct should be determined.

The protein coding sequence for the recombinant protein product of the expression construct should be verified. For extrachromosomal expression systems, the expression construct should be isolated and the nucleotide sequence encoding the product should be verified without further cloning. For cells with chromosomal copies of the expression construct, the nucleotide sequence encoding the product could be verified by recloning and sequencing of chromosomal copies. Alternatively, the nucleic acid sequence encoding the product could be verified by techniques such as sequencing of pooled cDNA clones or material amplified by the polymerase chain reaction. The nucleic acid sequence should be identical, within the limits of detection of the methodology, to that determined for the expression construct as described in section III.A. and should correspond to that expected for the protein sequence.

C. Limit for In Vitro Cell Age for Production

The limit for in vitro cell age for production should be based on data derived from production cells expanded under pilot plant scale or full scale conditions to the proposed in vitro cell age or beyond. Generally, the production cells are obtained by expansion of the WCB; the MCB could be used to prepare the production cells with appropriate justification.

The expression construct of the production cells should be analyzed once for the MCB as described in section III.B., except that the protein coding sequence of the expression construct in the production cells could be verified by either nucleic acid testing or analysis of the final protein product. Increases in the defined limit for in vitro cell age for production should be supported by data from cells which have been expanded to an in vitro cell age which is equal to or greater than the new limit for in vitro cell age.

IV. CONCLUSION

The characterization of the expression construct and the final purified protein are both important to ensure the consistent production of a recombinant DNA-derived product. As described above, it is considered that analytical data derived from both nucleic acid analysis and evaluation of the final purified protein should be evaluated to ensure the quality of a recombinant protein product.

GLOSSARY

Expression Construct—The expression vector which contains the coding sequence of the recombinant protein and the elements necessary for its expression.

Flanking Control Regions—Noncoding nucleotide sequences that are adjacent to the 5′ and 3′ end of the coding sequence of the product which contain important elements that affect the transcription, translation, or stability of the coding sequence. These regions include, for example, promoter, enhancer, and splicing sequences and do not include origins of replication and antibiotic resistance genes.

Integration Site—The site where one or more copies of the expression construct is integrated into the host cell genome.

In vitro Cell Age—Measure of time between thaw of the MCB vial(s) to harvest of the production vessel measured by elapsed chronological time in culture, by population doubling level of the cells, or by passage level of the cells when subcultivated by a defined procedure for dilution of the culture.

Master Cell Bank (MCB)—An aliquot of a single pool of cells, which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers, and stored under defined conditions. The MCB is used to derive all working cell banks. The testing performed on a new MCB (from a previous initial cell clone, MCB, or WCB) should be the same as for the MCB unless justified.

Pilot Plant Scale—The production of a recombinant protein by a procedure fully representative of and simulating that to be applied on a full commercial manufacturing scale. The methods of cell expansion, harvest, and product purification should be identical except for the scale of production.

Relevant Genotypic and Phenotypic Markers—Those markers permitting the identification of the strain of the cell line which should include the expression of the recombinant protein or presence of the expression construct.

Working Cell Bank (WCB)—The WCB is prepared from aliquots of a homogeneous suspension of cells obtained from culturing the MCB under defined culture conditions.

8

Stability Testing of Biotechnological/Biological Products

I. PREAMBLE

The guidance stated in the ICH harmonized tripartite guideline "Stability Testing of New Drug Substances and Products" (October 27, 1993) applies in general to biotechnological/biological products. However, biotechnological/biological products do have distinguishing characteristics to which consideration should be given in any well-defined testing program designed to confirm their stability during the intended storage period. For such products, in which the active components are typically proteins and/or polypeptides, maintenance of molecular conformation and, hence of biological activity, is dependent on noncovalent as well as covalent forces. The products are particularly sensitive to environmental factors such as temperature changes, oxidation, light, ionic content, and shear. In order to ensure maintenance of biological activity and to avoid degradation, stringent conditions for their storage are usually necessary.

The evaluation of stability may necessitate complex analytical methodologies. Assays for biological activity, where applicable, should be part of the pivotal stability studies. Appropriate physicochemical, biochemical, and immunochemical methods for the analysis of the molecular entity and the quantitative detection of degradation products should also be part of the stability program whenever purity and molecular characteristics of the product permit use of these methodologies.

With the above concerns in mind, the applicant should develop the proper supporting stability data for a biotechnological/biological product and consider many external conditions which can affect the product's potency, purity, and quality. Primary data to support a requested storage period for either drug substance or drug product should be based on long-term, real-time, and real-condition stability studies. Thus, the development of a proper long-term stability program becomes critical to the successful development of a commercial product. The purpose of this document is to give guidance to applicants regarding the type of stability studies that should be provided in support of marketing applications. It is understood that during the review and evaluation process, continuing updates of initial stability data may occur.

II. SCOPE OF THE ANNEX

The guidance stated in this Annex applies to well-characterized proteins and polypeptides, their derivatives and products of which they are components, and which are isolated from tissues, body fluids, cell cultures, or produced using rDNA technology. Thus, the document covers the generation and submission of stability data for products such as cytokines (interferons, interleukins, colony-stimulating factors, tumour necrosis factors), erythropoietins, plasminogen activators, blood plasma factors, growth hormones and growth factors, insulins, monoclonal antibodies, and vaccines consisting of well-characterized proteins or polypeptides. In addition, the guidance outlined in the following sections may apply to other types of products, such as conventional vaccines, after consultation with the appropriate regulatory authorities. The document does not cover antibiotics, allergenic extracts, heparins, vitamins, whole blood, or cellular blood components.

III. TERMINOLOGY

For the basic terms used in this Annex, the reader is referred to the "Glossary" in the ICH harmonized tripartite guideline "Stability Testing of New Drug Substances and Products" (October 27, 1993). However, since manufacturers of biotechnological/biological products sometimes use traditional terminology, traditional terms are specified in parentheses to assist the reader. A supplemental glossary is also included that explains certain terms used in the production of biotechnological/biological products.

IV. SELECTION OF BATCHES

A. Drug Substance (Bulk Material)

Where bulk material is to be stored after manufacture but prior to formulation and final manufacturing, stability data should be provided on at least three batches for which manufacture and storage are representative of the manufacturing scale of production. A minimum of 6 months stability data at the time of submission should be submitted in cases where storage periods greater than 6 months are requested. For drug substances with storage periods of less than 6 months, the minimum amount of stability data in the initial submission should be determined on a case-by-case basis. Data from pilot-plant scale batches of drug substance produced at a reduced scale of fermentation and purification may be provided at the time the dossier is submitted to the regulatory agencies with a commitment to place the first three manufacturing scale batches into the long-term stability program after approval.

The quality of the batches of drug substance placed into the stability program should be representative of the quality of the material used in preclinical and clinical studies and of the quality of the material to be made at manufacturing scale. In addition, the drug substance (bulk material) made at pilot-plant scale should be produced by a process and stored under conditions representative of that used for the manufacturing scale. The drug substance entered into the stability program should be stored in containers which properly represent the actual holding containers used during manufacture. Containers of reduced size may be acceptable for drug substance stability testing provided that they are constructed of

the same material and use the same type of container/closure system that is intended to be used during manufacture.

B. Intermediates

During manufacture of biotechnological/biological products, the quality and control of certain intermediates may be critical to the production of the final product. In general, the manufacturer should identify intermediates and generate in-house data and process limits that assure their stability within the bounds of the developed process. While the use of pilot-plant scale data is permissible, the manufacturer should establish the suitability of such data using the manufacturing scale process.

C. Drug Product (Final Container Product)

Stability information should be provided on at least three batches of final container product representative of that which will be used at manufacturing scale. Where possible, batches of final container product included in stability testing should be derived from different batches of bulk material. A minimum of 6 months data at the time of submission should be submitted in cases where storage periods greater than 6 months are requested. For drug products with storage periods of less than 6 months, the minimum amount of stability data in the initial submission should be determined on a case-by-case basis. Product expiration dating will be based upon the actual data submitted in support of the application. Since dating is based upon the real-time/real-temperature data submitted for review, continuing updates of initial stability data should occur during the review and evaluation process. The quality of the final container product placed on stability studies should be representative of the quality of the material used in the preclinical and clinical studies. Data from pilot-plant scale batches of drug product may be provided at the time the dossier is submitted to the regulatory agencies with a commitment to place the first three manufacturing scale batches into the long-term stability program after approval. Where pilot-plant scale batches were submitted to establish the dating for a product and, in the event that product produced at manufacturing scale does not meet those long-term stability specifications throughout the dating period or is not representative of the material used in preclinical and clinical studies, the applicant should notify the appropriate regulatory authorities to determine a suitable course of action.

D. Sample Selection

Where one product is distributed in batches differing in fill volume (e.g., 1 mL), 2 mL, or 10 mL), unitage (e.g., 10 units, 20 units, or 50 units), or mass (e.g., 1 mg, 2 mg, or 5 mg) samples to be entered into the stability program may be selected on the basis of a matrix system and/or by bracketing.

Matrixing, that is, the statistical design of a stability study in which different fractions of samples are tested at different sampling points, should only be applied when appropriate documentation is provided that confirms that the stability of the samples tested represents the stability of all samples. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same closure, and possibly, in some cases, different container/closure systems. Matrixing should not be applied to samples with differences that may affect stability, such as different strengths and different containers/closures, where it cannot be confirmed that the products respond similarly under storage conditions.

Where the same strength and exact container/closure system is used for three or more fill contents, the manufacturer may elect to place only the smallest and largest container size into the stability program, that is, bracketing. The design of a protocol that incorporates bracketing assumes that the stability of the intermediate condition samples are represented by those at the extremes. In certain cases, data may be needed to demonstrate that all samples are properly represented by data collected for the extremes.

V. STABILITY-INDICATING PROFILE

On the whole, there is no single stability-indicating assay or parameter that profiles the stability characteristics of a biotechnological/biological product. Consequently, the manufacturer should propose a stability-indicating profile that provides assurance that changes in the identity, purity, and potency of the product will be detected.

At the time of submission, applicants should have validated the methods that comprise the stability-indicating profile and the data should be available for review. The determination of which tests should be included will be product-specific. The items emphasized in the following subsections are not intended to be all-inclusive, but represent product characteristics that should typically be documented to adequately demonstrate product stability.

A. Protocol

The dossier accompanying the application for marketing authorization should include a detailed protocol for the assessment of the stability of both drug substance and drug product in support of the proposed storage conditions and expiration dating periods. The protocol should include all necessary information which demonstrates the stability of the biotechnological/biological product throughout the proposed expiration dating period including, for example, well-defined specifications and test intervals. The statistical methods that should be used are described in the tripartite guideline on stability.

B. Potency

When the intended use of a product is linked to a definable and measurable biological activity, testing for potency should be part of the stability studies. For the purpose of stability testing of the products described in this guideline, potency is the specific ability or capacity of a product to achieve its intended effect. It is based on the measurement of some attribute of the product and is determined by a suitable quantitative method. In general, potencies of biotechnological/biological products tested by different laboratories can be compared in a meaningful way only if expressed in relation to that of an appropriate reference material. For that purpose, a reference material calibrated directly or indirectly against the corresponding national or international reference material should be included in the assay.

Potency studies should be performed at appropriate intervals as defined in the stability protocol and the results should be reported in units of biological activity calibrated, whenever possible, against nationally or internationally recognized standard. Where no national or international reference standards exist, the assay results may be reported in in-house derived units using a characterized reference material.

In some biotechnological/biological products, potency is dependent upon the conjugation of the active ingredient(s) to a second moiety or binding to an adjuvant. Dissociation of the active ingredient(s) from the carrier used in conjugates or adjuvants should be examined in real-time/real-temperature studies (including conditions encountered during shipment). The assessment of the stability of such products may be difficult since, in some cases, in vitro tests for biological activity and physicochemical characterization are impractical or provide inaccurate results. Appropriate strategies (e.g., testing the product prior to conjugation/binding, assessing the release of the active compound from the second moiety, in vivo assays) or the use of an appropriate surrogate test should be considered to overcome the inadequacies of in vitro testing.

C. Purity and Molecular Characterization

For the purpose of stability testing of the products described in this guideline, purity is a relative term. Because of the effect of glycosylation, deamidation, or other heterogeneities, the absolute purity of a biotechnological/biological product is extremely difficult to determine. Thus, the purity of a biotechnological/biological product should be typically assessed by more than one method and the purity value derived is method-dependent. For the purpose of stability testing, tests for purity should focus on methods for determination of degradation products.

The degree of purity, as well as individual and total amounts of degradation products of the biotechnological/biological product entered into the stability studies, should be reported and documented whenever possible. Limits of acceptable degradation should be derived from the analytical profiles of batches of the drug substance and drug product used in the preclinical and clinical studies.

The use of relevant physicochemical, biochemical, and immunochemical analytical methodologies should permit a comprehensive characterization of the drug substance and/or drug product (e.g., molecular size, charge, hydrophobicity) and the accurate detection of degradation changes that may result from deamidation, oxidation, sulfoxidation, aggregation, or fragmentation during storage. As examples, methods that may contribute to this include electrophoresis (SDS-PAGE, immunoelectrophoresis, Western blot, isoelectrofocusing), high-resolution chromatography (e.g., reversed-phase chromatography, gel filtration, ion exchange, affinity chromatography), and peptide mapping.

Wherever significant qualitative or quantitative changes indicative of degradation product formation are detected during long-term, accelerated, and/or stress stability studies, consideration should be given to potential hazards and to the need for characterization and quantification of degradation products within the long-term stability program. Acceptable limits should be proposed and justified, taking into account the levels observed in material used in preclinical and clinical studies.

For substances that cannot be properly characterized or products for which an exact analysis of the purity cannot be determined through routine analytical methods, the applicant should propose and justify alternative testing procedures.

D. Other Product Characteristics

The following product characteristics, though not specifically relating to biotechnological/biological products, should be monitored and reported for the drug product in its final container:

- Visual appearance of the product (color and opacity for solutions/suspensions; color, texture, and dissolution time for powders), visible particulates in solutions or after the reconstitution of powders or lyophilized cakes, pH, and moisture level of powders and lyophilized products.
- Sterility testing or alternatives (e.g., container/closure integrity testing) should be performed at a minimum initially and at the end of the proposed shelf life.
- Additives (e.g., stabilizers, preservatives) or excipients may degrade during the dating period of the drug product. If there is any indication during preliminary stability studies that reaction or degradation of such materials adversely effect the quality of the drug product, these items may need to be monitored during the stability program.
- The container/closure has the potential to adversely affect the product and should be carefully evaluated (see below).

VI. STORAGE CONDITIONS

A. Temperature

Since most finished biotechnological/biological products need precisely defined storage temperatures, the storage conditions for the real-time/real-temperature stability studies may be confined to the proposed storage temperature.

B. Humidity

Biotechnological/biological products are generally distributed in containers protecting them against humidity. Therefore, where it can be demonstrated that the proposed containers (and conditions of storage) afford sufficient protection against high and low humidity, stability tests at different relative humidities can usually be omitted. Where humidity-protecting containers are not used, appropriate stability data should be provided.

C. Accelerated and Stress Conditions

As previously noted, the expiration dating should be based on real-time/real-temperature data. However, it is strongly suggested that studies be conducted on the drug substance and drug product under accelerated and stress conditions. Studies under accelerated conditions may provide useful support data for establishing the expiration date, provide product stability information for future product development (e.g., preliminary assessment of proposed manufacturing changes such as change in formulation, scale-up), assist in validation of analytical methods for the stability program, or generate information which may help elucidate the degradation profile of the drug substance or drug product. Studies under stress conditions may be useful in determining whether accidental exposures to conditions other than those proposed (e.g., during transportation) are deleterious to the product and also for evaluating which specific test parameters may be the best indicators of product stability. Studies of the exposure of the drug substance or drug product to extreme conditions may help to reveal patterns of degradation; if so, such changes should be monitored under proposed storage conditions. While the tripartite guideline on stability describes the conditions of the accelerated and stress study, the applicant should note that those conditions may not be appropriate for biotechnological/biological products. Conditions should be carefully selected on a case-by-case basis.

D. Light

Applicants should consult the appropriate regulatory authorities on a case-by-case basis to determine guidance for testing.

E. Container/Closure

Changes in the quality of the product may occur due to the interactions between the formulated biotechnological/biological product and container/closure. Where the lack of interactions cannot be excluded in liquid products (other than sealed ampoules), stability studies should include samples maintained in the inverted or horizontal position (i.e., in contact with the closure), as well as in the upright position, to determine the effects of the closure on product quality. Data should be supplied for all different container/closure combinations that will be marketed.

In addition to the standard data necessary for a conventional single-use vial, the applicant should demonstrate that the closure used with a multiple-dose vial is capable of withstanding the conditions of repeated insertions and withdrawals so that the product retains its full potency, purity, and quality for the maximum period specified in the instructions-for-use on containers, packages, and/or package inserts. Such labeling should be in accordance with relevant national/regional requirements.

F. Stability After Reconstitution of Freeze-Dried Product

The stability of freeze-dried products after their reconstitution should be demonstrated for the conditions and the maximum storage period specified on containers, packages, and/or package inserts. Such labeling should be in accordance with relevant national/regional requirements.

VII. TESTING FREQUENCY

The shelf lives of biotechnological/biological products may vary from days to several years. Thus, it is difficult to draft uniform guidelines regarding the stability study duration and testing frequency that would be applicable to all types of biotechnological/biological products. With only a few exceptions, however, the shelf lives for existing products and potential future products will be within the range of 0.5 to 5 years. Therefore, the guidance is based upon expected shelf lives in that range. This takes into account the fact that degradation of biotechnological/biological products may not be governed by the same factors during different intervals of a long storage period.

When shelf lives of 1 year or less are proposed, the real-time stability studies should be conducted monthly for the first 3 months and at 3-month intervals thereafter.

For products with proposed shelf lives of greater than 1 year, the studies should be conducted every 3 months during the first year of storage, every 6 months during the second year, and annually thereafter.

While the testing intervals listed above may be appropriate in the preapproval or prelicence stage, reduced testing may be appropriate after approval or licensure where data are available that demonstrate adequate stability. Where data exist that indicate the stability of a product is not compromised, the applicant is encouraged to submit a protocol, which supports elimination of specific test intervals (e.g., 9-month testing) for postapproval/postlicensure and long-term studies.

VIII. SPECIFICATIONS

Although biotechnological/biological products may be subject to significant losses of activity, physicochemical changes, or degradation during storage, international and national regulations have provided little guidance with respect to distinct release and end of shelf life specifications. Recommendations for maximum acceptable losses of activity, limits for physicochemical changes, or degradation during the proposed shelf life have not been developed for individual types or groups of biotechnological/biological products but are considered on a case-by-case basis. Each product should retain its specifications within established limits for safety, purity, and potency throughout its proposed shelf life. These specifications and limits should be derived from all available information using the appropriate statistical methods. The use of different specifications for release and expiration should be supported by sufficient data to demonstrate that clinical performance is not affected as discussed in the tripartite guideline on stability.

IX. LABELING

For most biotechnological/biological drug substances and drug products, precisely defined storage temperatures are recommended. Specific recommendations should be stated, particularly for drug substances and drug products that cannot tolerate freezing. These conditions, and where appropriate, recommendations for protection against light and/or humidity, should appear on containers, packages, and/or package inserts. Such labeling should be in accordance with relevant national/regional requirements.

GLOSSARY

Conjugated Product—A conjugated product is made up of an active ingredient (e.g., peptide, carbohydrate) bound covalently or noncovalently to a carrier (e.g., protein, peptide, inorganic mineral) with the objective of improving the efficacy or stability of the product.

Degradation Product—A molecule resulting from a change in the drug substance (bulk material) brought about overtime. For the purpose of stability testing of the products described in this guideline, such changes could occur as a result of processing or storage (e.g., by deamidation, oxidation, aggregation, proteolysis). For biotechnological/biological products, some degradation products may be active.

Impurity—Any component of the drug substance (bulk material) or drug product (final container product) which is not the chemical entity defined as the drug substance, an excipient, or other additives to the drug product.

Intermediate—For biotechnological/biological products, a material produced during a manufacturing process which is not the drug substance or the drug product but whose manufacture is critical to the successful production of the drug substance or the drug product. Generally, an intermediate will be quantifiable and specifications will be established to determine the successful completion of the manufacturing step prior to continuation of the manufacturing process. This includes

material which may undergo further molecular modification or be held for an extended period of time prior to further processing.

Manufacturing Scale Production—Manufacture at the scale typically encountered in a facility intended for product production for marketing.

Pilot-Plant Scale—The production of the drug substance or drug product by a procedure fully representative of and simulating that to be applied at manufacturing scale. The methods of cell expansion, harvest, and product purification should be identical except for the scale of production.

Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products

I. INTRODUCTION

A. Objective

The objective of this guideline is to provide broad guidance on appropriate standards for the derivation of human and animal cell lines and microbial cells to be used to prepare biotechnological/biological products defined in section 1.3, Scope, and for the preparation and characterization of cell banks to be used for production. The document, therefore, provides recommendations on the information in these areas that should be presented in market applications for these products.

B. Rationale

Historically, some quality concerns for cell-derived biological products have originated from the presence of adventitious contaminants or from the properties of the cells used to prepare the product. Recombinant DNA (rDNA)-derived products also carry quality concerns regarding the expression construct contained in the cell substrate. Thus, it is well established that the properties of the cell substrate and events linked to the cell substrate can affect resultant product quality and safety and, further, that effective quality control of these products requires appropriate controls on all aspects of handling the cell substrate.

This document complements other guidelines to provide a comprehensive approach to quality issues arising from biological aspects of processing products from metazoan and microbial cell culture.

C. Scope

This guideline covers cell substrates having a cell banking system. In this document, "cell substrate" refers to microbial cells or cell lines derived from human or animal sources that possess the full potential for generation of the desired biotechnological/biological products for human in vivo or ex vivo use. Reagents for in vitro diagnostic use are outside the scope of this document. Animal sources of cell lines include all those of metazoan origin. Both continuous cell lines of indefinite in vitro life span and diploid cells of finite in vitro life span are included. Microbial sources include bacteria, fungi, yeast, and other unicellular life forms.

"Biotechnological/biological products" refers to any products prepared from cells cultivated from cell banks with the exception of microbial metabolites such as, for example, antibiotics, amino acids, carbohydrates, and other low-molecular-weight substances. Cell banks used to prepare gene therapy products or vaccines should follow the recommendations presented in this document. Some biological products, such as certain viral vaccines, are prepared in primary cell cultures derived directly from animal tissues or organs. Primary cells are not banked and therefore are not addressed by this document. However, other considerations which may apply to primary cells are discussed further in Appendix 1 of this document.

II. GUIDELINES

A. Source, History, and Generation of the Cell Substrate

1. Introduction

It is important to provide supportive documentation which describes the history of the cell substrate that is used in the manufacture of a biotechnological/biological product, as well as any parental cell line from which it was totally or partially derived. Events during the research and development phases of the cell substrate may contribute significantly to assessment of the risks associated with the use of that particular cell substrate for production. The information supplied in this regard is meant to facilitate an overall evaluation, which will ensure the quality and safety of the product.

Careful records of the manipulation of the cell substrate should be maintained throughout its development. Description of cell history is only one tool of many used for cell substrate characterization. In general, deficiencies in documented history may not, by itself, be an impediment to product approval, but extensive deficiencies will result in increased reliance on other methods to characterize the cell substrate.

2. Origin, Source, and History of Cells

The source of cells (laboratory or culture collection) from which the cell substrate was derived should be stated, and relevant references from the scientific literature should be cited. Information obtained directly from the source laboratory is preferred. When this is not available, literature references may be utilized.

For human cell lines, it is relevant to describe the following characteristics of the original donor: Tissue or organ of origin, ethnic and geographical origin, age, sex, and general physiological condition. If known, the state of health or medical history of the donor should be reported along with the results of any tests of the donor for pathogenic agents. Specifically for human diploid fibroblasts, the age of the donor may influence the in vitro life span of the cell line and this information should be provided if available. For animal cell lines, relevant descriptions of the source include species, strains, breeding conditions, tissue or organ of origin, geographical origin, age and sex, the results of tests for pathogenic agents, and general physiological condition of the original donor.

For microbes, manufacturers should describe the species, strain, and known genotypic and phenotypic characteristics of the organism from which the cell substrate was derived. Manufacturers should also describe the pathogenicity, toxin production, and other biohazard information, if any.

The cultivation history of the cells should be documented. The method originally used for the isolation of the cells should be described as well as the procedures used in the culturing of the cells in vitro and any procedures used to establish cell lines (e.g., use of any physical, chemical, or biological procedure, or added nucleotide sequences). A description of any genetic manipulation or selection should be provided. All available information regarding the identification, characteristics, and results of testing of these cells for endogenous and adventitious agents should be provided.

For continuous cell lines of metazoan origin, it is usually adequate to quantitate culture duration by estimation of either number of population doublings, or number of subcultivations at defined dilution ratio, or time in days. For diploid cell lines possessing finite in vitro life span, accurate estimation of the number of population doublings during all stages of research, development, and manufacturing is important. For microbial cells, documentation of subcultivation frequency after cell substrate generation is considered adequate.

Regarding the generation of cell substrates, applicants should provide a thorough discussion of procedures which would provide exposure to infectious agents. Constituents of the culture medium should be described, in particular, information regarding exposure of the cells to materials of human or animal origin such as serum, enzymes, hydrolysates, or other living cells. The description should include the source, method of preparation and control, test results, and quality assurance. Relevant literature on these points may be referenced when available. This information will allow a detailed analysis of potential entry routes for adventitious agents from these sources, and will be part of the risk–benefit analysis of the product.

3. Generation of the Cell Substrate

A crucial step is the choice of a suitable parental cell line. For recombinant products, a parental cell line is typically the untransfected recipient cell line. The use of characterized parental cell banks is suggested, but is not considered essential. A characterized parental cell bank may be of benefit, especially when multiple cell substrates are generated from the same parental cell type, by providing a set of information on which the quality assessment of the Master Cell Bank (MCB) can be based. For example, the myeloma cell line may be banked as a parental cell line for hybridomas.

During the generation of the cell substrate, one or more specific procedures may be utilized in the ultimate development of the desired characteristics. These may include, for example, cell fusion, transfection, selection, colony isolation, cloning, gene amplification, and adaptation to specific culture conditions or media. Information regarding the methodologies utilized in developing the cell substrate can help to provide a clear understanding of the history of the cell substrate. Some cell substrates such as human diploid fibroblasts may not need extensive manipulation or cloning prior to cell banking.

For recombinant products, the cell substrate is the transfected cell containing the desired sequences, which has been cloned from a single cell progenitor. For further information on generation of rDNA-modified cell substrates, consult other relevant (e.g., regional or international) guidelines. For nonrecombinant products or nonrecombinant vaccines, the cell substrate is the cell from the parental cell line chosen for preparation of the MCB without further modification. For products derived from hybridomas, the cell substrate is the hybridoma cell line derived by fusion of the parental myeloma cell line with other parental cells, for example, immune spleen cells.

B. Cell Banking

One of the most important advantages of using serially subcultivated cells to produce biotechnological/biological products is the ability to have a characterized common starting source for each production lot, that is, the preserved bank of cells. Manufacturers may prepare their own cell banks, or may obtain them from external sources. Manufacturers are responsible for ensuring the quality of each cell bank and of the testing performed on each bank.

1. Cell Banking System

The concept of a two-tiered cell bank, in which the MCB which is used to generate Working Cell Banks (WCBs), is generally accepted as the most practical approach to providing a supply of cell substrate for continued manufacture of the product. Manufacturers should describe their strategy for providing a continued supply of cells from their cell bank(s), including the anticipated utilization rate of the cell bank(s) for production, the expected intervals between generation of new cell bank(s), and the criteria for qualification of cell bank(s).

Generally, the MCB is made first, usually directly from an initial clone or from a preliminary cell bank derived from an initial clone. It is not considered necessary to prepare cell banks from clones for certain types of cells (e.g., diploid cells, where limited in vitro life span or other technical factors make cell cloning impractical) or where the uncloned cell population is already adequately homogeneous for the intended use.

A WCB is derived from one or more containers of the MCB. It is the WCB which is typically used to directly provide cells for the manufacturing process. Additional WCBs are generated from the MCB as needed. A newly prepared WCB should be appropriately qualified by characterization and testing.

It should be noted that the MCB and WCB may differ from each other in certain respects, for example, culture components and culture conditions. Similarly, the culture conditions used to prepare the MCB and WCB may differ from those used for the production process. If changes in cell culture process do not affect product quality, it is not considered necessary to reclone the cells or to rebank the MCB or WCB. It is important that a characterized bank provides a consistent product.

A single-tiered banking system consisting only of the MCB but no WCBs could be used in principle, for example, if relatively few containers were needed each year to produce the desired product.

In some microbial expression systems, a new transformation is performed for each new cell substrate container lot, based upon using aliquots of thoroughly tested host cell banks and plasmid banks for each new transformation and on testing of each transformed cell substrate bank. This transformed cell substrate bank is considered the MCB, and it is used as the source of cell substrate for production. Host cell banks, plasmid banks, and MCBs are maintained by appropriate preservation methods. This alternative system is considered adequate because the transformation of bacteria and yeast is generally a very reproducible and easily performed process, unlike the events needed for transfection of metazoan cells. Manufacturers should provide information on the host cells, rDNA molecules (such

as plasmids), method of transformation and of cell banking, and the results of characterization studies.

2. Cell Banking Procedures

It is important to prevent a contaminated cell substrate (or bank) from being used in production and to avoid a loss of product availability or development time resulting from the need to recreate a cell bank found to be unusable due to contamination. It is recognized that no cell bank testing regimen is able to detect all potential contaminants; therefore, use of these preventive principles during cell banking is important to provide reasonable assurance of the absence of contamination and to provide a reliable source of the cell substrate.

Manufacturers should describe the type of banking system used, the size of the cell bank(s), the container (vials, ampoules, or other appropriate vessels) and closure system used, the methods used for preparation of the cell bank(s) including the cryoprotectants and media used, and the conditions employed for cryopreservation and storage.

Manufacturers should describe the procedures used to avoid microbial contamination and cross-contamination by other cell types present in the laboratory, and the procedures that allow the cell bank containers to be traced. This should include a description of the documentation system as well as that of a labeling system, which can withstand the process of preservation, storage, and recovery from storage without loss of labeling information on the container.

Manufacturers should describe their cell banking procedures. Cells are generally prepared for banking by expanding cultures in a progressively greater number or larger size of vessel until a pool of cells can be obtained which is sufficient to generate enough containers for the bank. To ensure the uniform composition of the contents of each container, a single pool of cells for banking should be prepared by combining the cells from all of the culture vessels, if more than one vessel is used.

Cells suspended in preservation medium are aliquoted from the single pool into sterilized containers which are then sealed and stored under appropriate conditions. For example, animal cells in media containing a cryoprotectant are frozen in the sealed containers under defined and controlled conditions, and then transferred to storage in the vapor or liquid phase of liquid nitrogen or at equivalent ultralow temperatures. Other methods of preservation and storage may be adequate depending on the organism used, but they should be capable of maintaining a level of cell viability upon reconstitution which is both consistent and adequate for production use.

To ensure continuous, uninterrupted production of pharmaceuticals, manufacturers should carefully consider the steps that can be taken to provide for protection from catastrophic events that could render the cell bank unusable. Examples of these events include fires, power outages, and human error. Manufacturers should describe their plans for such precautions; for example, these may include redundancy in the storage of bank containers in multiple freezers, use of back-up power, use of automatic liquid nitrogen fill systems for storage units, storage of a portion of the MCB and WCB at remote sites, or regeneration of the MCB.

The starting point of reference for estimates of in vitro cell age during manufacturing should be the thawing of one or more containers of the MCB. For diploid cell lines, in vitro life span should be estimated in terms of population doubling levels. The population doubling level at which senescence occurs should be determined for diploid cells.

C. General Principles of Characterization and Testing of Cell Banks

The characterization and testing of banked cell substrates is a critical component of the control of biotechnological and biological products. Characterization of the MCB allows the manufacturer to assess this source with regard to presence of cells from other lines, adventitious agents, endogenous agents, and molecular contaminants (e.g., toxins or antibiotics from the host organism). The objective of this testing is to confirm the identity, purity, and suitability of the cell substrate for manufacturing use. In some cases, additional testing such as tumorigenicity or karyology may be useful. The testing program chosen for a given cell substrate will vary according to the biological properties of the cells (e.g., growth requirements), its cultivation history (including use of human-derived and animal-derived biological reagents), and available testing procedures. The extent of characterization of a cell substrate may influence the type or level of routine testing needed at later stages of manufacturing. Manufacturers should perform tests for identity and purity once for each MCB, and tests of stability during cell cultivation once for each product to be registered. In addition, tests of purity and limited tests of identity should be performed once on each WCB. Also, applicants should consult the ICH guideline on viral safety. Relevant tests among those described below should be performed and described in the market application, along with the results of the testing.

For cell lines containing exogenously assembled expression constructs, the relevant ICH guideline on rDNA expression constructs should be consulted for guidance on the characterization of nucleotide and amino acid sequences. It may also be useful to examine, by similar methods, the coding sequences in some nonrecombinant DNA-derived cell lines where the gene sequences have been characterized and are well understood. However, it is not considered necessary to carry out investigations of the sequences encoding complex natural products, for example, families of related gene products, microbial vaccine antigens, or monoclonal antibodies from hybridomas.

Manufacturers are also encouraged to employ "state-of-the-art" methods and technological improvements in cell substrate characterization and testing as they become available, as long as the specificity, sensitivity, and precision of the newer methods are at least equivalent to those of existing methods.

The manufacturer may choose to characterize WCB instead of the MCB, if justified.

1. Tests of Identity

Appropriate tests should be performed to determine that the banked cell is what it is represented to be. Either phenotypic or genotypic characteristics may be used in identity testing. It is not considered necessary to do all the possible tests. Tests of identity are generally performed on the MCB. In addition, limited identity testing is generally performed on each WCB.

a. Metazoan Cells

For human or animal cells which grow attached to a substratum, morphological analysis may be a useful tool in conjunction with other tests. In most cases, isoenzyme analysis is sufficient to confirm the species of origin for cell lines derived from human or animal sources; other tests may be appropriate depending on the history of the cell line. Other technologies may be substituted to confirm species of origin, including, for example, banding cytogenetics or use of

species-specific antisera. An alternative strategy would be to demonstrate the presence of unique markers, for example, by using banding cytogenetics to detect a unique marker chromosome, or DNA analysis to detect a genomic polymorphism pattern (e.g., restriction fragment length polymorphism, variable number of tandem repeats, or genomic dinucleotide repeats). Either confirmation of species of origin or presence of known unique cell line markers is considered an adequate test of identity. Expression of the desired product may represent a complementary approach to confirmation of identity.

b. Microbial Cells

For most microbial cells, analysis of growth on selective media is usually adequate to confirm host cell identity at the species level for the host cell bank and the transformed cell bank. For *Escherichia coli*, where a variety of strains may be used, biological characterization methods such as phage typing should be considered as supplementary tests of identity. For plasmid banks, identity assessment can be accomplished as described by the ICH document on analysis of the expression construct. Expression of the desired product is also considered adequate to confirm the identity of the microbial expression system.

2. Tests of Purity

A critical aspect of cell development and banking is the assessment that the MCB and WCB are biologically pure, that is, are free from adventitious microbial agents and adventitious cellular contaminants. The impact of selective agents and antibiotics on the detection of adventitious microbial contaminants should be considered when planning and performing these tests.

a. Metazoan Cells

Tests for the presence of bioburden (bacteria and fungi) should be performed on individual containers (1% of the total number but not less than two containers) of the MCB and WCB. In all other aspects, the current methodologies described in either the European Pharmacopoeia (Ph. Eur.), the Japanese Pharmacopoeia (JP) or the U.S. Pharmacopoeia (USP) for testing microbial limits or microbial sterility may be considered adequate.

Tests for the presence of mycoplasma should be performed on the MCB and WCB. Current procedures considered adequate include both the agar and broth media procedures as well as the indicator cell culture procedure. Current methods for mycoplasma testing are described in Ph. Eur., JP, and "Points to Consider in the Characterisation of Cell Lines Used to Produce Biologicals" (FDA, CBER, 1993). Testing cells derived from a single container is generally considered adequate. For nonmammalian animal cell lines, alternative controls and/or assay conditions may be appropriate; manufacturers should consult with the national/regional regulatory authority for appropriate methodology.

If future efforts to harmonize bioburden and mycoplasma assays are fruitful, then the scientifically appropriate harmonized assay should be used.

Virus testing of cell substrates should be designed to detect a wide spectrum of viruses by using appropriate screening tests and relevant specific tests, based on the cultivation history of the cell line, to detect possible contaminating viruses. Applicants should consult the ICH guideline on viral safety. For product classes not covered by the viral safety guideline, the current WHO documents for use of animal cells may be consulted.

The purity of cell substrates can be compromised through contamination by cell lines of the same or different species of origin. The choice of tests to be performed depends upon whether opportunities have existed for cross-contamination by other cell lines. In some cases, it may be necessary to maintain growing cultures of different cell lines in the same laboratory. During procedures in cell banking where open manipulations are performed, care should be taken to ensure that simultaneous open manipulations of other cell lines are avoided to prevent cross-contamination. Whenever another cell line was present in the cell banking room at the same time that open cell banking procedures were being performed (such as cell expansion, pooling, or aliquoting of the chosen cell line), the cell banks should be tested for the presence of cells from (or products derived from) the second cell line. In general, the methods described in section 2.3.1 to assess cell identity are also considered adequate tests to detect cross-contamination by other cell lines. Additional assurance of lack of cross-contamination can be provided by successful preparation of the intended product from the cell substrate.

b. Microbial Cells

The design and performance of specific tests for adventitious microbial agents and adventitious cellular contaminants in microbial cell banks should take into account the properties of the banked cell, the likely contaminants based upon scientific literature, source, methods and materials used for cultivation, and other organisms present in the banking laboratory. For example, visual examination of the characteristics of well-isolated colonies is suggested, using several microbiological media, of which some do and some do not support growth of the cell substrate. However, it is not intended that manufacturers necessarily characterize resistant mutants of the cell substrate arising from such studies, or other artifacts of such assays. Rather, the purpose of such assays is to detect existing contaminants.

3. Cell Substrate Stability

Another dimension to cell characterization is appropriateness for intended use in production. There are two concerns for cell substrate stability: consistent production of the intended product and retention of production capacity during storage under defined conditions.

For the evaluation of stability during cultivation for production, at least two time points should be examined, one using cells which have received a minimal number of subcultivations, and another using cells at or beyond the limit of in vitro cell age for production use described in the marketing application. The limit of in vitro cell age for production use should be based on data derived from production cells expanded under pilot plant scale or commercial scale conditions to the proposed limit of in vitro cell age for production use or beyond. Generally, the production cells are obtained by expansion of cells from the WCB; cells from the MCB could be used with appropriate justification. This demonstration of cell substrate stability is commonly performed once for each product marketing application.

Evaluation of the cell substrate with respect to the consistent production of the intended product of interest should be the primary subject of concern. The type of testing and test article(s) used for such assessments will depend on the nature of the cell substrate, the cultivation methods, and the product. For cell lines containing recombinant DNA expression constructs, consistency of the coding sequence of the expression construct should be verified in cells cultivated to

the limit of in vitro cell age for production use or beyond by either nucleic acid testing or product analysis, as described in the relevant ICH guideline. For nonrecombinant cell lines in which the coding sequence for the desired product has already been analyzed at the MCB or WCB level, invariability of the protein coding sequence during production should be verified in the production cells cultivated to the proposed limit of in vitro cell age for production use or beyond by either nucleic acid testing or analysis of the purified protein product.

Where the product cannot be analyzed as described above, other specific traits which may include, for example, morphological characteristics, growth characteristics, biochemical markers, immunological markers, productivity of the desired product, or other relevant genotypic or phenotypic markers may be useful for the assessment of cell substrate stability. In some cases, where direct comparison of the characteristics of the MCB with those of the production cells at or beyond the limit of in vitro cell age is difficult or impossible, one may compare the characteristics of cells at the initial stages of cultivation or production to those of cells at or beyond the limit of in vitro cell age for production use in order to assess cell stability during production. Indices such as, for example, oxygen or glucose consumption rates, ammonia or lactate production rates may be useful for such testing. Increases in the defined limit of in vitro cell age for production use should be supported by data from cells which have been expanded to the proposed new limit of in vitro cell age. For diploid cell lines, data should be presented that establish the finite in vitro life span of the cells from the WCB under conditions representative of those employed for manufacturing use.

Evidence for banked cell stability under defined storage conditions will usually be generated during production of clinical trial material from the banked cells. Data from the determination of cell viability when the preserved cells are reconstituted for production of clinical trial supplies will verify that the revived cells have survived the preservation process. Data from the preparation of clinical materials will demonstrate that the revived cells can be used to prepare the desired product. Available data should be clearly documented in the application dossiers, plus a proposal for monitoring of banked cell stability should be provided. The proposed monitoring can be performed at the time that one or more containers of the cryopreserved bank is thawed for production use, when the product or production consistency is monitored in a relevant way, or when one or more containers of the cryopreserved MCB is thawed for preparation of a new WCB (and the new WCB is properly qualified), as appropriate. In the case when production does not take place for a long period of time, viability testing on the cell bank used as a source of the production substrate should be performed at an interval described in the marketing application. If the viability of the cell substrate is not significantly decreased, generally no further testing of the MCB or WCB is considered necessary.

4. Tests for Karyology and Tumorigenicity

Utilization of karyology and tumorigenicity testing for evaluating the safety of a diploid cell line or characterizing a new cell line may be useful depending on the cells, the nature of the product and the manufacturing process. Extensive analysis to determine the relative abundance of aneuploid cells has not been found to be useful. Karyology need not be determined for rodent cell lines or new cell lines known to be nondiploid. However, cytogenetic analysis may be an adequate method to assess cell substrate identity or purity as described in sections 2.3.1 and 2.3.2. Repetition of tumorigenicity testing for cells with already documented evidence of tumorigenicity is not considered necessary.

For products that are highly purified and that contain no cells, karyology and tumorigenicity testing are generally not considered necessary, provided that appropriate limits for residual host cell DNA are shown to be consistently met by either process validation studies or by lot release testing.

In general, products for which the presence of live cells cannot be excluded or which have little downstream purification (e.g., some conventional live virus vaccines) will need such characterization of the cell substrate. The utility of tumorigenicity testing and chromosomal analysis for new cell substrates for unpurified products should be evaluated on a case-by-case basis. Use of cell lines known to be tumorigenic or to possess abnormal karyology should be evaluated in terms of risk–benefit for each product application when the product contains cells or when not highly purified.

Products that are manufactured in genetically unmodified MRC-5 or WI-38 cells do not need characterization of these cell substrates by karyology or tumorigenicity since extensive characterization has already been performed and published for these cell lines. However, for each MRC-5 and WI-38 WCB generated, manufacturers should confirm, once, that the cells grown in the manner to be used in production are diploid and have the expected life span.

For new or previously uncharacterized diploid cell substrates, confirmation of diploid karyology should be presented and tumorigenic potential should be established, using cells from the MCB. Methods for karyological and tumorigenicity analysis may be found in the WHO document "WHO Requirements for Use of Animal Cells as in vitro Substrates for the Production of Biologicals" (WHO Technical Report Series, in press).

GLOSSARY

Cell Bank—A cell bank is a collection of appropriate containers, whose contents are of uniform composition, stored under defined conditions. Each container represents an aliquot of a single pool of cells.

Cell Line—Type of cell population which originates by serial subculture of a primary cell population, which can be banked.

Continuous Cell Line—A cell line having an infinite capacity for growth. Often referred to as "immortal" and previously referred to as "established".

Diploid Cell Line—A cell line having a finite in vitro life span in which the chromosomes are paired (euploid) and are structurally identical to those of the species from which they were derived.

Host Cells—See Parental Cells.

In Vitro Cell Age—Measure of time between thaw of the MCB vial(s) to harvest of the production vessel measured by elapsed chronological time, by population doubling level of the cells, or by passage level of the cells when subcultivated by a defined procedure for dilution of the culture.

Metazoan—Organism of multicellular animal nature.

MCB (Master Cell Bank)—An aliquot of a single pool of cells which generally has been prepared from

the selected cell clone under defined conditions, dispensed into multiple containers, and stored under defined conditions. The MCB is used to derive all working cell banks. The testing performed on a new MCB (from a previous initial cell clone, MCB or WCB) should be the same as for the MCB unless justified.

Parental Cells—Cell to be manipulated to give rise to a cell substrate or an intermediate cell line. For microbial expression systems, it is typical to also describe the parental cells as the host cell. For hybridomas, it is typical to also describe the parental cells as the cells to be fused.

WCB (Working Cell Bank)—The Working Cell Bank is prepared from aliquots of a homogeneous suspension of cells obtained from culturing the MCB under defined culture conditions.

REFERENCE

ICH Harmonized Tripartite Guideline Q5A(R1), US Food and Drug Administration 1998.

Appendix 1: Primary Cell Substrates

Introduction

The principles contained in this document apply in general to biotechnological/biological products prepared from characterized banked cells. However, a number of biological products, in particular certain viral vaccines, are prepared using primary cells.

Because primary cell cultures are used within the first passage after establishment from the tissue of origin, it is not possible to carry out extensive characterization of the cells prior to their use as is done for banked cell substrates. In addition, biological products produced using primary cell substrates often do not undergo extensive processing (e.g., purification). Despite these differences, the approach taken to assure the suitability and safety of primary cell substrates for production of biologicals is analogous, in many respects, to that outlined in this document and in other guidelines.

This Annex outlines cell substrate-related information that should be included in marketing applications for biological products prepared using primary cells. This information falls into three general categories: (1) Information concerning the source tissue (or organ) and other animal-derived raw materials used for the establishment of primary cell substrates, (2) information concerning the preparation of primary cell substrates, and (3) testing performed on primary cell substrates to ensure the safety of the product.

Source Tissue and Other Raw Materials

Information should be provided about the animals used as a source of tissue for the preparation of primary cell substrates. Tissue should be derived from healthy animals subjected to veterinary and laboratory monitoring to certify the absence of pathogenic agents. Whenever possible, donor animals should be obtained from closed, specific pathogen-free (when available) colonies or flocks. Animals used as tissue donors should not have been used previously for experimental studies. Animals should be adequately quarantined for an appropriate period of time prior to use for the preparation of cells. In some countries, animals may need to be quarantined in the country where the primary cells are prepared. Manufacturers should consult with national/regional authorities for specific requirements.

Information on materials and components used for the preparation of primary cell substrates should be provided, including the identity and source of all reagents of human or animal origin. A description of testing performed on components of animal origin to certify the absence of detectable contaminants and adventitious agents should be included.

Preparation of Primary Cell Substrates

Methods used for isolation of cells from tissue, establishment of primary cell cultures, and maintenance of cultures should be described.

Testing of Primary Cell Substrates

Tests performed on primary cell substrates to qualify them for use in production should be described. As noted, the nature of primary cell substrates precludes extensive testing and characterization prior to use. Testing to demonstrate the absence of adventitious agents in these substrates is therefore conducted concurrently and may include Observation of production or uninfected control cultures before, during, and beyond the period of production; inoculation of culture fluids from production and uninfected control cultures into various susceptible indicator cell cultures capable of detecting a wide range of relevant viruses, followed by examination for cytopathic changes and testing for the presence of hemadsorbing viruses; and other tests for specific agents (such as relevant retroviruses) as necessary. Additional information concerning specific viral tests may be found in the relevant national/regional/international guidelines.

Appropriate testing regimens and test methods for cells used in the production of specific products will vary depending on the donor species used as a source of tissue, adventitious agents potentially present, the nature of the product, its intended clinical use, aspects of the manufacturing process, and the extent of testing performed on the final product. Applicants should explain and justify the approach taken with respect to their specific product.

10

Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

I. INTRODUCTION

A. Objectives of the Guideline

The objective of this document is to provide principles for assessing the comparability of biotechnological/biological products before and after changes are made in the manufacturing process for the drug substance or drug product. Therefore, this guideline is intended to assist in the collection of relevant technical information, which serves as evidence that the manufacturing process changes will not have an adverse impact on the quality, safety, and efficacy of the drug product. The document does not prescribe any particular analytical, nonclinical, or clinical strategy. The main emphasis of the document is on quality aspects.

B. Background

Manufacturers[1] of biotechnological/biological products frequently make changes to manufacturing processes[2] of products[3] both during development and after approval. Reasons for such changes include improving the manufacturing process, increasing scale, improving product stability, and complying with changes in regulatory requirements. When changes are made to the manufacturing process, the manufacturer generally evaluates the relevant quality attributes of the product to demonstrate that modifications did not occur that would adversely impact[4] the safety and efficacy of the drug product. Such an evaluation should indicate whether or not confirmatory nonclinical or clinical studies are appropriate.

While ICH documents have not specifically addressed considerations for demonstrating comparability between prechange and postchange product, several ICH documents have provided guidance for technical information and data to be submitted in marketing applications that can also be useful for assessing manufacturing process changes. This document builds upon the previous ICH guidelines and provides additional direction regarding approaches to

- comparing postchange product to prechange product following manufacturing process changes and
- assessing the impact of observed differences in the quality attributes caused by the manufacturing process change for a given product as it relates to safety and efficacy of the product.

C. Scope

The principles adopted and explained in this document[5] apply to the following:

- Proteins and polypeptides, their derivatives, and products of which they are components, for example, conjugates. These proteins and polypeptides are produced from recombinant or nonrecombinant cell-culture expression systems and can be highly purified and characterized using an appropriate set of analytical procedures;
- Products where manufacturing process changes are made by a single manufacturer, including those made by a contract manufacturer, who can directly compare results from the analysis of prechange and postchange product; and
- Products where manufacturing process changes are made in development or for which a marketing authorization has been granted.

The principles outlined in this document might also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids. Manufacturers are advised to consult with the appropriate regional Regulatory Authority to determine applicability.

D. General Principles

The goal of the comparability exercise is to ensure the quality, safety, and efficacy of drug product produced by a changed manufacturing process, through collection and evaluation of the relevant data to determine whether there might be any adverse impact on the drug product due to the manufacturing process changes.

The demonstration of comparability does not necessarily mean that the quality attributes of the prechange and postchange product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.

A determination of comparability can be based on a combination of analytical testing, biological assays, and, in some cases, nonclinical and clinical data. If a manufacturer can provide assurance of comparability through

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[1] For convenience, when the term "manufacturer" is used, it is intended to include any third party having a contractual arrangement to produce the intermediates, drug substance, or drug product on behalf of the marketing authorization holder (or the developer, if prior to market authorization).

[2] For convenience, when the term "manufacturing process(es)" is used, it also includes facilities and equipment that might impact on critical processing parameters and, thereby, on product quality.

[3] For convenience, when the term "product" is used without modifiers, it is intended to refer to the intermediates, drug substance, and drug product.

[4] Improvement of product quality is always desirable and encouraged. If the results of the comparability exercise indicate an improved quality suggesting a significant benefit in efficacy and/or safety, the pre- and postchange product may not be comparable. However, this result could be considered acceptable. The manufacturer is advised to consult the appropriate regional Regulatory Authority.

[5] This document applies to situations in which all three of the bulleted conditions are present.

analytical studies alone, nonclinical or clinical studies with the postchange product are not warranted. However, where the relationship between specific quality attributes and safety and efficacy has not been established, and differences between quality attributes of the pre- and postchange product are observed, it might be appropriate to include a combination of quality, nonclinical, and/or clinical studies in the comparability exercise.

To identify the impact of a manufacturing process change, a careful evaluation of all foreseeable consequences for the product should be performed. In consideration of this evaluation, appropriate criteria to define highly similar postchange product can be established. Generally, quality data on the pre- and postchange product are generated, and a comparison is performed that integrates and evaluates all data collected, for example, routine batch analyses, in-process control, process validation/evaluation data, characterization, and stability, if appropriate. The comparison of the results to the predefined criteria should allow an objective assessment of whether or not the pre- and postchange product are comparable.

Following the evaluation of the quality attributes, the manufacturer could be faced with one of several outcomes, including the list as follows:

- Based on appropriate comparison of relevant quality attributes, pre- and postchange products are highly similar and considered comparable, that is, no adverse impact on safety or efficacy profiles is foreseen;
- Although the pre- and postchange product appears highly similar, the analytical procedures used are not sufficient to discern relevant differences that can impact the safety and efficacy of the product. The manufacturer should consider employing additional testing (e.g., further characterization) or nonclinical and/or clinical studies to reach a definitive conclusion;
- Although the pre- and postchange product appears highly similar, some differences have been observed in the quality attributes of the prechange and postchange product, but it can be justified that no adverse impact on safety or efficacy profiles is expected, based on the manufacturer's accumulated experience, relevant information, and data. In these circumstances, pre- and postchange product can be considered comparable;
- Although the pre- and postchange product appears highly similar, some differences have been identified in the comparison of quality attributes and a possible adverse impact on safety and efficacy profiles cannot be excluded. In such situations, the generation and analysis of additional data on quality attributes are unlikely to assist in determining whether pre- and postchange products are comparable. The manufacturer should consider performing nonclinical and/or clinical studies;
- Differences in the quality attributes are so significant that it is determined that the products are not highly similar and are therefore not comparable. This outcome is not within the scope of this document and is not discussed further.

II. GUIDELINES

A. Considerations for the Comparability Exercise

The goal of the comparability exercise is to ascertain that pre- and postchange drug product is comparable in terms of quality, safety, and efficacy. To meet this goal, the product should be evaluated at the process step most appropriate to detect a change in the quality attributes. This may entail evaluating the product at multiple stages of manufacture. For example, even though all process changes occurred in the manufacture of the drug substance, in cases where the drug product could be impacted by the change, it might be appropriate to collect data on both the drug substance and the drug product to support the determination of comparability. Comparability can often be deduced from quality studies alone (limited or comprehensive analysis, as appropriate), but might sometimes need to be supported by comparability bridging studies. The extent of the studies necessary to demonstrate comparability will depend on the following:

- The production step where the changes are introduced;
- The potential impact of the changes on the purity as well as on the physicochemical and biological properties of the product, particularly considering the complexity and degree of knowledge of the product (e.g., impurities, product-related substances);
- The availability of suitable analytical techniques to detect potential product modifications and the results of these studies; and
- The relationship between quality attributes and safety and efficacy, based on overall nonclinical and clinical experience.

When considering the comparability of products, the manufacturer should evaluate, for example, the following:

- Relevant physicochemical and biological characterization data regarding quality attributes;
- Results from analysis of relevant samples from the appropriate stages of the manufacturing process (e.g., intermediate, drug substance, and drug product);
- The need for stability data, including those generated from accelerated or stress conditions, to provide insight into potential product differences in the degradation pathways of the product and, hence, potential differences in product-related substances and product-related impurities;
- Batches used for demonstration of manufacturing consistency;
- Historical data that provide insight into potential "drift" of quality attributes with respect to safety and efficacy, following either a single or a series of manufacturing process changes. That is, the manufacturer should consider the impact of changes over time to confirm that an unacceptable impact on safety and efficacy profiles has not occurred.

In addition to evaluating the data, manufacturers should also consider the following:

- Critical control points in the manufacturing process that affect product characteristics, for example, the impact of the process change on the quality of in-process materials, as well as the ability of downstream steps to accommodate material from a changed cell culture process;
- Adequacy of the in-process controls including critical control points and in-process testing: In-process controls for the post-change process should be confirmed, modified, or created, as appropriate, to maintain the quality of the product;
- Nonclinical or clinical characteristics of the drug product and its therapeutic indications (see section 2.5).

B. Quality Considerations

1. Analytical Techniques

The battery of tests for the comparability exercise should be carefully selected and optimized to maximize the potential for

detecting relevant differences in the quality attributes of the product that might result from the proposed manufacturing process change. To address the full range of physicochemical properties or biological activities, it might be appropriate to apply more than one analytical procedure to evaluate the same quality attribute (e.g., molecular weight, impurities, secondary/tertiary structures). In such cases, each method should employ different physicochemical or biological principles to collect data for the same parameter to maximize the possibility that differences in the product caused by a change in the manufacturing process might be detected.

It can be difficult to ensure that the chosen set of analytical procedures for the prechange product will be able to detect modifications of the product due to the limitations of the assays (e.g., precision, specificity, and detection limit) and the complexity of some products due to molecular heterogeneity. Consequently, the manufacturer should determine the following:

- Whether or not existing tests remain appropriate for their intended use or should be modified. For example, when the manufacturing process change gives rise to a different impurity profile in the host cell proteins, manufacturers should confirm that the test used to quantitate these impurities is still suitable for its intended purpose. It might be appropriate to modify the existing test to detect the new impurities.
- The need to add new tests as a result of changes in quality attributes that the existing methods are not capable of measuring. That is, when specific changes in quality attributes are expected as a result of a process change (e.g., following addition of a new raw material or modification of a chromatographic purification step), it might be appropriate to develop new analytical procedures, that is, to employ additional analytical techniques above and beyond those used previously for characterization or routine testing.

The measurement of quality attributes in characterization studies does not necessarily entail the use of validated assays but the assays should be scientifically sound and provide results that are reliable. Those methods used to measure quality attributes for batch release should be validated in accordance with ICH guidelines (ICH Q2A, Q2B, Q5C, Q6B), as appropriate.

2. Characterization

Characterization of a biotechnological/biological product by appropriate techniques, as described in ICH Q6B, includes the determination of physicochemical properties, biological activity, immunochemical properties (if any), purity, impurities, contaminants, and quantity.

When a manufacturing process change has been made that has the potential to have an impact on quality attributes, a complete or limited (but rationalized) repetition of the characterization activity conducted for the market application is generally warranted to directly compare the prechange and postchange product. However, additional characterization might be indicated in some cases. For example, when process changes result in a product characterization profile that differs from that observed in the material used during nonclinical and clinical studies or other appropriate representative materials (e.g., reference materials, marketed batches), the significance of these alterations should be evaluated. Results of comprehensive characterization of the material used in pivotal clinicial trials could provide a useful point of reference for subsequent comparability excercises.

Each of the following criteria should be considered as a key point in the conduct of the comparability exercise:

***Physicochemical Properties*:** The manufacturer should consider the concept of the desired product (and its variants) as defined in ICH Q6B when designing and conducting a comparability exercise. The complexity of the molecular entity with respect to the degree of molecular heterogeneity should also be considered. Following a manufacturing process change, manufacturers should attempt to determine that higher order structure (secondary, tertiary, and quaternary structure) is maintained in the product. If the appropriate higher order structural information cannot be obtained, a relevant biological activity assay (see biological activity below) could indicate a correct conformational structure.

***Biological Activity*:** Biological assay results can serve multiple purposes in the confirmation of product quality attributes that are useful for characterization and batch analysis, and, in some cases, could serve as a link to clinical activity. The manufacturer should consider the limitations of biological assays, such as high variability, that might prevent detection of differences that occur as a result of a manufacturing process change.

In cases where the biological assay also serves as a complement to physicochemical analysis, for example, as a surrogate assay for higher order structure, the use of a relevant biological assay with appropriate precision and accuracy might provide a suitable approach to confirm that change in specific higher order structure has not occurred following manufacturing process changes. Where physicochemical or biological assays are not considered adequate to confirm that the higher order structure is maintained, it might be appropriate to conduct a nonclinical or clinical study.

When changes are made to a product with multiple biological activities, manufacturers should consider performing a set of relevant functional assays designed to evaluate the range of activities. For example, certain proteins possess multiple functional domains that express enzymatic and receptor-mediated activities. In such situations, manufacturers should consider evaluating all relevant functional activities.

Where one or more of the multiple activities are not sufficiently correlated with clinical safety or efficacy or if the mechanism of action is not understood, the manufacturer should justify that nonclinical or clinical activity is not compromised in the postchange product.

Immunochemical Properties: When immunochemical properties are part of the characterization (e.g., for antibodies or antibody-based products), the manufacturer should confirm that postchange product is comparable in terms of the specific properties.

Purity, Impurities, and Contaminants: The combination of analytical procedures selected should provide data to evaluate whether a change in purity profile has occurred in terms of the desired product.

If differences are observed in the purity and impurity profiles of the postchange product relative to the prechange product, the differences should be evaluated to assess their potential impact on safety and efficacy. Where the change results in the appearance of new impurities, the new impurities should be identified and characterized when possible. Depending on the impurity type and amount, it might be appropriate to conduct nonclinical or clinical studies to confirm that there is no adverse impact on safety or efficacy of the drug product.

Contaminants should be strictly avoided and/or suitably controlled with appropriate in-process acceptance criteria or action limits for drug substance or drug product. New contaminants should be evaluated to assess their potential impact on the quality, safety, and efficacy of the product.

3. Specifications

The tests and analytical procedures chosen to define drug substance or drug product specifications alone are generally not considered adequate to assess the impact of manufacturing process changes since they are chosen to confirm the routine quality of the product rather than to fully characterize it. The manufacturer should confirm that the specifications after the process change are appropriate to ensure product quality. Results within the established acceptance criteria, but outside historical manufacturing control trends, might suggest product differences that warrant additional study or analysis. Modification, elimination, or addition of a test (i.e., in the specification) might be indicated where data suggest that the previous test is no longer relevant for routine batch analysis of the postchange product. For example, the elimination of bovine serum from the cell culture process would remove the need for related analyses. However, a widening of the acceptance criteria is generally not considered appropriate unless justified. In some cases, additional tests and acceptance criteria on the relative amount of specific new impurities might be appropriate if the impurity profile is different following the manufacturing process changes. When evaluating both the test methods and acceptance criteria for the postchange product, it is important to consider the general principles for setting specifications as defined in Q6B, that is, the impact of the changes on the validated manufacturing process, characterization studies, batch analysis data, stability data, and nonclinical and clinical experience.

4. Stability

For certain manufacturing process changes, even slight modifications of the production procedures might cause changes in the stability of the postchange product. Any change with the potential to alter protein structure or purity and impurity profiles should be evaluated for its impact on stability, since proteins are frequently sensitive to changes, such as those made to buffer composition, processing and holding conditions, and the use of organic solvents. Furthermore, stability studies might be able to detect subtle differences that are not readily detectable by the characterization studies. For example, the presence of trace amounts of a protease might only be detected by product degradation that occurs over an extended time period; or, in some cases, divalent ions leached from the container closure system might change the stability profile because of the activation of trace proteases not detected in stability studies of the prechange product. Therefore, real-time/real temperature stability studies on the product potentially affected by the change should be initiated, as appropriate.

Accelerated and stress stability studies are often useful tools to establish degradation profiles and provide a further direct comparison of prechange and postchange product. The results thus obtained might show product differences that warrant additional evaluation, and also identify conditions indicating that additional controls should be employed in the manufacturing process and during storage to eliminate these unexpected differences. Appropriate studies should be considered to confirm that suitable storage conditions and controls are selected.

ICH Q5C and Q1A(R) should be consulted to determine the conditions for stability studies that provide relevant data to be compared before and after a change.

C. Manufacturing Process Considerations

A well-defined manufacturing process with its associated process controls assures that acceptable product is produced on a consistent basis. Approaches to determining the impact of any process change will vary with respect to the specific process, the product, the extent of the manufacturer's knowledge of and experience with the process, and development data generated. The manufacturer should confirm that the process controls in the modified process provide at least similar or more effective control of the product quality, compared to those of the original process.

A careful consideration of potential effects of the planned change on steps downstream and quality parameters related to these steps is extremely important (e.g., for acceptance criteria, in-process specification, in-process tests, in-process hold times, operating limits, and validation/evaluation, if appropriate). This analysis will help identify which tests should be performed during the comparability exercise, which in-process or batch release acceptance criteria or analytical procedures should be reevaluated and which steps should not be impacted by the proposed change. For example, analysis of intermediates might suggest potential differences that should be evaluated to determine the suitability of existing tests to detect these differences in the product. The rationale for excluding parts of the process from this consideration should be justified.

While the process will change and the associated controls might be redefined, the manufacturer should confirm that prechange and postchange products are comparable. To support the comparison, it is often useful to demonstrate, for example, that specific intermediates are comparable or that the modified process has the capability to provide appropriate levels of removal for process- and product-related impurities, including those newly introduced by the process change. To support process changes for approved products, data from commercial-scale batches are generally indicated.

The process assessment should consider such factors as the criticality of the process step and proposed change, the location of the change and potential for effects on other process steps, and the type and extent of change. Information that can aid this assessment is generally available from several sources. The sources can include knowledge from process development studies, small-scale evaluation/validation studies, experience with earlier process changes, experience with equipment in similar operations, changes in similar manufacturing processes with similar products, and literature. Although information from external sources is useful to some extent, it is within the context of the specific manufacturing process and specific product that the change should be assessed.

When changes are made to a process, the manufacturer should demonstrate that the associated process controls, including any new ones, provide assurance that the modified process will also be capable of providing comparable product. The modified process steps should be reevaluated and/or revalidated, as appropriate. The in-process controls, including critical control points and in-process testing, should ensure that the postchange process is well controlled and maintains the quality of the product. Typically, reevaluation/revalidation activities for a simple change might be limited to the affected process step, if there is no evidence to indicate that there is impact on the performance of

subsequent (downstream) process steps, or on the quality of the intermediates resulting from the subsequent steps. When the change considered affects more than a single step, more extensive analysis of the change and resultant validation might be appropriate.

Demonstration of state of control with the modified/changed manufacturing process might include, but is not limited to, such items as

- establishment of modified specifications for raw, source and starting materials, and reagents;
- appropriate bioburden and/or viral safety testing of the postchange cell banks and cells at the limit of in vitro cell age for production;
- adventitious agent clearance;
- removal of product- or process-related impurities, such as residual host cell DNA and proteins; and
- maintenance of the purity level.

For approved products, an appropriate number of postchange batches should be analyzed to demonstrate consistent performance of the process.

To support the analysis of the changes and the control strategy, the manufacturer should prepare a description of the change that summarizes the prechange and the postchange manufacturing process and that clearly highlights modifications of the process and changes in controls in a side-by-side format.

D. Demonstration of Comparability during Development

During product development, it is expected that multiple changes in the manufacturing process will occur that could impact drug product quality, safety, and efficacy. Comparability exercises are generally performed to demonstrate that nonclinical and clinical data generated with prechange product are applicable to postchange product in order to facilitate further development and, ultimately, to support the marketing authorization. Comparability studies conducted for products in development are influenced by factors such as the stage of product development, the availability of validated analytical procedures, and the extent of product and process knowledge, which are limited at times due to the available experience that the manufacturer has with the process.

Where changes are introduced in development before nonclinical studies, the issue of assessing comparability is not generally raised because the manufacturer subsequently conducts nonclinical and clinical studies using the postchange product as part of the development process. During early phases of nonclinical and clinical studies, comparability testing is generally not as extensive as for an approved product. As knowledge and information accumulate, and the analytical tools develop, the comparability exercise should use available information and will generally become more comprehensive. Where process changes are introduced in late stages of development and no additional clinical studies are planned to support the marketing authorization, the comparability exercise should be as comprehensive and thorough as one conducted for an approved product. Some outcomes of the comparability studies on quality attributes can lead to additional nonclinical or clinical studies.

In order for a comparability exercise to occur during development, appropriate assessment tools should be used. Analytical procedures used during development might not be validated, but should always be scientifically sound and provide results that are reliable and reproducible. Because of the limitations of the analytical tools in early clinical development, physicochemical and biological tests alone might be considered inadequate to determine comparability, and therefore, bridging nonclinical and/or clinical studies, as appropriate, might be needed.

E. Nonclinical and Clinical Considerations

1. Factors to be Considered in Planning Nonclinical and Clinical Studies

Determinations of product comparability can be based solely on quality considerations (see section 2.2) if the manufacturer can provide assurance of comparability through analytical studies as suggested in this document. Additional evidence from nonclinical or clinical studies is considered appropriate when quality data are insufficient to establish comparability. The extent and nature of nonclinical and clinical studies will be determined on a case-by-case basis in consideration of various factors, which include among others the following:

Quality findings

- Drug product—The type, nature, and extent of differences between the postchange product and the prechange product with respect to quality attributes including product-related substances, the impurity profile, stability and excipients. For example, new impurities could warrant toxicological studies for qualification.
- Results of the evaluation/validation studies on the new process including the results of relevant in-process tests.
- Availability, capability, and limitation of tests used for any comparability studies.

The nature and the level of knowledge of the product

- Product complexity, including heterogeneity and higher order structure—Physicochemical and in vitro biological assays might not be able to detect all differences in structure and/or function.
- Structure-activity relationship and strength of the association of quality attributes with safety and efficacy.
- Relationship between the therapeutic protein and endogenous proteins and the consequences for immunogenicity.
- Mode(s) of action (unknown vs. known, single vs. multiple active sites).

Existing nonclinical and clinical data relevant to the product, aspects of product use, and product class

- Therapeutic indications/target patient groups—The impact of possible differences can vary between patient groups, for example, risk for unintended immunogenicity. It may be appropriate to consider the consequences separately for each indication.
- Posology, for example, dosing regimen, route of administration—The risk of certain possible consequences of a difference, such as immunogenicity, could be higher with chronic administration as compared to short-term administration; subcutaneous administration might induce immunogenicity more often than intravenous administration.
- The therapeutic window/dose-response curve—The impact of a certain change could be different for products that have a wide therapeutic window as compared to those with a more narrow window. The safety or efficacy of products with a steep or a bell-shaped dose-response curve can be affected by minor changes in pharmacokinetics or receptor binding.

- Previous experience, for example, immunogenicity, safety—The experience with the original product or with other products in the same class can be relevant, especially with regard to rare adverse effects, for example, knowledge about the consequences of immunogenicity.
- PK/PD relation, distribution, and clearance.

2. Type of Studies

The nonclinical and clinical studies referred to in this document might include, depending on the situation, PK studies, PD studies, PK/PD studies, clinical efficacy studies, specific safety studies, immunogenicity studies, and pharmacovigilance studies. The purpose of these studies is to enable comparison of pre- and postchange product. Where appropriate, these studies should be direct comparative studies.

GLOSSARY

Comparability Bridging Study—A study performed to provide nonclinical or clinical data that allows extrapolation of the existing data from the drug product produced by the current process to the drug product from the changed process.

Comparable—A conclusion that products have highly similar quality attributes before and after manufacturing process changes and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical or clinical data might contribute to the conclusion.

Comparability Exercise—The activities, including study design, conduct of studies, and evaluation of data, that are designed to investigate whether the products are comparable.

Quality Attribute—A molecular or product characteristic that is selected for its ability to help indicate the quality of the product. Collectively, the quality attributes define identity, purity, potency and stability of the product, and safety with respect to adventitious agents. Specifications measure a selected subset of the quality attributes.

REFERENCES

Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin (ICH Guideline Q5A).

Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (ICH Guideline Q5B).

Stability Testing of Biotechnological/Biological Products (ICH Guideline Q5C).

Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products (ICH Guideline Q5D).

Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (ICH Guideline Q6B).

Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (ICH Guideline Q7A).

Validation of Analytical Procedures (ICH Guideline Q2A).

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Stability Testing of New Drug Substances and Products (ICH Guideline Q1A) (Second Revision).

Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH Guideline S6).

Statistical Principles for Clinical Trials (ICH Guideline E9).

Choice of Control Group and Related Issues in Clinical Trials (ICH Guideline E10).

11

Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

I. INTRODUCTION

A. Objective

This guidance document provides general principles on the setting and justification, to the extent possible, of a uniform set of international specifications for biotechnological and biological products to support new marketing applications.

B. Background

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product, or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. "Conformance to specification" means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

Specifications are one part of a total control strategy designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterization during development, upon which many of the specifications are based, adherence to Good Manufacturing Practices, a validated manufacturing process, raw materials testing, in-process testing, stability testing, and so on.

Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization and should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.

C. Scope

The principles adopted and explained in this document apply to proteins and polypeptides, their derivatives, and products of which they are components (e.g., conjugates). These proteins and polypeptides are produced from recombinant or nonrecombinant cell-culture expression systems and can be highly purified and characterized using an appropriate set of analytical procedures.

The principles outlined in this document may also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids. To determine applicability, manufacturers should consult with the appropriate regulatory authorities.

This document does not cover antibiotics, synthetic peptides and polypeptides, heparins, vitamins, cell metabolites, DNA products, allergenic extracts, conventional vaccines, cells, whole blood, and cellular blood components. A separate ICH Guideline, "Specifications: Test Procedures and Acceptance Criteria for New Drugs Substances and New Drug Products: Chemical Substances" addresses specifications, and other criteria for chemical substances.

This document does not recommend specific test procedures or specific acceptance criteria nor does it apply to the regulation of preclinical and/or clinical research material.

II. PRINCIPLES FOR CONSIDERATION IN SETTING SPECIFICATIONS

A. Characterization

Characterization of a biotechnological or biological product (which includes the determination of physicochemical properties, biological activity, immunochemical properties, purity, and impurities) by appropriate techniques is necessary to allow relevant specifications to be established. Acceptance criteria should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency and data from stability studies, and relevant development data.

Extensive characterization is performed in the development phase and, where necessary, following significant process changes. At the time of submission, the product should have been compared with an appropriate reference standard, if available. When feasible and relevant, it should be compared with its natural counterpart. Also, at the time of submission, the manufacturer should have established appropriately characterized in-house reference materials, which will serve for biological and physicochemical testing of production lots. New analytical technology and modifications to existing technology are continually being developed and should be utilized when appropriate.

1. Physicochemical Properties

A physicochemical characterization program will generally include a determination of the composition, physical properties, and primary structure of the desired product. In some cases, information regarding higher-order structure of the desired product (the fidelity of which is generally inferred by its biological activity) may be obtained by appropriate physicochemical methodologies.

An inherent degree of structural heterogeneity occurs in proteins due to the biosynthetic processes used by living organisms to produce them; therefore, the desired product can be a mixture of anticipated posttranslationally modified forms (e.g., glycoforms). These forms may be active and their presence may have no deleterious effect on the safety and efficacy of the product (section 2.1.4). The manufacturer should define the pattern of heterogeneity of the desired product and demonstrate consistency with that of the lots used in preclinical and clinical studies. If a consistent pattern of product heterogeneity is demonstrated, an evaluation of the activity,

efficacy, and safety (including immunogenicity) of individual forms may not be necessary.

Heterogeneity can also be produced during manufacture and/or storage of the drug substance or drug product. Since the heterogeneity of these products defines their quality, the degree and profile of this heterogeneity should be characterized, to assure lot-to-lot consistency. When these variants of the desired product have properties comparable to those of the desired product with respect to activity, efficacy, and safety, they are considered product-related substances. When process changes and degradation products result in heterogeneity patterns, which differ from those observed in the material used during preclinical and clinical development, the significance of these alterations should be evaluated.

Analytical methods to elucidate physicochemical properties are listed in Appendix 6.1. New analytical technology and modifications to existing technology are continually being developed and should be utilized when appropriate.

For the purpose of lot release (section 4), an appropriate subset of these methods should be selected and justified.

2. Biological Activity

Assessment of the biological properties constitutes an equally essential step in establishing a complete characterization profile. An important property is the biological activity that describes the specific ability or capacity of a product to achieve a defined biological effect.

A valid biological assay to measure the biological activity should be provided by the manufacturer. Examples of procedures used to measure biological activity include

- animal-based biological assays, which measure an organism's biological response to the product;
- cell culture-based biological assays, which measure biochemical or physiological response at the cellular level; and
- biochemical assays, which measure biological activities such as enzymatic reaction rates or biological responses induced by immunologic interactions.

Other procedures such as ligand and receptor binding assays, may be acceptable.

Potency (expressed in units) is the quantitative measure of biological activity based on the attribute of the product, which is linked to the relevant biological properties, whereas, quantity (expressed in mass) is a physicochemical measure of protein content. Mimicking the biological activity in the clinical situation is not always necessary. A correlation between the expected clinical response and the activity in the biological assay should be established in pharmacodynamic or clinical studies.

The results of biological assays should be expressed in units of activity calibrated against an international or national reference standard, when available and appropriate for the assay utilized. Where no such reference standard exists, a characterized in-house reference material should be established and assay results of production lots reported as in-house units.

Often, for complex molecules, the physicochemical information may be extensive but unable to confirm the higher-order structure which, however, can be inferred from the biological activity. In such cases, a biological assay, with wider confidence limits, may be acceptable when combined with a specific quantitative measure. Importantly, a biological assay to measure the biological activity of the product may be replaced by physicochemical tests only in those instances where

- sufficient physicochemical information about the drug, including higher-order structure, can be thoroughly established by such physicochemical methods, and relevant correlation to biologic activity demonstrated; and
- there exists a well-established manufacturing history.

Where physicochemical tests alone are used to quantitate the biological activity (based on appropriate correlation), results should be expressed in mass.

For the purpose of lot release (section 4), the choice of relevant quantitative assay (biological and/or physicochemical) should be justified by the manufacturer.

3. Immunochemical Properties

When an antibody is the desired product, its immunologic properties should be fully characterized. Binding assays of the antibody to purified antigens and defined regions of antigens should be performed, as feasible, to determine affinity, avidity, and immunoreactivity (including cross-reactivity). In addition, the target molecule bearing the relevant epitope should be biochemically defined and the epitope itself defined, when feasible.

For some drug substances or drug products, the protein molecule may need to be examined using immunochemical procedures (e.g., ELISA and Western-blot) utilizing antibodies which recognize different epitopes of the protein molecule. Immunochemical properties of a protein may serve to establish its identity, homogeneity or purity, or serve to quantify it.

If immunochemical properties constitute lot release criteria, all relevant information pertaining to the antibody should be made available.

4. Purity, Impurities, and Contaminants

- **Purity**

  The determination of absolute, as well as relative purity, presents considerable analytical challenges, and the results are highly method-dependent. Historically, the relative purity of a biological product has been expressed in terms of specific activity (units of biological activity per mg of product), which is also highly method-dependent. Consequently, the purity of the drug substance and drug product is assessed by a combination of analytical procedures.

  Because of the unique biosynthetic production process and molecular characteristics of biotechnological and biological products, the drug substance can include several molecular entities or variants. When these molecular entities are derived from anticipated posttranslational modification, they are part of the desired product. When variants of the desired product are formed during the manufacturing process and/or storage and have properties comparable to the desired product, they are considered product-related substances and not impurities (section 2.1.1).

  Individual and/or collective acceptance criteria for product-related substances should be set, as appropriate.

  For the purpose of lot release, (section 4), an appropriate subset of methods should be selected and justified for determination of purity.

- **Impurities**

  In addition to evaluating the purity of the drug substance and drug product, which may be composed of the desired product and multiple product-related substances, the manufacturer should also assess impurities, which may be present. Impurities may be either process or product related. They can be of known structure, partially characterized, or unidentified. When adequate quantities of

impurities can be generated, these materials should be characterized to the extent possible and, where possible, their biological activities should be evaluated.

Process-related impurities encompass those that are derived from the manufacturing process, that is, cell substrates (e.g., host cell proteins, host cell DNA), cell culture (e.g., inducers, antibiotics, or media components), or downstream processing (see "Appendix", section 6.2.1). Product-related impurities (e.g., precursors, certain degradation products) are molecular variants arising during manufacture and/or storage, which do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety.

Further, the acceptance criteria for impurities should be based on data obtained from lots used in preclinical and clinical studies and manufacturing consistency lots.

Individual and/or collective acceptance criteria for impurities (product-related and process-related) should be set, as appropriate. Under certain circumstances, acceptance criteria for selected impurities may not be necessary (section 2.3).

Examples of analytical procedures, which may be employed to test for the presence of impurities, are listed in Appendix 6.2. New analytical technology and modifications to existing technology are continually being developed and should be utilized when appropriate.

For the purpose of lot release (section 4), an appropriate subset of these methods should be selected and justified.

- **Contaminants**

  Contaminants in a product include all adventitiously introduced materials not intended to be part of the manufacturing process, such as chemical and biochemical materials (e.g., microbial proteases), and/or microbial species. Contaminants should be strictly avoided and/or suitably controlled with appropriate in-process acceptance criteria or action limits for drug substance or drug product specifications (section 2.3). For the special case of adventitious viral or mycoplasma contamination, the concept of action limits is not applicable, and the strategies proposed in ICH Harmonized Tripartite Guidelines "Quality of Biotechnological/Biological Products: Viral Safety Evaluation of Biotechnology Derived Products Derived from Cell Lines of Human or Animal Origin" and "Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products" should be considered.

5. Quantity

Quantity, usually measured as protein content, is critical for a biotechnological and biological product and should be determined using an appropriate assay, usually physicochemical in nature. In some cases, it may be demonstrated that the quantity values obtained may be directly related to those found using the biological assay. When this correlation exists, it may be appropriate to use measurement of quantity rather than the measurement of biological activity in manufacturing processes, such as filling.

B. Analytical Considerations

1. Reference Standards and Reference Materials

For drug applications for new molecular entities, it is unlikely that an international or national standard will be available. At the time of submission, the manufacturer should have established an appropriately characterized in-house primary reference material, prepared from lot(s) representative of production and clinical materials. In-house working reference material(s) used in the testing of production lots should be calibrated against this primary reference material. Where an international or national standard is available and appropriate, reference materials should be calibrated against it. While it is desirable to use the same reference material for both biological assays and physicochemical testing, in some cases, a separate reference material may be necessary. Also, distinct reference materials for product-related substances, product-related impurities, and process-related impurities, may need to be established. When appropriate, a description of the manufacture and/or purification of reference materials should be included in the application. Documentation of the characterization, storage conditions, and formulation supportive of reference material(s) stability should also be provided.

2. Validation of Analytical Procedures

At the time the application is submitted to the regulatory authorities, applicants should have validated the analytical procedures used in the specifications in accordance with the ICH Harmonized Tripartite Guidelines "Validation of Analytical Procedures: Definitions and Terminology" and "Validation of Analytical Procedures: Methodology," except where there are specific issues for unique tests used for analyzing biotechnological and biological products.

C. Process Controls

1. Process-Related Considerations

Adequate design of a process and knowledge of its capability are part of the strategy used to develop a manufacturing process, which is controlled and reproducible, yielding a drug substance or drug product that meets specifications. In this respect, limits are justified based on critical information gained from the entire process spanning the period from early development through commercial scale production.

For certain impurities, testing of either the drug substance or the drug product may not be necessary and may not need to be included in the specifications if efficient control or removal to acceptable levels is demonstrated by suitable studies. This testing can include verification at commercial scale in accordance with regional regulations. It is recognized that only limited data may be available at the time of submission of an application. This concept may, therefore, sometimes be implemented after marketing authorization, in accordance with regional regulations.

2. In-Process Acceptance Criteria and Action Limits

In-process tests are performed at critical decision making steps and at other steps where data serve to confirm consistency of the process during the production of either the drug substance or the drug product. The results of in-process testing may be recorded as action limits or reported as acceptance criteria. Performing such testing may eliminate the need for testing of the drug substance or drug product (section 2.3.1). In-process testing for adventitious agents at the end of cell culture is an example of testing for which acceptance criteria should be established.

The use of internal action limits by the manufacturer to assess the consistency of the process at less critical steps is also important. Data obtained during development and validation runs should provide the basis for provisional action limits to be set for the manufacturing process. These limits, which are the responsibility of the manufacturer, may be used to initiate investigation or further action. They should be further

refined as additional manufacturing experience and data are obtained after product approval.

3. Raw Materials and Excipient Specifications

The quality of the raw materials used in the production of the drug substance (or drug product) should meet standards, appropriate for their intended use. Biological raw materials or reagents may require careful evaluation to establish the presence or absence of deleterious endogenous or adventitious agents. Procedures which make use of affinity chromatography (e.g., employing monoclonal antibodies), should be accompanied by appropriate measures to ensure that such process-related impurities or potential contaminants arising from their production and use do not compromise the quality and safety of the drug substance or drug product. Appropriate information pertaining to the antibody should be made available.

The quality of the excipients used in the drug product formulation (and in some cases, in the drug substance), as well as the container/closure systems, should meet pharmacopoeial standards, where available and appropriate. Otherwise, suitable acceptance criteria should be established for the nonpharmacopoeial excipients.

D. Pharmacopoeial Specifications

Pharmacopoeias contain important requirements pertaining to certain analytical procedures and acceptance criteria, which, where relevant, are part of the evaluation of either the drug substance or drug product. Such monographs, applicable to biotechnological and biological products, generally include, but are not limited to tests for sterility, endotoxins, microbial limits, volume in container, uniformity of dosage units, and particulate matter. With respect to the use of pharmacopoeial methods and acceptance criteria, the value of this guidance is linked to the extent of harmonization of the analytical procedures of the pharmacopoeias. The pharmacopoeias are committed to developing identical or methodologically equivalent test procedures and acceptance criteria.

E. Release Limits vs. Shelf life Limits

The concept of release limits versus shelf life limits may be applied where justified. This concept pertains to the establishment of limits, which are tighter for the release than for the shelf life of the drug substance or drug product. Examples where this may be applicable include potency and degradation products. In some regions, the concept of release limits may only be applicable to in-house limits and not to the regulatory shelf life limits.

F. Statistical Concepts

Appropriate statistical analysis should be applied, when necessary, to quantitative data reported. The methods of analysis, including justification and rationale, should be described fully. These descriptions should be sufficiently clear to permit independent calculation of the results presented.

III. JUSTIFICATION OF THE SPECIFICATION

The setting of specifications for drug substance and drug product is part of an overall control strategy which includes control of raw materials and excipients, in-process testing, process evaluation or validation, adherence to Good Manufacturing Practices, stability testing, and testing for consistency of lots. When combined in total, these elements provide assurance that the appropriate quality of the product will be maintained. Since specifications are chosen to confirm the quality rather than to characterize the product, the manufacturer should provide the rationale and justification for including and/or excluding testing for specific quality attributes. The following points should be taken into consideration when establishing scientifically justifiable specifications.

- *Specifications are linked to a manufacturing process.*
  Specifications should be based on data obtained from lots used to demonstrate manufacturing consistency. Linking specifications to a manufacturing process is important, especially for product-related substances, product-related impurities, and process-related impurities. Process changes and degradation products produced during storage may result in heterogeneity patterns, which differ from those observed in the material used during preclinical and clinical development. The significance of these alterations should be evaluated.
- *Specifications should account for the stability of drug substance and drug product.*
  Degradation of drug substance and drug product, which may occur during storage, should be considered when establishing specifications. Because of the inherent complexity of these products, there is no single stability-indicating assay or parameter that profiles the stability characteristics. Consequently, the manufacturer should propose a stability-indicating profile. The result of this stability-indicating profile will then provide assurance that changes in the quality of the product will be detected. The determination of which tests should be included will be product-specific. The manufacturer is referred to the ICH Harmonized Tripartite Guideline: "Stability Testing of Biotechnological/Biological Products."
- *Specifications are linked to preclinical and clinical studies.*
  Specifications should be based on data obtained for lots used in preclinical and clinical studies. The quality of the material made at commercial scale should be representative of the lots used in preclinical and clinical studies.
- *Specifications are linked to analytical procedures.*
  Critical quality attributes may include items such as potency, the nature and quantity of product-related substances, product-related impurities, and process-related impurities. Such attributes can be assessed by multiple analytical procedures, each yielding different results. In the course of product development, it is not unusual for the analytical technology to evolve in parallel with the product. Therefore, it is important to confirm that data generated during development correlate with those generated at the time the marketing application is filed.

IV. SPECIFICATIONS

Selection of tests to be included in the specifications is product specific. The rationale used to establish the acceptable range of acceptance criteria should be described. Acceptance criteria should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency, and data from stability studies, and relevant development data.

In some cases, testing at production stages rather than at the drug substance or drug product stages may be appropriate and acceptable. In such circumstances, test results should be considered as in-process acceptance criteria and

included in the specification of drug substance or drug product in accordance with the requirements of the regional regulatory authorities.

A. Drug Substance Specification

Generally, the following tests and acceptance criteria are considered applicable to all drug substances (for analytical procedures see section 2.2.2). Pharmacopoeial tests (e.g., endotoxin detection) should be performed on the drug substance, where appropriate. Additional drug substance specific acceptance criteria may also be necessary.

1. Appearance and Description

A qualitative statement describing the physical state (e.g., solid, liquid) and color of a drug substance should be provided.

2. Identity

The identity test(s) should be highly specific for the drug substance and should be based on unique aspects of its molecular structure and/or other specific properties. More than one test (physicochemical, biological, and/or immunochemical) may be necessary to establish identity. The identity test(s) can be qualitative in nature. Some of the methods typically used for characterization of the product as described in section 2.1 and in Appendix 6.1 may be employed and/or modified as appropriate for the purpose of establishing identity.

3. Purity and Impurities

The absolute purity of biotechnological and biological products is difficult to determine and the results are method-dependent (section 2.1.4.). Consequently, the purity of the drug substance is usually estimated by a combination of methods. The choice and optimization of analytical procedures should focus on the separation of the desired product from product-related substances and from impurities.

The impurities observed in these products are classified as process-related and product-related impurities:

- Process-related impurities (section 2.1.4) in the drug substance may include cell culture media, host cell proteins, DNA, monoclonal antibodies, or chromatographic media used in purification, solvents, and buffer components. These impurities should be minimized by the use of appropriate well-controlled manufacturing processes.
- Product-related impurities (section 2.1.4) in the drug substance are molecular variants with properties different from those of the desired product formed during manufacture and/or storage.

For the impurities, the choice and optimization of analytical procedures should focus on the separation of the desired product and product-related substances from impurities. Individual and/or collective acceptance criteria for impurities should be set, as appropriate. Under certain circumstances, acceptance criteria for selected impurities may not be required (section 2.3).

4. Potency

A relevant, validated potency assay (section 2.1.2) should be part of the specifications for a biotechnological or biological drug substance and/or drug product. When an appropriate potency assay is used for the drug product (section 4.2.4), an alternative method (physicochemical and/or biological) may suffice for quantitative assessment at the drug substance stage. In some cases, the measurement of specific activity may provide additional useful information.

5. Quantity

The quantity of the drug substance, usually based on protein content (mass), should be determined using an appropriate assay. The quantity determination may be independent of a reference standard or material. In cases where product manufacture is based upon potency, there may be no need for an alternate determination of quantity.

B. Drug Product Specification

Generally, the following tests and acceptance criteria are considered applicable to all drug products. Each section (4.2.1–4.2.5) is cross-referenced to respective sections (4.1.1–4.1.5) under Drug Substance. Pharmacopoeial requirements apply to the relevant dosage forms. Typical tests found in the pharmacopoeia include, but are not limited to sterility, endotoxin, microbial limits, volume in container, particulate matter, uniformity of dosage units, and moisture content for lyophilized drug products. If appropriate, testing for uniformity of dosage units may be performed as in-process controls and corresponding acceptance criteria set.

1. Appearance and Description

A qualitative statement describing the physical state (e.g., solid, liquid), color, and clarity of the drug product should be provided.

2. Identity

The identity test(s) should be highly specific for the drug product and should be based on unique aspects of its molecular structure and for other specific properties. The identity test(s) can be qualitative in nature. While it is recognized that in most cases, a single test is adequate, more than one test (physicochemical, biological, and/or immunochemical) may be necessary to establish identity for some products. Some of the methods typically used for characterization of the product as described in section 2.1 and in Appendix 6.1 may be employed and/or modified as appropriate for the purpose of establishing identity.

3. Purity and Impurities

Impurities may be generated or increased during manufacture and/or storage of the drug product. These may be either the same as those occurring in the drug substance itself, process-related, or degradation products which form specifically in the drug product during formulation or during storage. If impurities are qualitatively and quantitatively (i.e., relative amounts and/or concentrations) the same as in the drug substance, testing is not necessary. If impurities are known to be introduced or formed during the production and/or storage of the drug product, the levels of these impurities should be determined and acceptance criteria established.

Acceptance criteria and analytical procedures should be developed and justified, based upon previous experience with the drug product, to measure changes in the drug substance during the manufacture and/or storage of the drug product.

The choice and optimization of analytical procedures should focus on the separation of the desired product and product-related substances from impurities including degradation products, and from excipients.

4. Potency

A relevant, validated potency assay (section 2.1.2) should be part of the specifications for a biotechnological and biological drug substance and/or drug product. When an appropriate potency assay is used for the drug substance, an alternative

method (physicochemical and/or biological) may suffice for quantitative assessment of the drug product. However, the rationale for such a choice should be provided.

5. Quantity

The quantity of the drug substance in the drug product, usually based on protein content (mass), should be determined using an appropriate assay. In cases where product manufacture is based upon potency, there may be no need for an alternate determination of quantity.

6. General Tests

Physical description and the measurement of other quality attributes is often important for the evaluation of the drug product functions. Examples of such tests include pH and osmolarity.

7. Additional Testing for Unique Dosage Forms

It should be recognized that certain unique dosage forms may need additional tests other than those mentioned above.

GLOSSARY

Acceptance Criteria—Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures which the drug substance or drug product or materials at other stages of their manufacture should meet.

Action Limit—An internal (in-house) value used to assess the consistency of the process at less critical steps.

Biological Activity—The specific ability or capacity of the product to achieve a defined biological effect. Potency is the quantitative measure of the biological activity.

Contaminants—Any adventitiously introduced materials (e.g., chemical, biochemical, or microbial species) not intended to be part of the manufacturing process of the drug substance or drug product.

Degradation Products—Molecular variants resulting from changes in the desired product or product-related substances brought about overtime and/or by the action of, for example, light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Such changes may occur as a result of manufacture and/or storage (e.g., deamidation, oxidation, aggregation, proteolysis). Degradation products may be either product-related substances, or product-related impurities.

Desired Product—(1) The protein which has the expected structure, or (2) the protein which is expected from the DNA sequence and anticipated posttranslational modification (including glycoforms), and from the intended downstream modification to produce an active biological molecule.

Drug Product (Dosage Form; Finished Product)—A pharmaceutical product type that contains a drug substance, generally, in association with excipients.

Drug Substance (Bulk Material)—The material which is subsequently formulated with excipients to produce the drug product. It can be composed of the desired product, product-related substances, and product- and process-related impurities. It may also contain excipients including other components such as buffers.

Excipient—An ingredient added intentionally to the drug substance which should not have pharmacological properties in the quantity used.

Impurity—Any component present in the drug substance or drug product, which is not the desired product, a product-related substance, or excipient including buffer components. It may be either process or product related.

In-house Primary Reference Material—An appropriately characterized material prepared by the manufacturer from a representative lot(s) for the purpose of biological assay and physicochemical testing of subsequent lots, and against which in-house working reference material is calibrated.

In-house Working Reference Material—A material prepared similarly to the primary reference material that is established solely to assess and control subsequent lots for the individual attribute in question. It is always calibrated against the in-house primary reference material.

Potency—The measure of the biological activity using a suitably quantitative biological assay (also called potency assay or bioassay), based on the attribute of the product which is linked to the relevant biological properties.

Process-Related Impurities—Impurities that are derived from the manufacturing process. They may be derived from cell substrates (e.g., host cell proteins, host cell DNA), cell culture (e.g., inducers, antibiotics, or media components), or downstream processing (e.g., processing reagents or column leachables).

Product-Related Impurities—Molecular variants of the desired product (e.g., precursors, certain degradation products arising during manufacture, and/or storage) which do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety.

Product-Related Substances—Molecular variants of the desired product formed during manufacture and/or storage, which are active and have no deleterious effect on the safety and efficacy of the drug product. These variants possess properties comparable to the desired product and are not considered impurities.

Reference Standards—Refer to international or national standards.

Specification—A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. "Conformance to specification" means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

REFERENCES

International Conference on Harmonisation Topic Q6A. *Specifications: Test Procedures and Acceptance Criteria for New Drugs Substances and New Drug Products: Chemical Substance*, May 2000.

ICH Harmonized Tripartite. *Quality of Biotechnological/Biological Products: Viral Safety Evaluation of Biotechnology Derived Products Derived from Cell Lines of Human or Animal Origin*, Mar 1997.

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ICH Harmonized Tripartite. *Validation of Analytical Procedures: Methodology*, December 1996 (Part II).

ICH Harmonized Tripartite. *Stability Testing of Biotechnological/Biological Products*, July 1996.

APPENDICES

6.1 Appendix for Physicochemical Characterization

This appendix provides examples of technical approaches which might be considered for structural characterization and confirmation, and evaluation of physicochemical properties of the desired product, drug substance, and/or drug product. The specific technical approach employed will vary from product to product and alternative approaches, other than those included in this Appendix, will be appropriate in many cases. New analytical technology and modifications to existing technology are continuously being developed and should be utilized when appropriate.

6.1.1. Structural Characterization and Confirmation

(a) Amino acid sequence
The amino acid sequence of the desired product should be determined to the extent possible using approaches such as those described in items (b) through (e) and then compared with the sequence of the amino acids deduced from the gene sequence of the desired product.

(b) Amino acid composition
The overall amino acid composition is determined using various hydrolytic and analytical procedures, and compared with the amino acid composition deduced from the gene sequence for the desired product, or the natural counterpart, if considered necessary. In many cases, amino acid composition analysis provides some useful structural information for peptides and small proteins, but such data are generally less definitive for large proteins. Quantitative amino acid analysis data can also be used to determine protein content in many cases.

(c) Terminal amino acid sequence
Terminal amino acid analysis is performed to identify the nature and homogeneity of the amino- and carboxy-terminal amino acids. If the desired product is found to be heterogeneous with respect to the terminal amino acids, the relative amounts of the variant forms should be determined using an appropriate analytical procedure. The sequence of these terminal amino acids should be compared with the terminal amino acid sequence deduced from the gene sequence of the desired product.

(d) Peptide map
Selective fragmentation of the product into discrete peptides is performed using suitable enzymes or chemicals and the resulting peptide fragments are analyzed by HPLC or other appropriate analytical procedure. The peptide fragments should be identified to the extent possible using techniques such as amino acid compositional analysis, N-terminal sequencing, or mass spectrometry. Peptide mapping of the drug substance or drug product using an appropriately validated procedure is a method that is frequently used to confirm desired product structure for lot release purposes.

(e) Sulfhydryl group(s) and disulfide bridges
If, based on the gene sequence for the desired product, cysteine residues are expected, the number and positions of any free sulfhydryl groups and/or disulfide bridges should be determined, to the extent possible. Peptide mapping (under reducing and nonreducing conditions), mass spectrometry, or other appropriate techniques may be useful for this evaluation.

(f) Carbohydrate structure
For glycoproteins, the carbohydrate content (neutral sugars, amino sugars, and sialic acids) is determined. In addition, the structure of the carbohydrate chains, the oligosaccharide pattern (antennary profile), and the glycosylation site(s) of the polypeptide chain is analyzed, to the extent possible.

6.1.2. Physicochemical Properties

(a) Molecular weight or size
Molecular weight (or size) is determined using size exclusion chromatography, SDS-polyacrylamide gel electrophoresis (under reducing and/or nonreducing conditions), mass spectrometry, and other appropriate techniques.

(b) Isoform pattern
This is determined by isoelectric focusing or other appropriate techniques.

(c) Extinction coefficient (or molar absorptivity)
In many cases, it will be desirable to determine the extinction coefficient (or molar absorptivity) for the desired product at a particular UV/visible wavelength (e.g., 280 nm). The extinction coefficient is determined using UV/visible spectrophotometry on a solution of the product having a known protein content as determined by techniques such as amino acid compositional analysis, or nitrogen determination, and so on. If UV absorption is used to measure protein content, the extinction coefficient for the particular product should be used.

(d) Electrophoretic patterns
Electrophoretic patterns and data on identity, homogeneity, and purity can be obtained by polyacrylamide gel electrophoresis, isoelectric focusing, SDS-polyacrylamide gel electrophoresis, Western-blot, capillary electrophoresis, or other suitable procedures.

(e) Liquid chromatographic patterns
Chromatographic patterns and data on the identity, homogeneity, and purity can be obtained by size exclusion chromatography, reverse-phase liquid chromatography, ion-exchange liquid chromatography, affinity chromatography, or other suitable procedures.

(f) Spectroscopic profiles
The ultraviolet and visible absorption spectra are determined as appropriate. The higher-order structure of the product is examined using procedures such as circular dichroism, nuclear magnetic resonance (NMR), or other suitable techniques, as appropriate.

6.2 Appendix for Impurities

This appendix lists potential impurities, their sources, and examples of relevant analytical approaches for detection. Specific impurities and technical approaches employed, as in the case of physicochemical characterization, will vary from product to product and alternative approaches, other than those listed in this appendix will be appropriate in many

cases. New analytical technology and modifications to existing technology are continuously being developed, and should be applied when appropriate.

6.2.1. Process-Related Impurities and Contaminants

These are derived from the manufacturing process (section 2.1.4) and are classified into three major categories: cell substrate-derived, cell culture-derived, and downstream-derived.

(a) Cell substrate-derived impurities include, but are not limited to, proteins derived from the host organism and nucleic acid (host cell genomic, vector, or total DNA). For host cell proteins, a sensitive assay for example, immunoassay, capable of detecting a wide range of protein impurities is generally utilized. In the case of an immunoassay, a polyclonal antibody used in the test is generated by immunization with a preparation of a production cell minus the product-coding gene, fusion partners, or other appropriate cell lines. The level of DNA from the host cells can be detected by direct analysis on the product (such as hybridization techniques). Clearance studies, which could include spiking experiments at the laboratory scale, to demonstrate the removal of cell substrate-derived impurities such as nucleic acids and host cell proteins may sometimes be used to eliminate the need for establishing acceptance criteria for these impurities.
(b) Cell culture-derived impurities include, but are not limited to, inducers antibiotics, serum, and other media components.
(c) Downstream-derived impurities include, but are not limited to, enzymes, chemical and biochemical processing reagents (e.g., cyanogen bromide, guanidine, oxidizing and reducing agents), inorganic salts (e.g., heavy metals, arsenic, nonmetallic ion), solvents, carriers, ligands (e.g., monoclonal antibodies), and other leachables.

For intentionally introduced, endogenous and adventitious viruses, the ability of the manufacturing process to remove and/or inactivate viruses should be demonstrated as described in ICH Harmonized Tripartite Guideline "Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin."

6.2.2. Product-Related Impurities Including Degradation Products

The following represents the most frequently encountered molecular variants of the desired product and lists relevant technology for their assessment. Such variants may need considerable effort in isolation and characterization in order to identify the type of modification(s). Degradation products arising during manufacture and/or storage in significant amounts should be tested for and monitored against appropriately established acceptance criteria.

(a) Truncated forms: Hydrolytic enzymes or chemicals may catalyze the cleavage of peptide bonds. These may be detected by HPLC or SDS-PAGE. Peptide mapping may be useful, depending on the property of the variant.
(b) Other modified forms: Deamidated, isomerized, mismatched S-S linked, oxidized, or altered conjugated forms (e.g., glycosylation, phosphorylation) may be detected and characterized by chromatographic, electrophoretic, and/or other relevant analytical methods (e.g., HPLC, capillary electrophoresis, mass spectroscopy, circular dichroism).
(c) Aggregates: The category of aggregates includes dimers and higher multiples of the desired product. These are generally resolved from the desired product and product-related substances, and quantitated by appropriate analytical procedures (e.g., size exclusion chromatography, capillary electrophoresis).

12

Essential Clean-Room Design Elements

One of the most important components of pharmaceutical manufacturing is the environment under which the production is carried out. The design and layout of a manufacturing facility is critical to preventing cross-contamination, exposure to workers, and generally making a safe product for human or animal consumption. These considerations are more important in the processing of sterile products where contamination of any type can render the product unsuitable. These products are thus processed in clean rooms. A clean room is defined by ISO 14644-1 as "a room in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room and in which other relevant parameters, e.g. temperature, humidity, and pressure, are controlled as necessary." The design of clean room HVAC systems is a specialty area requiring the unique understanding of cleanliness guidelines, airflow, room pressurization, code requirements, specialty equipment, precise control, and many more details.

In this chapter, details regarding the design components of various types of clean-room environments found in a sterile manufacturing area are discussed. Smart designing requires that the facility be put together in a most cost-effective manner, have the lowest possible maintenance cost, and be readily validated. Generally, clean rooms are highly energy intensive to operate as these rooms systems include process equipment, HVAC systems, lighting, etc. HVAC systems in clean rooms are dramatically different from their counterparts in commercial buildings in terms of reliability, safety requirements, and scale. Benchmarking energy use in clean rooms is particularly important in that there is little industry data available to compare energy use. The lack of energy data and standard metrics makes comparison difficult or impossible. It is also difficult to set appropriate design goals, compare performance over time, and compare performance against other similar clean rooms. Clean-room energy benchmarking can provide baseline information to better understand clean-room energy performance and can provide information to identify energy-saving opportunities.

The conventional unit of measurement for fine particles is the μm or micrometer. A micrometer or μm is a millionth of a meter, or approximately 0.000040 of an inch. A human hair varies from 30 to 200 μ in diameter, with the average human hair being approximately 100 μm. Airborne particles range in size from 0.001 to 1000 μm, the latter having a very short "life." Atmospheric rain is a good example of a 1000-μm particle. Particles of 0.001 μm are bordering on molecular size. Earlier designs of clean rooms were concerned with controlling particles in the 0.5 μm and larger size range. In the 1980s, the limit was lowered to the 0.3 μm and larger size range and a decade later the range was 0.1 μm; today, we control particles sizes of 0.05 μm and larger.

Pharmaceutical clean rooms offer a different challenge from those encountered in electronics industry or medical procedure rooms because the general requirement and the level of contaminants are predictable and constant. Since the smallest particle human body sheds is approximately 7 μm (based on the finest capillary diameter in humans), which is also the approximate size of a bacteria, restricting particles to a smaller size than this would substantially reduce pyrogenic materials. As a result, the particles of 5 micron size are generally excluded from clean room environment. Naturally occurring contaminants include microorganisms, sand, organic matter, excrements of animals, and pollen; man-produced contaminants include tobacco smoke, unburned hydrocarbons, fly ash, farm dusts, construction dusts, engine exhausts, and unfiltered industrial exhausts. Manufacturing operation-generated contaminants come from garments, packaging materials, and mechanical operations. Humans constitute on the largest source of contamination. On an average, a person sheds approximately 1.5 lb of skin per year, scale by scale; add this to dandruff, makeup, hair, and clothing fibers and we have an active particle-generating machine. Contaminants are divided as organic or inorganic with varied structural complexity, ability to coalesce, and disperse in air, making it very difficult to profile the contamination profile of a room or a process. Even though attempts have been made to quantify the contamination potential using various permutations and combinations of activities, garments, and other room conditions, these remain of limited value in designing the clean rooms based on contamination potential. The basic rules of fewest operators (machines are less contaminating), fewer abrupt motions, appropriate garments, and strict adherence to entry and exit SOPs remain the strongest measure of containing contaminants.

Clean rooms are categorized by their cleanliness levels and the type of airborne material that is controlled; the latter definition is more pertinent to design of aseptic areas where the goal is to reduce the quantity of living organisms or their by-products, these are called bio–clean rooms. A "white room" is an area where visible particles larger than 25 μm are controlled; the designation comes from the white painted rooms of the past to show their cleanliness; this is designated as 500K areas. Other classifications include 100K, 10K, 0.1K, 0.01K, 0.001K clean rooms, aseptic areas, and bio–clean rooms. The basic principle in controlling particles in the air involves recirculation of the room air through filter that removes these particles; in a more conventional system where the air moves in the room in a turbulent matter, even settled particles are picked up; this puts strain on the system compared to a laminar flow system where the air flows in a designated vertical or horizontal path. Thus, the quality or room air is highly dependent on the air-handling system where the effectiveness is determined by the type and number of air filters, the number of room air changes per hour, and the air distribution patterns within the room. The air patterns are determined by where the diffuser is located; if there is one diffuser in the room providing a spread of air, this will have a sweeping action throughout the room and is likely to leave many "dead" air pockets in the room and even increasing the air changes per hour will not help much since

Table 1 The ISO 14644-1 Clean Room Standards

	Maximum Particles/m^3						
Class	≥0.1μ	≥0.2μ	≥0.3μ	≥0.5μ	≥1μ	≥5μ	209E Equiv.
ISO 1	10	2					
ISO 2	100	24	10	4			
ISO 3	1000	237	102	35	8		Class 1
ISO 4	10,000	2370	1020	352	83		Class 10
ISO 5	100,000	23,700	10,200	3520	832	29	Class 100
ISO 6	1,000,000	237,000	102,000	35,200	8320	293	Class 1000
ISO 7				352,000	83,200	2930	Class 10,000
ISO 8				3,520,000	832,000	29,300	Class 100,000
ISO 9				35,200,000	8,320,000	293,000	Room air

higher velocity might kick more dust in the air. The most efficient systems would have low air velocity and covering a larger surface area of the ceiling to produce a steady or constant down flow of clean air, which would gently sweep the air in the room. This type of design is called a "vertical laminar flow clean room," the most expensive type of facility to construct but justified for contamination sensitive products; a good example is the laboratory-scale laminar flow hood that can be used to protect the samples from humans and also humans from samples depending on the flow pattern and direction. When applied into a room, good vertical laminar flow can be achieved with air changes of approximately 600 or more per hour only with the entire ceiling acting as diffuser and the floor serving the return flow. Obviously, this would be a very high-cost facility; cost reductions are possible by using multiple diffusers appropriately placed and using low-level wall returns and keeping them as close as possible to areas where most particles are generated.

Clean facilities are rated in terms of the amount of airborne contaminants present; the first document recognizing this was the United States Air Force Technical Order 00-25-203, which was followed by the U.S. Federal Standard 209 that provided a more universal industry standard; this was officially abandoned in 2001 and replaced by ISO 14644-1 but continues to be widely quoted. In 209E, there were no particles larger than 5 μm which are allowed in Class 10,000 or better mainly to eliminate pyrogenic materials. The ISO 14644-1 also recognized particles 5 U or larger and none are allowed in Class 10,000 or ISO 4 environment (Table 1).

The designers and operators of clean rooms are directed to a series of documents published by the ISO organization that pertain to design and operations of these rooms; these are listed below in the chronologic order of their issuance (http:/www.iso.org):

ISO 14644-1:1999: Cleanrooms and associated controlled environments-–Part 1: Classification of air cleanliness. Edition: 1 | Stage: 90.92 | TC 209. ICS: 13.040.35. Document available as of: 1999-05-06.

ISO 14644-2:2000: Cleanrooms and associated controlled environments-–Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1. Edition: 1 | Stage: 90.92 | TC 209. ICS: 13.040.35. Document available as of: 2000-09-07.

ISO 14644-4:2001: Cleanrooms and associated controlled environments-–Part 4: Design, construction and start-up. Edition: 1 | Stage: 90.93 | TC 209. ICS: 13.040.35. Document available as of: 2001-04-12.

ISO 14698-1:2003: Cleanrooms and associated controlled environments-–Biocontamination control-–Part 1: General principles and methods. Edition: 1 | Stage: 90.20 | TC 209. ICS: 13.040.35. Document available as of: 2003-09-17.

ISO 14698-2:2003: Cleanrooms and associated controlled environments-–Biocontamination control-–Part 2: Evaluation and interpretation of biocontamination data. Edition: 1 | Stage: 90.20 | TC 209. ICS: 13.040.35. Document available as of: 2003-10-10.

ISO 14644-5:2004: Cleanrooms and associated controlled environments-–Part 5: Operations. Edition: 1 | Stage: 90.93 | TC 209. ICS: 13.040.35. Document available as of: 2004-08-13.

ISO 14644-7:2004: Cleanrooms and associated controlled environments-–Part 7: Separative devices (clean air hoods, gloveboxes, isolators and mini-environments). Edition: 1 | Stage: 90.60 | TC 209. ICS: 13.040.35. Document available as of: 2004-10-07.

ISO 14644-3:2005: Cleanrooms and associated controlled environments—Part 3: Test methods. Edition: 1 | Stage: 90.20 | TC 209. ICS: 13.040.35. Document available as of: 2005-12-06.

ISO 14644-8:2006: Cleanrooms and associated controlled environments—Part 8: Classification of airborne molecular contamination. Edition: 1 | Stage: 60.60 | TC 209. ICS: 13.040.35. Document available as of: 2006-08-10.

ISO 21501-4:2007: Determination of particle size distribution—Single particle light interaction methods—Part 4: Light scattering airborne particle counter for clean spaces. Edition: 1 | Stage: 60.60 | TC 24/SC 4. ICS: 19.120. Document available as of: 2007-05-07.

ISO 14644-6:2007: Cleanrooms and associated controlled environments—Part 6: Vocabulary. Edition: 1 | Stage: 60.60 | TC 209. ICS: 13.040.35. Document available as of: 2007-07-04.

Room design starts with identifying the contaminants to assure that the design is not an overkill—as it happens more often, adding to the cost of the product. The most expensive clean rooms are the vertical laminar flow type and the least expensive are horizontal flow turbulent rooms. In most instances, a facility would have several different types of air-quality rooms to focus air type contact based on need. The following flowchart describes the decreasing order of cost of clean rooms:

> Vertical laminar flow and perforated floor and return through floor → Vertical flow and solid floor and sidewall returns and laminar flow benches → Vertical and solid floor and sidewall returns → Controlled areas with laminar flow benches dispersed throughout the floor plan → Uncontrolled area with vertical laminar flow benches clustered together.

In a vertical flow laminar room with air returning through the floor, a laminar flow is maintained throughout the room preventing cross-contamination within the room; when the floor is solid and the air returns through low-level returns, the air takes a sweeping action, often turbulent action and cross-contamination from items within the room is less stringent; in this case, the cleanliness of the room is maintained through a scrubbing action through repeated exchanges of air through HEPA filters. The most significant cost-reduction measure is the use of spot air where the contamination is to be avoided. It is best achieved by providing laminar downdraft clean air over the specific process or product instead of the entire room, which can be maintained at a lesser quality conserving substantial cost (e.g., a Class 100 downdraft laminar flow air over vial filling machines in a Class 10,000 room). Spot laminar draft is also very useful where different temperature needs to be maintained such as in the case of downstream processing of biological drug purification. Ideally, the chromatography process is conducted under a laminar flow with low temperature of 5°C to 8°C. Keeping the entire room cold increases the cost of operation and makes it difficult for the operators to work, making them less efficient. In such cases, the ideal design would be a belt of laminar flow downdraft at a colder temperature. Obviously, this approach is not recommended if the operations are spread out through the entire room and cannot be integrated and restricted to a particular area of the room.

Whereas the standard of clean rooms is rising in many industries including the electronics industry, such is not the case for the pharmaceutical industry since here the main source of contamination remains the operator—humans. Given the smallest capillary in humans is approximately 5 μm, the size of the smallest particle shed by humans is fixed. With more automation and use of robotic systems, it is possible to reduce the cleanliness requirements making the product less expensive to manufacture. It is for this reason that the planning for designing clean rooms requires complete understanding of the process, measures to optimize and automate the process, and reduce as much as possible human traffic in clean rooms, whether for the process needs or maintenance needs. An optimal design would require a time-motion analysis, slack removal, and optimal placement of equipment. An important consideration rather unique to pharmaceutical clean rooms is the avoidance of pyrogenic materials in sterile product manufacturing; this may require extraordinary measures to keep the room cleaner and validated.

I. OPTIMIZED DESIGNS

Since clean rooms have complex mechanical systems and high construction, operating, and energy costs, it is important to perform the clean-room design in a methodical way. Given below is a listing of major considerations in optimizing the cost of installation and operation of clean rooms:

1. Layout, material, and personnel flow: It is important to evaluate the people and material flow within the clean-room suite. People are the largest contamination source and all critical processes should be isolated from personnel access doors and pathways. The most critical spaces should have a single access to prevent the space from being a pathway to other less critical spaces. Some pharmaceutical and biopharmaceutical processes are susceptible to cross-contamination from other pharmaceutical and biopharmaceutical processes. Process cross-contamination needs to be carefully evaluated for raw material inflow routes and containment, material process isolation, and finished product outflow routes and containment.
2. Degree of space cleanliness and classification: To be able to select a clean-room classification, it is important to know the primary clean-room classification standard and what the particulate performance requirements are for each cleanliness classification. The Institute of Environmental Science and Technology (IEST) Standard 14644-1 provide the different cleanliness classifications (1, 10, 100, 1000, 10,000, and 100,000) and the allowable number of particles at different particle sizes. For example, a Class 100 clean room is allowed a maximum of 3500 particles/cu ft at 0.1 μm and larger, 750 particles/cu ft at 0.2 μm and larger, 300 particles/cu ft at 0.3 μm and larger, 100 particles/cu ft at 0.5 μm and larger, and 24 particles/cu ft at 1.0 μm and larger. Space cleanliness classification has a substantial impact on a clean-room cost, and maintenance. It is important to carefully evaluate reject/contamination rates at different cleanliness classifications and regulatory agency requirements, such as the FDA. Typically, the more sensitive the process, the more stringent cleanliness classification should be used. There should be no more than two orders of magnitude difference in cleanliness classification between connecting spaces. For example, it is not acceptable for a Class 100,000 clean room to open into a Class 100 clean room, but it is acceptable for a Class 100,000 clean room to open into a Class 1000 clean room.
3. Space pressurization: Maintaining a positive space air pressure, in relation to adjoining dirtier cleanliness classification spaces, is essential in preventing contaminants from infiltrating into a clean room. It is very difficult to consistently maintain the cleanliness classification when it has neutral or negative space pressurization. As a rule of thumb, a pressure differential of 0.03 to 0.05 in w.g. is effective in reducing contaminant infiltration. Space pressure differentials above 0.05 in. w.g. do not provide substantially better contaminant infiltration control than 0.05 in. w.g. Since higher space pressure differential means higher energy cost and difficulty in complying, minimal pressure differences that work should be used. Also, a higher-pressure differential requires more force in opening and closing doors and may lead to these being held open for longer time. The recommended maximum pressure differential across a door is 0.1 in. w.g. At 0.1 in. w.g., a 3-by-7-ft door requires 11 lb of force to open and close. A clean-room suite may need to be reconfigured to keep the static pressure differential across doors within acceptable limits. The same cleanliness classification. Air infiltration should not go from a dirtier cleanliness classification space to a cleaner cleanliness classification space.
4. Space supply airflow: The numbers of air changes determine the cleanliness classification. For example, a Class 100,000 clean room has a 15 to 30 ach (air changes per hour) range. The rate of air change should take the anticipated activity within the clean room into account. A Class 100,000 (ISO 8) clean room having a low occupancy rate, low particle-generating process, and positive space pressurization in relation to adjacent dirtier cleanliness spaces might use 15 ach, while the same clean room having high occupancy, frequent in/out traffic, high particle-generating process, or neutral space pressurization will

probably need 30 ach. The designer needs to evaluate the specific application and determine the air change rate to be used. Other variables affecting space supply airflow are process exhaust airflows, air infiltrating in through doors/openings, and air leakage out through doors/openings. IEST has published recommended air change rates in Standard 14644-4. "Gown/Degown" has the most in/out travel but is not a process critical space, resulting in 20 ach. Sterile air lock adjacent to critical production spaces may be used as a buffer with 40 ach. A Class 1000 (ISO 6) clean room may require a 150-ach rate.

5. Space air leak: The majority of clean rooms are under positive pressure, resulting in planned air leakage into adjoining spaces having lower static pressure and unpredictable air leakage through electrical outlets, light fixtures, window frames, door frames, wall/floor interface, wall/ceiling interface, and access doors. It is important to understand that rooms are not hermetically sealed and do have leakage. A well-sealed clean room will have a 1% to 2% volume leakage rate. When using active supply, return, and exhaust air control devices, there needs to be a minimum of 10% difference between supply and return airflow to statically decouple the supply, return, and exhaust air valves from each other. If the valves are not statically separated, their controls can end up fighting each other. The amount of air leakage through doors is dependent upon the door size, the pressure differential across the door, and how well the door is sealed (gaskets, door drops, and closure). As an example, the air leakage through the 3-by-7-ft door is approximately 190 cfm with a differential static pressure of 0.03 in. w.g. and 270 cfm with a differential static pressure of 0.05 in. w.g.
6. Space and air balance: Space air balance consists of adding all the airflow into the space (supply and infiltration) and all the airflow leaving the space (exhaust, leakage, and return) being equal.
7. Other variables:
   a. Temperature: Clean-room workers wear smocks or full bunny suits over their regular clothes to reduce particulate generation and potential contamination. Because of this extra clothing, it is important to maintain a lower space temperature for worker comfort. A space temperature range between 66 and 70°F will provide comfortable conditions.
   b. Humidity:Because of a high airflow, a large electrostatic charge is developed in clean-room air. When the ceiling and walls have high electrostatic charge and space has low relative humidity, airborne particulate will attach to the surface. When the space relative humidity increases, the electrostatic charge is discharged and all the captured particulate is released in a short time period, causing the clean room to go out of specification. Having high electrostatic charge can also damage electrostatic discharge sensitive materials. It is important to keep the space relative humidity high enough to reduce the electrostatic charge build up. A relative humidity of 45% + 5% is considered the optimal humidity level.
   c. Luminosity: Very critical processes might require laminar flow to reduce the chance of contaminants getting into the air stream between the HEPA filter and the process. IEST Standard #IESTWGCC006 provides airflow luminosity requirements.
   d. Electrostatic discharge: Beyond the space humidification, some processes are very sensitive to electrostatic discharge damage and it is necessary to install grounded conductive flooring.
   e. Noise levels and vibration: Some precision processes are very sensitive to noise and vibration.
8. Mechanical system layout: Unlike normal air-conditioning systems, clean-room systems have substantially more supply air than needed to meet cooling and heating loads. Class 100,000 (ISO 8) and lower ach Class 10,000 (ISO 7) clean rooms can have all the air go through the AHU. The return air and outside air are mixed, filtered, cooled, reheated, and humidified before being supplied to terminal HEPA filters in the ceiling. To prevent contaminant recirculation in the clean room, the return air is picked up by low wall returns. For higher ach Class 10,000 (ISO 7) and cleaner clean rooms, the airflows are too high for all the air to go through the AHU; a small portion of the return air is sent back to the AHU for conditioning and the remaining air is returned to the recirculation fan.
9. Heating and cooling calculations: When performing the clean-room heating/cooling calculations, take the following into consideration:
   a. Use the most conservative climate conditions (99.6% heating design, 0.4% dry-bulb/median wet-bulb cooling design, and 0.4% wet-bulb/median dry-bulb cooling design data)
   b. Include infiltration into calculations
   c. Include humidifier manifold heat into calculations
   d. Include process load into calculations
   e. Include recirculation fan heat into calculations
10. Mechanical room space: Clean rooms are mechanically and electrically intensive. As the cleanliness classification becomes cleaner, more mechanical infrastructure space is needed to provide adequate support to the clean room. Using a 1000-sq-ft clean room as an example, a Class 100,000 (ISO 8) clean room will need 250 to 400 sq ft of support space, a Class 10,000 (ISO 7) clean room will need 250 to 750 sq ft of support space, a Class 1000 (ISO 6) clean room will need 500 to 1000 sq ft of support space, and a Class 100 (ISO 5) clean room will need 750 to 1,500 sq ft of support space. The actual support square footage will vary depending upon AHU airflow and complexity (simple: filter, heating coil, cooling coil, and fan; complex: sound attenuator, return fan, relief air section, outside air intake, filter section, heating section, cooling section, humidifier, supply fan, sound attenuator, and discharge plenum) and number of dedicated clean-room support systems (exhaust, recirculation air units, chilled water, hot water, steam, and DI/RO water). It is important to make provision for the required mechanical equipment space square footage to the project architect early in the design process.
11. Problem avoidance: The following are some of the most frequent problems found in clean-room design. These problems are, of course, of a general nature but are repeated time and again:
   a. Horizontal surface materials are selected, which hide, rather than illuminate and display contaminants to the employees.
   b. Clean benches and tables have sharp edges, which wear garments, and produce large amounts of contaminants directly at the workstation.
   c. Normally, white is chosen as the prime color for any clean room. However, this is not the best color from the industrial consultant's point of view. Colors do not affect the cleanliness of the room.

d. Bench heights found in clean rooms sometimes do not follow industrial engineering recommendations of general industry.
e. There is a lack of testing, checking-out, and certifying clean-room equipment for acceptable use in clean rooms.
f. Automatic material handling equipment is excluded from the clean environment.
g. Equipment is supplied to the clean room in a contaminated state.
h. Use of approved clean-room material is low.

12. Types of Contaminants. While great emphasis is placed on number of particles in the air, the type of particles are often more important for bio–clean rooms where viable airborne particles create special problem situations. These particles come from personnel emission (sneezing, coughing, exhalations, and perspiration), growth of fungi and bacteria in room crevices, and unclean areas. Microorganisms are carried by dust particles and thus reducing particles generally reduce viable counts as well. However, when allowed to grow, single bacteria can grow into a million count within 10 to 12 hours, particularly where liquid products are handled, providing moisture and nutrition for growth. While general cleanliness with reduced particle count will improve all operations requiring clean environment, there must be a cost-advantage analysis made in the design of clean rooms. Not all particles are bad; so we need to define not only the number and size of particles allowed but also the nature of these particles. In the case of parenteral products, contamination in the form of particulate matter is defined as unwanted mobile insoluble matter that may originate from an intrinsic or extrinsic source. Intrinsic contamination is material not removed from the solution and the extrinsic particle comes from air during filling operations.
13. Air changes: The minimum air-handling system for clean rooms is designed to change the room air through HEPA filters eight times per hour. This number of room air changes will provide a Class 100,000 condition per Federal Standard 209E, provided that the room volume is not very large or of any unusual dimension. Turbulent flow–designed rooms, which depend on room air changes to achieve their cleanliness level greater than 24,000 cu ft, present difficulties in airborne contamination control. A room air change rate of 20 per hour will provide a Class 10,000 clean-room condition. A room air change rate of 45 per hour will provide Class 1000 conditions. As the size of clean room increases, difficulties arise in predicting the efficiency of HVAC systems as the airflow patterns become difficult to predict, not only because of the hydrodynamic effects but for the complex interactions with larger number of operators, their entry and exit paths, work movements, and equipment that would be found in larger rooms. Long distances to exits and personnel traffic patterns in large rooms are also significant factors, which contribute to increased airborne particulate levels.
14. Room pressure: Whereas tight-sealing doors are used to isolate room environment, these are seldom very effective since these must be continually opened and closed and always have air leakage. To assure that room air is only allowed to travel in a specified path, clean rooms are pressurized; the function of increased pressure is to force clean air out of any cracks or openings, thus preventing contaminated outside air from forcing its way into the room. The increased pressure also creates an outward flow of air when the entry doors are open, reducing the entry of outside air. Rooms are pressurized by discharging excess room air through a pressure sensing-regulated barometric damper. However, this requires making up the lost air not only through leaks but also to keep the quality of air needed by the operators. A minimum of 200 cu ft of fresh air per hour per employee is usually required. In many areas, local government regulations will mandate the quantity of fresh air that is required. A positive pressure of no more than 0.10 in water gauge between the clean room and uncontrolled areas is adequate for most applications. If more than one room is involved, it may be necessary to raise this value so that the rooms may be staged from the most closely controlled room to the least-controlled room. Where rooms are staged, a 0.05 in water gauge differential pressure is sufficient between rooms. It is important to realize that higher differential of pressure between rooms makes the doors difficult to operate and results in large fluctuations or pressure that may not be desirable.
15. Filters: Filters to remove room particles are rated by the percentage of airborne particles they remove. Generally, HEPA filter should be rated at least 99.97% by the DOP (dioctylphthalate) test. If a filter system allows too many smaller particles to go through, these particles may coalesce in the room and result in larger count, so it is important that a filter not only restrict a specific size of particles but the overall number of particles, albeit small, it allows to go through. More efficient HEPA-ULPA can be are more efficient than HEPA filters and can be used with a maximum resistance differential pressures of 10 in or 25 cm water gauge. The allowable pressure differential in filter resistance is determined by the fan capacity and thus a fan of suitable capacity must be selected to deliver the desired airflow against the total resistance constituted by the ductwork and the dust- or particle-loaded filter. Variable speed fans that are controlled by a feedback mechanism allow constant airflow despite increase in the filter resistance and are highly recommended to avoid frequent adjustments to the HVAC control systems. However, with increased speed of fans, the pressure rises at the filter surface leading to risk of perforation and it is for this reason that all filters are to be replaced periodically.
16. Garments: People and process produce the highest number of contaminant particles; the personnel emissions are further increased when wearing improper garments. Proper clean garment selection, cleaning, maintenance, repairing, and wearing are major concerns of a good clean rooms or bio-clean-rooms operation. These factors are of equal importance to the design of clean rooms. An effective way to upgrade a clean facility is to remove street clothes before dressing with clean garments. Street clothes have billions of particles on their surfaces. Leaving these clothes outside the room reduces contaminant levels in the clean room or bio–clean room. The type of garment used in the clean rooms is of great significance; for example, in light movement, snap smock produces approximately 500,000 particles, standard coverall approximately 50,000, 2-piece coverall 20,000, Tyvek coverall 5,000, and membrane coverall only 50 particles.
17. Construction materials: The construction material used in clean rooms is critical to maintaining the room classification. Whereas there are different tolerances of specification of construction material for different classifications

(to keep the cost low), some general principles are applicable to all clean rooms.

- Free of discontinuities, openings, pits, porosity, crevices, etc. by which contaminating material can be retained or enter.
- Resistant to deterioration abrasion or other damage in the normally expected usage (more particularly the specific contaminants anticipated).
- Able to dissipate dissipation of electrostatic charges (more important in environments where low humidity is inevitable or desired).
- Sound dampening.
- Reflective of ambient light and of desired (appealing and nonfatiguing) color.
- Insulating against temperature and/or moisture.
- Easily workable with similar and other materials (e.g., glass, steel etc.)
- Available in different shapes, sizes, and specification as needed.
- Repairable or replaceable during the life of the facility without breaching cleanliness.
- Will not warp or shrink (to prevent leakages and contaminants collecting) and sustain constraints of structure, minor ground movements (earthquake), and vibrations. If a material of acceptable cost cannot be found that would meet above requirements, materials can be combined that provide different qualities as described above. For example, a low-cost wall material can be gypsum wall with a vinyl laminate on the clean room side and the gypsum board appropriately sealed to prevent particle shedding. Recently, many prefabricated wall systems have become available that are highly suitable for special use rooms like bio–clean rooms.

II. TURBULENT TYPE CLEAN ROOMS

Clean rooms are differentiated based on types of airflow. When the airflow is predictable, these are called laminar flow rooms and the other type is turbulent flow room, which also have similar unidirectional flow (as air is circulated through returns), the difference between two types is significant. Both type of rooms remove particles by the process of dilution and filtration, in one case it is random and in the other the particles generated are immediately removed (laminar) requiring much higher air exchange rates and appropriate placement of diffusers to make sure that there are no dead spaces left in the room.

Clean rooms can be a single freestanding room or a single room with a locker and air-shower entry, or a complex of clean rooms with pressure gradients between rooms. Clean rooms require a support space or area adjacent to the clean facility. It has a cleanliness level between Class 100,000 and 500,000. It is positioned between the clean area and the rest of the factory and allows material to be prepared to enter the clean room as well as product to exit and be prepared for transport and storage. This area is needed in order to handle boxes, etc. for loading and unloading materials. This support space is usually designed as a controlled area. This support space is usually forgotten during the design and then has to be added on after room construction.

Turbulent clean rooms use a variety of wall surfaces that must be of low particle shedding type. Floors can vary from vinyl tiles to epoxy (the preferred type). The floors should have sealed seams. Ceilings for turbulent flow rooms should be rigid enough to support the stress of high air moving diffusers. They can be painted to prevent shedding particles. Cross-contamination in clean rooms is prevented by using pressurized controls, both positive and negative depending on whether the contamination is to be prevented or controlled from spreading out. A comprehensive design would provide both through a sink created in the entry module.

Filters used must be rated and tested frequently. Methods for testing the efficiency of air filters vary widely and these tests are not always comparable, a note of caution in comparing various filter products. The DOP smoke test is used to rate HEPA filters. The word "smoke", as used by the filter testers, means a high particle density of airborne particles. The term does not refer to any type of combustion process or burning of material. The generation of DOP smoke is closely controlled to maintain the particle diameter of the droplets at 0.3 μm, which is usually considered the most difficult size to remove. A light scattering penetration meter or particle counter is used to evaluate the results and establish the filter's efficiency.

III. VERTICAL FLOW CLEAN ROOMS

An efficient vertical laminar clean-room design envisions a comprehensive layout that allows sufficient room for working conditions but not too much more than what is needed. The reason for this minimalist approach is the cost or installation, maintenance, and operation. Larger rooms are more difficult to validate and to keep validated. For example, the aisles need be no wider than 5 ft, unless larger equipment or supply movement is anticipated. In a research clean room, little regard might be given to the height of the equipment, or its position relative to other room equipment. It is important, however, that at least 4 to 6 in of space separate items of equipment, such as a console and workbench. It is of prime importance that the area above the work be open from the ceiling for maintenance. This allows the contaminant-free air to flow from the ceiling down over the workstation and then to the floor.

In this type of facility, contaminant-generating operations may be performed anywhere in the room without the risk of contaminating the product. This is because there is no transfer of contamination by random airflow between workstations. All air flowing over an individual workstation passes directly from the workstation to the floor and then is refiltered. Each workstation can be considered as totally isolated from every other workstation by the essentially laminar airflow pattern of the room.

The major advantages of a laminar vertical flow include the following:

1. Ability to completely isolate every operation by streamlines of laminar airflow.
2. Produce the shortest distance from contaminant generation to contaminant removal from the room.
3. Yields the lowest contamination level of all the room designs.
4. Prevents heat buildup, since the volume of air available to absorb heat is great and distance the air must travel to air return is at the minimum.

The major disadvantages of a laminar flow vertical flow include the following:

1. Installation cost: Some cost savings can be made through creative and cost-cutting measure yet almost always cost of product produced is a significant factor in justifying use of this design.
2. Maintenance cost: this is proportional to the number of filters used and the high-energy input required.

IV. LAMINAR FLOW CLEAN ROOMS

Turbulent flow clean rooms are less efficient because they lack self-cleanup capabilities to offset contamination brought into the room by personnel and equipment. Contaminants generally settle to the floor and attach to other surfaces and may be reintroduced into the air by changes in air currents or by activity in the room. Turbulent airflow is also not uniform and also the particles are not removed uniformly and personnel often contribute more heavily to contaminants in such turbulent flow rooms. These shortcomings are overcome in a laminar flow design where clean environment is created almost independent of the operations or activity since the particles generated are immediately removed from the surrounding without diluting in the room.

How much of a laminar airflow is (horizontal or vertical) designed into clean rooms depends on the target classification. For example, operational of less than Class 1000, horizontal laminar flow clean rooms are appropriate where a full wall of HEPA filters is positioned to take up the entire cross section of the room through which air passes at rates of 100 ft/min. The airflow patterns are balanced to ensure that a unidirectional flow is established so that particles released by personnel are directed toward the exit end of the room. The exit end of the room is the opposite wall to the HEPA filter bank and the air-conditioning is provided to the room upstream of the HEPA filters. Class 100 and better conditions are better provided by vertical laminar flow clean rooms.

The clean bench provides an ultraclean work area without the expense of constructing an entire room. This spot application of clean air in a laminar flow is obtained by using the HEPA filters at the back of the bench through which air is evenly distributed in a unidirectional flow at a velocity of 100 ft/min. The air streamlines are parallel and any particles created in the processing are simply pushed out of the area without contaminating; the design also allows an open area for operators to maneuver freely. The air quality of the clean bench is rated a minimum of a Class 100, per Federal Standard 209E. Because of the very high cost of air circulation, spot Class 100 environment offers the most cost-effective solutions; for example, in a sterile product filling line, the room can be Class 10,000 while the air above the filling line is Class 100 (laminar flow with soft curtains).

V. HORIZONTAL LAMINAR FLOW CLEAN ROOMS

Use of horizontal laminar flow clean rooms allows ready achievement of Classes of 10 to 1000. In the design of horizontal laminar flow clean rooms, a wall of the room is used as a filter bank, which contains HEPA filters. The choice of which wall to be used will determine the downstream operational contamination level.

The air-conditioning system for a horizontal laminar flow clean room delivers the conditioned air into the return air plenum. Usually, this plenum is above the room, although it may also be on the side of the room or below the room. The over-the-ceiling return may consist of a complete plenum, or it may be constructed of ductwork. The side-of-the-room air return may only be the service corridor, while the below-the-floor air return may be a portion of the floor below or a cellar space. The longer the period of time that the conditioned air has to mix with the primary return air, the more even will be the temperature distribution as the air exits from the HEPA filter wall. This means that the air-mixing operation which is required to produce an even temperature distribution can be less sophisticated.

The effect of changes in temperature, because of the temperature differential within this room, is often more significant as personnel approach the inlet wall and it is for this reason that these rooms are overdesigned to assure that the threshold of contamination is not reached normally. To reduce the air-conditioning requirements, equipment that generates large heat is generally vented out directly or placed such that it is in the downstream pattern to prevent heat from dissipating into room.

Construction material requirements for walls, floors, and ceilings are similar to what is required for other types of rooms.

The horizontal laminar flow clean room will achieve cleanliness levels, approximately two orders of magnitude cleaner than conventional or nonlaminar or turbulent flow clean rooms, at approximately the same cost. However, the horizontal flow room will not isolate operations from each other. These can be achieved by vertical laminar flow patterns. Since operations downstream will be in a dirtier atmosphere than those upstream, staggering the operations requiring cleaner air close to filters solves the problem partly.

Vertical laminar flow clean rooms and bio–clean rooms are differentiated by completeness of the HEPA or ULPA filter ceiling, and then secondly, by whether or not air passes through the floor or has a solid floor. For example, a room that using an entire ceiling grid of top-loaded HEPA filters with standard ceiling height of approximately 8 ft, the air velocity is generally set at 100 ft/min, the number of room air changes per hour will be 750, or one room air-change per every 4.8 seconds. If the filters are properly rated, tested, and certified in place, the particle counter is unlikely to detect even one particle per cubic foot of 0.3 μm and larger. If this room meets its design criteria, this room can be classified as cleaner than a Class I condition. If personnel actions are controlled and clean membrane type garments are worn, the room will operate in this condition also.

Vertical laminar flow rooms are designed as high-bay clean rooms with less than a complete ceiling of filters to allow the lighting to be spaced between rows of filters and to space out the filters to reduce cost.

A second way in which these rooms are described is by the type of floor installed. In raised floors, airflow panels are standard 2′ × 2′ lay-in perforated panels supported on pedestals, which can vary in height from 12 to 30 in. These panels can be obtained also with dampers built into them.

A different approach to airflow floors uses a metal grate approach with prefilters located below the grate. The grate spacing in this particular room is less comfortable to stand on. Larger grate flooring with closer spacing is more comfortable to the feet. Grate flooring also presents problems for supporting chairs and tables.

Generally, long narrow rooms seem to optimize some factors since these rooms are likely to have only one aisleway restricting the movement of personnel to one side of the room; the movement can be further curtailed if the entryway is in the center of the room so that personnel need not walk the

entire length of the aisleway. If the processes are built into both of the walls with a service corridor behind them, they have an additional protection. Personnel emissions, which are the heaviest when walking, are in the center aisleway moving toward the floor protecting the processes.

Aseptic filling operations should be done preferably long, narrow rooms keeping the equipment either in the center or to one side of the room. When double filling operations are performed in the same room, the center corridor is used for personnel traffic. The bio–clean room is laid out with the filling equipment along each wall reducing random walking patterns of personnel forcing compliance without the need to continuously train workers. (Lifetime experience in designing and operating clean rooms tells that whatever can be enforced with design should not be left to training and SOP.)

Another advantage of long narrow rooms is that it allows for utilities to be piped in along the wall and servicing the lines without entering the clean rooms. Many arrangements in the shape of letter I or E are possible depending on the limitations in space reorganization.

Wall construction can be of rigid or panel construction. A modular panel wall system offers advantages for maintenance of electronic consoles and for controlling heat load within the clean room. Wall panels can contain either floor to ceiling or window size removable insert covers for consoles. Consoles can be placed into these insert positions while allowing the main body of the console to remain outside the clean room allowing maintenance personnel to remain outside the clean room. It also allows the heat load of the consoles to be dumped into less controlled spaces. Consoles can be moved easily to remote location for repairs.

Providing required lumens in a vertical flow room can be challenging since placement of recessed lights in the ceiling inevitably reduces the number of HEPA filters and their positioning in the ceiling. This requires adjustment of airflow rates to compensate for the loss of ceiling area. At times, $2' \times 4'$ light panels are inserted into the filter grid system. This design requires extra care in conjunction with room layout to assure that the light must not be positioned where it would cause contamination problems below it. A plastic egg-crate can be installed below the filters and lights to give a more aesthetic appearance as well as providing a reflector for the light.

Alternately, thin line tube mounted below the filter bank can be used; this is a good approach since it does not disturb the filter bank and airflow as long as the shape of the tube mount is aerodynamic and does not protrude any sharp edges. Another method is to use exposed bulbs evenly spaced across the filter hank; this also does not interfere with airflow and gives even light distribution. In high-bay clean rooms, the bulbs can have filters that direct the light toward the floor to maximize the illumination of workspace; this is more important for larger engineering projects.

The rest of the discussion in this chapter will pertain to the qualification and design of the three most commonly encountered classes of clean rooms in pharmaceutical manufacturing: 500K for general use, 100K for clean process, and 10K for sensitive process; in all instances, use of spot vertical laminar areas is made to minimize the cost of processing where applicable and possible.

A. Design of Class 500K Rooms

These rooms are the first level of cleanliness offered in a pharmaceutical manufacturing area and since there are SOPs involved in entering and leaving the area, these are called controlled rooms. Many variations are possible to fit the budgetary needs; many rooms can be retrofitted to comply with this requirement. Prefabricated rooms are also a good choice to achieve this level of cleanliness.

Filtered air in the room need not be through an HEPA filter but at least an 85% efficient filter with several room air changes per hour. Good smooth walls and doors are important whereas wall can be of standard construction, good grade enamel paint is used to cover surfaces. Normally, if the facility is a room and it will be constructed on-site of building materials, as opposed to the erection of a prefabricated panel system, it will be constructed of metal studs with gypsum board attached as the wall facing. This plasterboard needs to be coated. A good grade enamel paint, not latex, should be used. Other basic surface treatments can be used if they can be justified such especially where washing or solvent cleaning is required; more elaborate surface treatments are not usually recommended since the benefit is not seen in room airborne contaminant reduction. Thus the use of stainless steel, vinyl coating, fiberglass sheeting, and Formica-type sheeting are not required in this type of area. In addition, coving installed at the wall/floor interface is not required. Measures taken to eliminate contamination from the walls in these types of areas should not be expensive since the amount of contaminants contributed by walls is always overestimated in comparison to other factors. A smooth, durable surface subject to little or no chipping and flaking is acceptable. Gypsum board or a plaster wall with a good quality enamel paint is sufficient in most cases where impact strength is not essential. Hollow concrete masonry or cinder block construction, owing to its fire resistance and low cost, is also acceptable. If this type of construction is used, every effort should be made to get the finished surface as smooth and hard as possible. This requires filler material to be applied to the masonry or cinder blocks to produce a smooth surface. This surface is then sealed. Epoxy paints have proved very satisfactory in sealing these wall surfaces. The use of wood is not recommended because of fire hazard as well as the changes in wall clearance as a result of variations in room humidity. The use of masonry walls, metal studs and bar joists, and/or metal furring is preferred for this reason. If static charges are a problem, antistatic surface treatments can be applied to the wall materials. Grounding of surfaces is also possible.

Lights may or may not be recessed. There is good concentration on housekeeping practices, once the facility is operating. With that in mind, there is usually a very strong emphasis on floor materials during construction. In these basic areas, it is recognized that the floor will be dirty and that it must be maintained if any degree of dust control is going to be provided by the facility design. Since these areas are primarily concerned with visible contaminants, particles which are at least 25 μm and larger in size, these particles settle quickly on the floor and thus the need to have a good floor level return of air is preferred. Ceiling level returns are problematic as it would not be possible to remove large particles easily. The ceiling supply should have diffusers to spread the air around and allow a sweeping motion to the flow pattern. Air-conditioning systems that control comfortable temperature are needed not for comfort but to reduce the shedding of heavy particles from operators.

The filter bank containing at least medium efficiency filters may be located fairly close to the room. Many times the air-conditioning system is a packaged air-conditioning unit and that is an acceptable option; however, the unit should be positioned so that access to the filter bank is not hindered. Since there is a possibility that the facility may later be fitted

with HEPA filters, provisions for this should be allowed in the early design to avoid large expenses later.

Air ducts downstream of filtration should be non-flaking and smooth; aluminum ducting is recommended although large clean flexible ducting is also acceptable. Stainless steel ducting is not necessary in this type of facility. The filter bank of these areas can be as simple as the prefilters supplied to packaged air-conditioning units or higher efficiency prefilters supplied to a filter bank on a large air-conditioning unit. It is recommended that efficiencies of at least 85% by the National Institute of Standards and Technology (NISTA) test be used. These filters will remove visible and larger particles. It is this sized particle which needs to be controlled in these facilities.

Floors are a particular problem in clean rooms as walking on them subjects them to shear force and generation of particles into hundreds of millions in micron size range as the surface wears off. As a result, flooring that is long-lasting and sturdy is a requirement. Smooth seamless floor surfaces prevent buildup and smooth cleaning through low-level returns and to facilitate this, the joints between floor and walls should be smooth, particularly in bio–clean rooms. When floors are subjected to heavy floor loadings or chemical spills, epoxy and polyester toppings are recommended. The use of tiles creates the risk of cracking of tiles regardless of whether these are rubber or vinyl. Rubber tile and sheet rubber flooring and cove bases should not be used where subject to contact with oily materials. Cove would be recommended if wet floor condition would exist. Flooring with higher electrical resistance may be provided by using static dissipative-type flooring often is recommended; however, solvent explosion hazard exists, use of these types of flooring is not recommended.

Light-colored floors are preferred for their reflectivity ability. Colors should become progressively lighter as the eye travels from the work to the immediate work area, to machines and equipment, to nearby walls, and to other walls and the ceiling. The points of contrast are between the work itself and the bench tops, and the bench tops and the surrounding machinery.

The ceiling of controlled areas is of standard building construction. It can be plaster or gypsum board; in high bays the ceiling is of no consequence, since the area is so open. A ceiling of plaster or gypsum board requires painting. Enamel paint is a sufficient coating for these surfaces. More elaborate coatings will not produce lower contamination levels for this type of facility.

The lights in controlled areas are usually standard fluorescent lighting fixtures as ceiling mounted or suspended type, the latter requiring more housekeeping as they collect particles due to interaction of hydrocarbons in the air (oil) that develop electrical charge and get deposited onto the light fixture along with dust particles that attach to these floating grease droplets. This is not a serious problem in better class rooms such as 100K or 10K where HEPA filters remove these floating droplets but is a known concern in 500K rooms where fluorescent light acting as low-grade electrostatic precipitator requiring frequent cleaning of lighting fixtures.

The entry into Class 500K rooms is not special but lockers should be provided outside the area to allow storage of street-level cover. In many entry areas, because of the outdoor local surroundings, personnel are required to use shoe-cleaning equipment. These shoe cleaners should be provided at the entrance to the clean room. Since the purpose is to reduce visible contaminants, personnel should be required to wash hands prior to entering and this can be done by providing a basic washstand; the purpose is to eliminate gross contaminants collected on the exposed skin; a hot-air drier instead of cloth or paper towel is recommended.[1] The entry room can also double as change room where operators don smocks that can of various types but non-shedding-type and since in this area, both shedding and non-shedding-type clothing may be stored, lockers that seal well are recommended.

A location for a walk-off mat should be provided just prior to the entry into the controlled area. These mats can be made of washable material, which is common at entryways to various office complexes. The purpose is to reduce gross contaminants on the bottom of shoes. Such a mat should be of sufficient length to be effective for wiping shoes, as personnel travel over it. Shoe cleaners can be used to further reduce gross contaminants on shoes of personnel entering into these areas.

In general, a good rule is to operate the Class 500K facility as if it were a Class 100K facility in the SOPs for changing and keeping the contaminants out of the area. The change room or area would ideally have the following:

1. Personnel lockers for weather protective clothing. The construction material for lockers should be non-shedding-type (mostly coming from flaky paint on rusted surfaces).
2. A mechanical shoe cleaner. This is more critical when outside weather conditions are adverse such as snow, mud, or dust is common.
3. Washstands. These can be self-contained systems where the discharge is collected and discarded if plumbing is not available.
4. Hot-air driers of sufficient flow to dry hands quickly; not all operators have the patience required for complete drying.
5. An area or location to put on a basic synthetic fabric smock.
6. A storage cabinet for garments that will be reused. The cabinet must seal properly.
7. A basic air shower; whereas the utility of this pass-through has often been questioned, the fact that each entrant goes through a final blow-down reduces the risk inherent in all SOP-based procedures. It is expensive but if the number of workers is large and entry frequent, this investment is recommended. Some of the earliest air showers were air hoses with nozzles; the current systems make extensive of properly designed nozzles that create a blast to clean surface-attached particles quickly.
8. A location for a walk-off mat. Disposable mat sheets are now most common over washable surfaces; however, these sticky mats often do not work well for capturing larger particles. So, if sticky mats are provided, these should come after a general use friction mat.

The Class 500K can be fitted with spot laminar flow hoods that discharge air into larger area or even packaged air-conditioning units with ducts to spot cool or provide cleaner air.

Utilities in Class 500K rooms should not contribute to particles; for example, when using compressed air, it should be filtered to remove both particles and moisture.

B. Design of Class 100K Rooms

Natural currents of open air spaces are able to maintain air quality of less than 100,000 particles per cubic feet, 0.5 μm

[1] *Note*: The importance of hand washing should be embedded into all training programs and repeated as often as possible as most operators easily become careless

and larger. It takes people to make it worse. The Class 100K rooms are of two types depending on the ceiling height. The low-bay or standard ceiling height clean room has the air supply registers located in the ceiling and the air exhaust grills located at several positions in the wall. The ceiling diffusers mix the cooled air with the room air very effectively. They also mix the contaminated room air with the clean incoming air. This mixing process increases recovery time. A contaminated room requires a long period of time to clean up. The particles have a difficult time being purged out of the room due to this mixing circulation. Airflow patterns are not predictable. Particles make many passes over workstations before being removed. As a result, a Class 100K environment can be achieved with 8-room air changes per hour. The high-bay facility also exhibits turbulent flow conditions and removal of airborne particles is primarily by dilution. When applying the 8 room air changes per hour rule for high-bay clean rooms, an air change is considered the area of the room, times 10 ft.

The wall surface in a Class 100K room is very important; the flaking of wall covering materials contributing most significantly requiring use of materials such as stainless steel, vinyl coating, fiberglass sheeting, and Formica-type sheet. In addition, coving is installed in all corners in a further effort to prevent contaminant problems at the wall/floor interface.

Measures taken to eliminate contamination deriving from the walls have been expensive. In addition, the amount of contaminants contributed by walls has been overestimated. Before present knowledge was available, the tendency was to use whatever material would produce the fewest particles, with almost no regard to cost. A smooth, durable surface subject to little or no chipping and flaking should be acceptable. Gypsum board with good quality paint is satisfactory where impact strength is not essential. When the application of a wainscot is required for impact resistance, the use of hardboard, job-painted factory or prefabricated hardboard, metal (prefinished or job-painted) and an epoxy or similar durable paint is recommended. There should be no horizontal-dividing strip installed between the two wall materials. A flush joint is required.

Hollow concrete masonry is desirable because of its fire resistance and lower cost and its use is allowed in clean rooms, provided the surface is finished smoothly and that may require use of filling materials followed by sealing and painting, preferably with an epoxy material. The use of wood in structural elements is not recommended due to its fire hazard and changes in the frame seals due to moisture effects. The use of masonry walls, metal studs and bar joists, and/or metal furring is preferred for this reason. Coved wall corners are not necessary unless they can be justified by the time saved during cleaning of the walls, as is required in bio–clean rooms, or which may be necessary because of a peculiar operation. The sealing of the walls should be adequate to prevent any large losses in pressure.

Window and door frames and the doors themselves should be constructed of metal and set into the clean room so that they come close to being flush with the interior walls. Window frames may be constructed of aluminum, steel, plastic, or other highly durable material.

In designing clean rooms, it is advisable to take out any operation controls and consoles outside of room sine these panels produce a lot of heat and particles; control panel of a lyophilizer would be a good example of this. Similarly, any equipment that can be installed in a wall so that it could be serviced from outside substantially reduced particle load inside the clean room; again, a large lyophilizer or autoclave should be designed in the walls with opening in the clean room. The use of modular wall panels can greatly enhance the operation of the clean room.

Visibility in a clean room is a highly desirable feature not only to reduce claustrophobia of workers but also allow monitoring of the work inside as well as inspections by visitors. Glass has all the surface advantages of porcelain enamel or stainless steel and is comparable in cost.

Floors contribute significantly to particle count as the surface wears off. High resistance floors include vinyl, which is tough and somewhat elastic reducing the sheer force of friction by deflecting it through the surface. Coved corners, where the floor meets the walls, will simplify the cleaning operation. The joints should be tight and sealed if possible. There are two methods of sealing joints in vinyl sheeting. One method uses a solvent to dissolve the adjoining sheets and run them together. This method experiences difficulty in the seam area because of permanent softening, which allows contaminants to collect. If this procedure is used, it is necessary that the seam area be returned to the original flooring hardness if satisfactory results are to be obtained. Generally, this method of sealing vinyl flooring is not recommended because of the difficulties with existing installations. The other method uses heat to seal the vinyl, usually placing a bead of material on the joint and heat-sealing it in a precision routed grove, which joins the vinyl sheet material or large vinyl tiles. When long lengths of coiled floor material, such as vinyl, arc to be used for surfacing the floor of a clean room, it is suggested that the covering be first laid out over the area and allowed to flatten out for several days before being bonded to the floor to allow for shrinking.

Resilient flooring such as vinyl is not recommended in facilities where equipment floor loadings can be high. For these areas, a surface treatment bonding with floor is required. This treatment can be a tough surface coating or a tough surface topping. Two types of surface coatings are epoxy and polyurethane. These coatings are also very chemical resistant. The epoxy coating, which is recommended for clean rooms, must be troweled onto the floor surface. It is a putty or jelly-like two-part system, which combines to form a hard, durable, chemically resistant, and monolithic surface. It has excellent wear resistance properties, which translates into a low contaminant-emitting surface. Some of the disadvantages of this coating including that it reflects sound, it is a hard surface and thus uncomfortable to stand on for longer period of time and is liable to develop cracks if the underlayment moves because epoxy is a hard continuous coating.

Polyurethane is a more efficient material than epoxy for coating concrete floors in chemical process areas. It has greater qualities of expansion and contraction, has approximately five times the abrasion resistance, and its resistance to acids is comparable. It does provide a monolithic floor condition. The stability of the subfloor is of prime importance in all flooring material. Concrete floors must be bone dry during the process of installation.

If floor loading is not a concern, then resilient flooring with its ability to span minor fissures has a great advantage. If there is any movement in a concrete floor, it will, obviously, work to the disadvantage of rigid floors. Their lack of flexibility will cause cracks to develop comparable to the substrate. Resilient flooring, such as a vinyl sheet, will expand with slight floor movement and will prevent cracks in the flooring.

Since ceilings are not subjected to potential impact, they may be surfaced with any material that does not produce or collect contaminants and is easily cleaned. Many clean-room

ceilings are of the suspended type where the panels and lights are set in channels suspended from the existing ceiling. This type of support must be properly constructed. Since the lay-in panels are held in place by the channel edge and gravity, there is ample space for pressure loss and contamination entry unless proper panel sealing is provided.

The area above the clean room is usually highly contaminated resulting in dust accumulation over ceiling panels; thus, if these are moved or cracks develop as a result of negative pressure in the room, this dust can readily enter the clean room. As a result, a very study grid system must be used when using ceiling panels. Also, these ceilings cannot be removed from inside the room requiring their maintenance from the topside of the ceiling and that requires enough work space or a mezzanine above the clean rooms.

Ceiling surfacing materials can be less abrasion proof than walls and floors, but most of the other characteristics, which are required in clean-room materials, are valid here. The electrical engineer for lighting fixtures form a large part of the ceiling, normally specifies lenses. Care should be taken in using any ceiling material in a suspended system to avoid flutter and uncontrolled escape of air pressure. The ceiling should be detailed with some form of clip-down device. Since pressure in the room is designed in most cases to be greater than in the plenum above, the ceiling panels will have a tendency to rise. It is for this reason that the very light corrugated plastic panels frequently used in luminous ceilings should not be used in clean rooms.

The ceiling diffusers are of standard type located in the ceiling of the clean room. The filter bank is located near the air-conditioning unit, and so the primary purpose of the ceiling diffusers is to mix the cool conditioned air with the warmer air of the room as quickly and turbulently as possible. But in mixing the air for temperature distribution, it is also mixing the entrained airborne contaminants continually. This reduces the ability of the room to recover from an induced high particulate emission. It is strongly suggested that if such an air delivery system is used, that an HEPA filter diffuser be used instead, so that duct contaminants, because of poor main filter bank seals and violations, do not enter the room.

The most economical design suggests a base level illumination of 100-ft candles at bench level for the room supplemented by high-intensity light sources at those workstations requiring it. In an effort to reduce contaminant sources in a clean room, many clean rooms have installed flush ceiling lights, which can be serviced from above the ceiling. Servicing recessed lights with flush faceplates from below is a far better solution than servicing lights from above the ceiling. Flush mounted lights should not have framing surfaces with recesses to prevent collection of contaminants. When lights are to be serviced from inside the clean room, they should be changed all at one time on a scheduled basis. Data on optimum lamp replacement time are available from the manufacturer. This maintenance should be performed when the room is shut down. Sufficient time can then be allowed after replacement to permit the room contamination level to return to normal.

Fluorescent and other discharge-type lamps are by nature a potential source of radio (RF) interference. RF interference can adversely affect sensitive electronic equipment, resulting in erroneous or erratic readings or disturbing static. Corning Glass Works #70 Low Brightness Lens Panels, or an equal substitute, should be provided on all fluorescent fixtures with possible RF interference.

When pressurization of clean rooms is used, it is necessary that the pressure be maintained during entry to and exit from the room. This is accomplished by means of an air lock. An air lock is a small chamber with interlocked doors. The size of the air lock depends upon its use. A personnel air lock may be only large enough for one person or it may be large enough for a group of people, depending upon the number of people that must enter the clean room in a given length of time. Pass boxes, used for tools and equipment, should be designed as air locks unless their size is so small that the pressure loss would be insignificant.

Equipment should not be moved into or out of the clean room during normal operation. Replacement or new equipment should be installed when the room is not in operation. Ample time should also be allowed after completion of the task to permit the room to "clean up." If it is anticipated that equipment will have to be moved during room operation, an equipment air lock should be provided.

Sinks in all clean rooms, which are used for the final washing of hands, should have valves, which do not require hand control and instead operated by wrist, forearm, knee, foot, or sensor triggered.

It is important that personnel leave their jewelry, wristbands, and other attachments outside the clean-room area.

Utility placement and method of distribution are to be considered carefully. The distribution of service lines (water, electrical power, vacuum, compressed gas, etc.) presents a problem to the clean-room user who must build flexibility into his clean working area. For rooms with a stable workload, this may not be as much of a problem. Lines must be brought to equipment in various room locations, and these lines should not present a dust-collecting surface or interfere with air or workflow. In some cases, trenching has been provided throughout the room so that a connection is not far from any location. Trenching should not be used in bio–clean rooms as it offers great difficulty in removing trench covers and a loose fit would attract dirt. A narrow metal edge at the trench joint flushed with the flooring on each side helps solve this problem.

Lines arc also brought in through wall connections by means of specially built utility panels in rows of workbenches. Utility penetrations should be sealed to prevent pressure loss, airborne contaminants, and living organisms such as ants, spiders, etc. Airborne contamination entry occurs because of outside wind conditions causing pressure changes within the building. The utility chases are the path of least resistance and can act as a miniature duct system to channel contaminants into a clean area.

If it is necessary to run horizontal exposed lines into the room, they should be covered and coved into the wall surface. Placing the piping against the wall and covering with fiberglass and epoxy compound also works well.

Technical power systems of different frequencies should be run separately. Higher-frequency systems must be shielded to prevent interference with test equipment.

Specific provisions for constant, thorough clean up throughout the construction of a clean facility must be a part of the design. Constant, thorough cleaning and vacuuming of furred wall spaces and other potential sources of dust should be performed until the spaces are closed off. All dust-producing construction activities such as sawing, planning, and sanding should be accomplished if possible outside the clean areas. Construction planners should consider the sequence of operations in order to schedule dirty work such as cutting or plastering, breaking up concrete, and excavating ahead of other operations.

All air-handling ducts intended for use downstream of HEPA filters should be thoroughly cleaned and sealed at the

factory prior to shipment. After erection, the ducts should be vacuum cleaned with an industrial type vacuum cleaner and sealed until used. All openings in the duct system must remain sealed during construction. Air must never be permitted to flow into or out of the ducts unless the HEPA filters are in place.

All equipment, furniture, utilities, and material installed under the construction contract should be thoroughly cleaned by the general contractor prior to his turning the facility over to the user. When equipment is placed in the room prior to acceptance, provisions should be made to clean the equipment. The above precautionary measures should be clearly outlined in the specifications and included in the facility design.

Location of a clean room should be seriously considered before construction begins. Localized ground vibrations, as experienced at most industrial areas, should not be overlooked. Transmitted energies from ground vibrations and/or air-carried vibrations in the range of 0 to 200 cps can disrupt fine precision measurements.

Consideration should be given to isolating the noise and vibration generated by equipment and machinery in support areas from clean rooms where precision work with delicate instruments is being performed. Duct liners should not be used in air ducts for any reason to dampen HVAC noise.

Conventional vibration isolation pads should prove satisfactory for high-frequency vibration. Care should be exercised, however, to ensure that the isolators do not become dust generators or collectors. Low-frequency isolation pads should be specially designed. Above-floor isolating devices for low frequencies should be avoided in order to prevent vibration transmission through ceilings, walls, and floors into the structure.

Since the conventional clean-room operator must control the contamination entering the room, the accepted practice has been to include support rooms adjoining clean areas. Support rooms can include locker rooms, wash and rest rooms, change rooms, and offices. These rooms are generally constructed of the same materials as the clean room. The air-handling system, for the sake of economics, is usually not so elaborate as that in the clean room. Change rooms are provided as an area for employees to change into their clean-room garments. The purpose of a change room is to provide a transition for the employee from a contaminated object to a decontaminated object. The contamination control of personnel depends upon clean garment changing disciplines; however, the design of the change room area can reduce mistakes that take place in this area.

Fire codes normally require several entrances to a large clean room through which personnel can exit in an emergency. These exits are usually designed into the facility and contain a door, which opens by means of a panic bar. Periodically, Fire Department personnel must violate the clean room to check these doors. When these doors are opened, contamination enters into the room. Fire doors, which are not alarmed, can easily become shortcuts for personnel traffic to and from the outside area. Sometimes it is the sales department or upper management, who being pressed for time on a tour of facilities, will violate the clean area by opening up the fire door to let customers see the clean room without having to dress in clean garments.

An alternate fail-safe emergency exit can be constructed using polystyrene foam. Instead of an emergency door covered with vinyl sheet material, fill that door opening with the polystyrene foam. An individual can easily walk through this material in an emergency. This will eliminate room violations at this exit. Personnel cannot use this point to enter the room. It becomes a one way, one time use exit.

Air showers were developed to de-dust personnel prior to their entry into the clean room. Since there is a very delicate balance between the contamination level and the amount of personnel activity in the clean room, it was necessary to clean the contamination clinging to an individual's garments prior to his entry into the clean room. In theory, this was an excellent idea, but in practice it often does not work. One of the difficulties with the air-shower theory is that clean-room operators overestimated the amount of contamination that could be prevented from entering their clean room through the use of air showers. The other primary difficulty was the design of the air showers. Many of them were ineffective. Air velocities on the individual were not high enough to produce efficient contaminant removal. The air-shower exhaust was also inefficient and resulted in subsequent re-entrainment of particulate matter that had been overlooked. All these factors helped to give the air shower a bad reputation.

In facilities containing two or more clean rooms, line-of-sight communication becomes important. This line-of-sight communication is made possible by the installation of a significant amount of windows. Partial or full glass walls are also effective. Line-of-sight communication is the ability of a person to locate or signal another person in a different area without physically moving to that area. By the use of windows and glass walls, production is increased by reducing wasted motions and lost time.

In most production areas, which are not clean rooms or controlled areas, this line-of-sight communication is taken for granted since there are no walls, just large open hay areas. However, in many clean-room complexes, this form of communication is usually not possible because walls without windows were erected and are not easily modified. Large window areas will permit visual communication, in addition to allowing visitors to view the area without actually entering it. This assists production in reducing personnel distractions.

Standard metal doors with glass panels are recommended for this level clean room. If the doors are installed in an air lock or air shower, they may be interlocked. In certain applications, large doors may be necessary because of the size of the product. These doors should be treated to make their interior surface compatible with the clean room. This may require a more durable surface finish such as an epoxy coating.

Building codes and fire codes for clean rooms fall under H6 of the Uniform Building Code in most of the states in the United States. Generally, constructions in the eastern and southern sections of the United States are not covered by it. H6 codes apply to anything where hazardous chemicals are used. These codes apply to new construction as well as modification of existing facilities to which changes are being made.

Clean rooms do not have to be white. Whiteness does not make cleanliness. Usually whiteness fools the eye into believing surfaces are clean. When a color scheme is chosen, it should not cause eye fatigue. Poor color scheme strains eye such as when the areas are not defined or the same color is used for walls, floors, and equipment-containing areas. Making bench tops of different color reduces tension; also when there are dark and light areas in the same room, this produces additional vision fatigue. Any color scheme that make appearance of sunlight helps and in some Scandinavian countries, there is a building code requirement to actually allow sunshine in since they are deprived of it around the year.

Furniture and fixtures for a clean-room use should be selected with care. Materials should be chosen to resist the generation of particles by chipping, flaking, oxidizing, or other deterioration. Latex paint should not be used on surfaces, which are subject to repeated contact with personnel or other objects in the clean room. Should these surfaces require painting, an epoxy, polyester, or similar surface coating should be used. Instructions for the preparation and application of these coatings must be followed exactly in order to obtain desired results. Surfaces must be prepared properly.

Contemplated usage should dictate the choice of materials for clean-room furniture and fixtures. Items, which can expect to be humped, knocked, or scraped by personnel, should possess a tough, resilient, low particle-generating surface. A Formica-type material, or material of equivalent surface qualities, is a good choice for tabletops. Most furniture and fixtures may be of conventional design. Sound engineering economy principles should prevail.

In order to maintain good housekeeping in these facilities, it is recommended that a central vacuum system be installed. The material collected in the room is directed out of the room environment through the vacuum tubes. A wet/dry vacuum system will enhance room clean up.

If a central vacuum is not installed, standard vacuums are not recommended. This is because of the large amount of visible dust, which passes through the low-efficiency filtration installed on these vacuums. There is an exception to this statement. Those portable vacuums, which collect and hold dust materials by passing them through water baths or water filters, are acceptable. These water filter vacuums have much higher collection efficiency and do not discharge visible contaminants back into the room environment. Of course, a clean-room vacuum can be used, which has a HEPA filter on its exhaust.

C. Design of Class 10,000 Clean Rooms

Conventionally designed clean rooms of Class 10,000 cleanliness level are turbulent flow facilities. Cleanliness in the room is accomplished by massive amounts of clean air, when compared to normal air-conditioning standards needed to cool a production space. Clean air dilution and air mixing achieve cleanliness. A Class 10,000 environment can be achieved with 20 room air changes per hour. Standard air-conditioning practice might only require 10% to 20% of this air for cooling requirements.

This type of facility, without the aid of additional air-cleaning benefits of laminar flow clean benches, is about the lowest room operational cleanliness that can be economically and consistently achieved by turbulent airflow techniques. The reason for this is that room personnel are continually emitting airborne contaminants, which in turn are being continually mixed by turbulent airflow diffusers. The room is continually mixing and diluting airborne particles.

There are three primary air patterns used in a conventionally designed clean room. The first air pattern is where air enters into the room through ceiling diffusers, which mix and dilute the room air turbulently. A diffuser is installed typically to cover approximately every 150 ft^2. The second type of air pattern is turbulent but more confined to individual vertical planes. Air enters the room through a single linear slot. The third type of air pattern is similar to the second; however, a large perforated plenum, which runs the length of the room, is used to deliver the air to the room. An improvement to this air delivery system is to use an entire ceiling as a perforated plenum to reduce air turbulence. An improvement on this last air delivery system would be to use terminal diffusers, which can be substituted, in all of the above diffuser patterns. Diffusers should not be located in less than every eight ceiling panels in order to give sufficient contaminant removal.

Terminal Diffuser Filters are ducted, hooded minipleat, bead-separator style filter units. They are lightweight, low in profile and are available in HEPA and ULPA efficiencies. These filter units are designed to offer minimum air resistance at any given level of efficiency.

Each filter shall be tested and certified to have an efficiency of not less than a given percentage on micrometer particles. Each filter shall be scan tested at the factory and certified that it has no pinhole leaks in accordance with IES-RP-CC-001. The clean filter static pressure drop shall be no greater than water gauge when operated at an airflow rate of a given cubic feet per minute. Filter medium shall be pleated glass with adhesive bead separators. The media pack shall be sealed on all sides with a solid resin sealant to form a leak proof seal. The filter frame shall be constructed of anodized extruded aluminum per AAC22A31, providing a structurally rigid frame with dimensions of "height × width" depth. Overall dimensions shall be correct to within −1/8" to 0". The back plate/collar assembly shall be one piece 24 ga.-galvanized steel in 10" or 12" diameter. The center divider shall have one access port for leak testing and airflow balancing. Circular diffusion disc shall be 0.050" perforated aluminum, screwdriver adjustable to 90 fpm (± 20%). The grille screen shall be 24 ga. white epoxy-coated carbon steel. This eliminates the possibility of leaks at welded collars.

Clean rooms of the Class 10,000 cleanliness level come in all sizes and ceiling heights. The rooms can be differentiated into low-bay and high-bay rooms, or clean rooms of a standard ceiling height of 8 to 10 ft. Clean rooms can also be of much greater height, some of which exceed 100 ft in height, for satellite and space-related operations.

Generally speaking, these rooms maintain Class 10,000 operational levels by the air-handling system, providing a range of 20 room air changes per hour. If these same amounts of room air changes are provided by a combination of air-handling system and room air recirculation clean benches, such as horizontal laminar flow units, Class 10,000 clean-room environments will be maintained.

As a general observation, standard ceiling height clean rooms have been designed with rectangular floor plans. This has allowed additional wall areas to accept modular panels containing operational equipment, such as electronic consoles or process equipment.

Small rooms of less than 500 ft^2 generally have a square floor plan, while rooms larger than this size have rectangular floor plans. By numerical count, there are many more rooms of greater than 500 ft^2. This is usually because of the overall total investment in equipment, such as air showers, change rooms, and air-handling equipment. The cost of the physical construction of the room is a smaller expense compared to the total cost of building the room. Thus to add additional floor area for future expansion at the time of construction is not a major percentage increase. The initial square room is expanded on one wall even before construction is complete and the resulting floor plan is rectangular.

Sometimes the floor plan of a clean room is "U" shaped or "E" shaped, to increase wall area and facilitate wall penetration from the service area. The service areas are the open ends of the letter plans. The reason for doing this is to restrict dirty items of equipment from the clean room. By providing these floor plans, sufficient wall space is available to make necessary wall penetrations. The second reason is that the

heat load of this equipment does not have to be processed through the clean room air-handling system. The heat load is placed in the service area.

Clean-room complexes have no general floor plans that are similar. The floor plans of these facilities are generated based on product operations. Individual rooms are designated for operations and a product flow is established. The rooms are then situated to allow that flow of product to pass smoothly through the facility. Sometimes entry into these facilities is at one end of the complex. Other times, the entry corridor brings personnel in a garment change area that is located in the center of the complex.

Measures taken to eliminate contamination deriving from the walls have been expensive. In addition, the amount of contaminants contributed by the walls has been overestimated. Before present knowledge was available, the tendency was to use whatever material would produce the fewest particles, with almost no regard to cost.

A smooth, durable surface subject to little or no chipping and flaking will be a satisfactory wall material. In some designs, gypsum board with good quality paint is satisfactory where impact strength is not essential. When the application of a wainscot is required for impact resistance, metal is recommended. It is also recommended that no horizontal dividing strip be installed between two wall materials. A flush joint is preferred.

In an effort to reduce construction costs, reduce the time of construction, and produce an excellent clean-room environment, various companies have developed clean-room wall and ceiling systems. Modular systems consist of wall panels attached to each other through a single draw rod attachment method. The panels are constructed of aluminum-clad hardboard over a corrugated core material. Wood stiles and rails are used for other edges. The panels are painted with a no shedding lacquer. Panels meet a Class A Flame Spread Rating, National Code No. 101. Wall panels are easily removed providing a clear opening for equipment installation or removal.

Doors are generally having a 2-in-thick aluminum frame. Clear or colored Plexiglas panels form the center sections. Push and pull-type hardware is standard with locking hardware optional. Doors are factory hung and shipped with standard panel hardware for quick installation.

Window panels are ideally floor-to-ceiling 8-ft panels either 2-ft or 4-ft wide, with painted steel frames. The center section is clear of colored Plexiglas. The window area is either 19-1/2-in or 43-1/2-in wide by 91-1/2-in high. A 4-ft wide guardrail is supplied for the exterior of the panel in most applications. Window panels are mounted in the same manner as wall panels.

A heavy duty white enameled, 1-1/2-in deep T-bar interlocking steel grid, white enameled, with a resealable gasket material for all lay-in components, is recommended. The grid structure is attached to an overhead structural member, which is part of the clean-room facility. No host building attachments are required for ceiling support in standard ceiling widths. Ceiling structures are self-supporting, wall to wall, for spans up to 20′. Wider spans will require either overhead attachment to host the building or serve as a column support. Ceiling tiles are Class 100 compatible 2′ × 4′ lay-in type.

All internal room wiring and control circuits are appropriately located for servicing. Duplex outlets are provided as required. Sealed 2′ × 4′ lay-in light fixtures are supplied in sufficient quantity to provide 100-ft candles at desktop level. A pluggable buss duct system for power distribution is used where necessary to simplify power hookup of the facility to one drop per buss run. Buss runs can be as long as required for power distribution. Each 10′ section of buss will provide 12 pluggable outlets for service distribution, of which approximately 40% will be available for process equipment hookup.

Plate glass has been the product of choice for many years in clean rooms. One of its drawbacks is its static charge buildup. If a room has much glass area, it can have significant glass surface static charges. A product, which eliminates this static problem, is a static dissipative window. The key to effective static charge removal is the proper installation of the material.

There are many materials which can be used to provide a sufficient floor covering for a Class 10,000 clean room. The economic selection depends on the production use of the clean room. A vinyl square on the floor is sufficient for the clean room under these conditions: if an area is going to be used for light assembly of small components, if there will not be a spillage of fluids on the floor, if there is no biological constraints on the room, if there is no heavy floor loading due to wheeled traffic, if there is not much personnel traffic or movement in the room, and if there will be little need for much liquid chemical cleaning on the floor.

If, however, any of the above conditions change, (such as there will be a fluid spillage on the floor, or there is a biological concern, or there is much personnel traffic in the room, or there will be much fluid chemical cleaning), then a monolithic sheet material is indicated. This material should be seamless to prevent cracks from forming wherein fluids or bacteria can settle. This sheet material should be vinyl if there are no incompatibilities involved.

When sheet vinyl is used on floors, as indicated above, coving of this material to the wall is recommended. Coving is brought up to the wall. If there are chemical incompatibilities, then the sheet floor material that might be selected could be rubber-based material. An alternate solution to the chemical problem, as well as to the heavy floor-loading problem, is to use an epoxy coating over the base concrete floor. A urethane coating could also be used to gain both chemical resistance and a high-wear surface.

The ceilings in Class 10,000 clean rooms can be of plaster or of a suspended type. When using a plaster or plasterboard material, the ceiling should be coated. The minimum coating should be enamel paint. Wall/ceiling interfaces should be filled with a head of material, so that contaminants do not lodge in a sharp corner during cleaning. Ceiling surfaces do attract particles electrostatically, and they will have to be cleaned. Suspended ceilings use "T" bar grid systems with lay-in panels. The "T" bar grid should be of a high quality material and be able to support the ceiling tiles without distortion. The "T" bar system will need to support lay-in light fixtures, as well as terminal HEPA filters, or at the very least, air supply diffusers. The ceiling tiles should have a smooth vinyl surface, or similar smooth reformed surface coating. Ceiling tiles are usually 2′ × 4′ panels, some of, which can also provide acoustical treatment. A smooth ceiling is desirable, which will provide ease of cleaning and offer fewer surfaces to collect fine particles. Fixtures, which attach to the ceiling and are a sealed assembly, may also be used. However, they offer more surface area to collect particles and require more time for cleaning. Further, some fixtures will act as electrostatic attractors and collect more than their share of contaminants—requiring more frequent cleaning.

When a suspended ceiling is used, it must contain a method of clipping down the ceiling panels. This is necessary since most rooms operate at a positive pressure. The ceiling panels must be rigid enough so that when they are clipped

down, they do not flex or bend, because of the positive air pressure, which can cause an arching or upward bowing to the panel. The reverse condition of downward bowing would happen if the rooms were under negative pressure.

Light levels at working surfaces should be 125-ft candles of shadowless illumination. This lighting level is a comfortable intensity for employee work functions, which require visual acuity. The eye compensates for light intensities above this value when the eye pupil restricts light entry. Increasing the light intensity usually is a waste of money because lighting fixtures are bought, which are not required, and power is expended, which is not needed. Further, additional air-conditioning and power will be needed to cool the lights that are not needed. Recessed light fixtures are recommended in facilities of this type. Light patterns can vary from clean room to clean room. Another approach to give shadowless illumination is to install a "T" bar grid system with translucent panels; these "T" bar systems may have air slots in it to allow a more even air distribution pattern.

The use of various vinyl materials to construct an inexpensive clean room is a proven method of design. These units are provided with HEPA-filtered air at the ceiling of the unit. Lighting is through the transparent ceiling. The key to the cleanliness level in these facilities is the amount of clean air delivered to the enclosure. In order to maintain a Class 10,000 condition, the total volume of the enclosure must be changed every 3 minutes with HEPA-filtered air. In the case of the small units above, one 2-by-4-ft HEPA filter ceiling module provides 800 cu ft of air per minute, which will provide more than one air change per minute. This is more than the 20 air changes per hour, which is needed to maintain Class 10,000 conditions in a clean room.

Because it is so difficult to maintain Class 10,000 environments by turbulent flow techniques, these facilities are provided with good air showers and garment change areas in which personnel can fully prepare for clean-room entry.

There are many variations on the proper order and technique of dressing prior to entering into a bio–clean room. The location for entry contains secure type clothing storage lockers for personnel weather protective clothing, jewelry, and other items of value normally carried or worn by personnel. These lockers should be designed to allow the hanging of coats, store overshoes, and have holding bins for jewelry, watches, bracelets, rings, wallets, keys, purses, etc. The locker is provided with a means of attaching a combination lock. The area selected should be large enough to handle the entire shift at one time. These lockers are usually located in a wide aisleway, leading to the change room entrance. Also provided is a shoe cleaner with rotating brushes. It may contain one or more shoe cleaners, depending on the number of persons entering in a short period of time. A central vacuum system location point should be placed in this shoe. A walk-off mat is positioned after shoe cleaning and at the entrance to the first air shower. This air shower is meant to clean heavy- and medium-sized particle off the surface of personnel street clothes. If the entrants to the clean room will be required to remove their street clothes before donning clean garments, then this air shower can be eliminated.

When personnel exit the first air-shower location, they should enter into a washbasin area where they operate it remotely. Washstands of conventional types may be used. Personnel should be required to wash hands and face to remove cosmetics and after-shave talc from their faces. Linen towels can be provided here since it is very difficult to dry the face with a hot-air drier. If personnel are to enter into a bio–clean room, this washstand should be constructed of stainless steel. It can be equipped with a foot-, knee-, or hand position sensor-operated water control valves. The next location contains a hot air, HEPA-filtered hand dryer. This dryer can be sensor operated or foot operated. A large "ON" button switch is not desirable, because people forget and will hit the switch with their clean hands rather than with their elbow. The next station contains a dispenser for under gloves if they are to be used. This dispenser should contain the various size gloves in compartments that are easily opened. If they are disposable gloves and there is packaging associated with the glove, a trash receptacle should be located nearby. The next station provides alcohol or other hand-sanitizing dispenser for personnel entering a bio–clean room. The next station is where personnel dress with headwear, face mask, and then the outer garment cover. Then a spray bottle containing sodium hypochlorite (standard liquid household bleach) and disposable wipes are located in a holding shelf for personnel entering into a bio–clean room. Each individual will use this material prior to putting on shoes or shoe covers. Finally, a bench divides the room and is designed to allow continual use of disinfectant on its surface. Just prior to the next station, a full-length mirror should be located near this area at the exit point of the area. A space should be provided alongside that mirror to display a full-sized photo poster of one of the clean-room employees properly garmented. As persons finally exit from the area, they should step onto a tacky mat and then enter into the second air shower if the garments are not synthetic material, are not processed through a clean-room laundry, or the garment will be used for more than one entry into the clean room. If clean laundered garments are provided with a Class A or B rating, and the garments are only going to be worn once and then recycled to be cleaned, then the second air shower is not needed. However, if garments are of a dirtier class cleanliness level, per ASTM-51-73 method, or garments are going to be reused, then a second air shower is indicated. If in this air shower air velocities are greater than 60 miles per hour of localized impact on the garment surface to be used, then safety goggles should be required in the air shower. This is to prevent airborne particles from being blown in the eyes.

The storage of garments is under HEPA-filtered air in storage cabinet to store garments in a clean condition until the garments are worn again. A clean air storage cabinet, or storage location under the HEPA filters, should be provided so that garments, that will be reused, can be stored without being contaminated by the air of the change area.

The distribution of utilities in Class 10,000 clean rooms depends on the product to be manufactured within the room. A light assembly operation in a large area may function acceptably with standard electrical outlets in walls and in floor penetrations. Since floor penetration is not allowed in pharmaceutical manufacturing, ceiling drops are needed except for the wall receptacles.

Wherever utility penetrations are made, they must be sealed into the penetrated surface. This is to prevent atmosphere changes associated with violent weather conditions from forcing contaminants through these openings into the room. This situation can occur during electrical storms when weather fronts put a wind load on one side of a building, where the utility chases are located, and when an exhaust vent from the clean room to the roof is at a negative pressure and there is a power failure. Because of the exhaust vent and lack of air-conditioning, the clean room changes to a negative pressure. The utility chases are at a positive pressure. The result is that contaminants are driven into the clean room. Sealed utility chases prevent this from occurring.

Control panels, which are user friendly, should be installed in clean rooms. They should be readily accessible. Displays on control panels should be arranged so that only critical information value is prominently presented. This will allow rapid reaction to undesirable events.

One solution to air handling in panel constructed facilities is to use individual blower modules to draw the air from the air return grill at the floor level and move it back over the ceiling to the "T" bar mounted air supply diffuser.

Support rooms and areas should be provided between the clean room and factory or warehouse areas. These areas generally are designed as Class 500,000 areas. They provide a relatively clean location for entry of materials into the clean room and a location for final package of products destined for storage or shipping. These areas contain pass-through boxes to allow material entry and exit. Support space is a function of the process and the volume of product to be handled. Here, pass-through boxes allow materials to enter and exit the clean rooms in a clean state. This support area uses a sheet vinyl floor, which is bounded on one side by the clean room, and on the other three sides by standard wall construction and enamel paint. Air supplied by the diffusers is filtered through 95% efficient filters.

Pass-through boxes are subjected to a large amount of wear and should be constructed of a material that will resist abrasion and rough use. Stainless steel is best. However, a laminate material will be satisfactory for light loads. The box edges should be reinforced. A double door design with an interlock to permit only one door to be opened at a time, will prevent direct contact of personnel between the clean room and the outside areas through the opening. Another method provides a turntable arrangement with one opening, which must be turned to one side for access. Pass-through box framing should be metal to ensure rigid support. Since pass-through boxes are designed to prevent a direct opening between rooms, a means of communication should be provided alongside the box. This can be an intercommunication system, a voice diaphragm, or a speaking tube. An air vent may also be provided in the box to help purge it of contaminants.

VI. THE USP <797> GUIDELINES

Since July 2004, USP Chapter <797> had been undergoing scrutiny and the updated version of the chapter was posted on http://www.usp.org on December 3, 2007, and it has become official on June 1, 2008. The revised chapter is based on thousands of comments received during 30 months of open review and is the result of countless hours of work on the part of the USP Sterile Compounding Expert Committee (2005–2010). This is a broad presentation to facilitate compliance with USP <797> provisions regarding architectural, environmental, and physical standards required for compounding sterile drug preparations.

A. Issues

USP issued its revised version of Chapter 797 (<797>) with a number of changes clarifying issues related to physical infrastructure such as mechanical, electrical, and architectural items for both sterile compounding and hazardous sterile compounding of drug products. The USP <797> is a valuable set of guidelines based on contemporary consensus-based safe practices that describe a best practice for establishing safe processes in compounding sterile medications. USP <797> is considered to be an official minimum standard for compounding sterile medications and it is therefore enforceable by the FDA, state boards of pharmacy, and other regulatory agencies. As such, USP <797> is an enforceable requirement that mandates procedures and processes for sterile drug compounding (mixing) of pharmaceuticals in a clean-room environment. USP <797> establishes ISO requirements for acceptable clean-room airborne particulate concentrations and assessment procedures.

B. Definitions

1. Clean room (also known as the buffer room) is a space in which the concentration of the airborne particles is controlled to meet a specified cleanliness class. For hazardous and nonhazardous clean rooms, mentioned below in Paragraph E with the recommended Option 2, the required level of cleanliness is ISO Class 7. Class 7 clean room limits the maximum concentration of particles to 10,000 particles per cubic feet (352,000 per cubic meter of 0.5 μm or larger).
2. Anteroom is a space leading into and out of the hazardous or nonhazardous clean rooms. This is a transitional space in which activities such as, hand hygiene, garbing procedures, staging of components, and other activities are performed. While the ISO classification of the anteroom serving the hazardous clean room shall be same as the clean room, that is, ISO 7, the ISO classification of the anteroom serving the nonhazardous clean room shall be ISO 8 (or ISO 7, if the architectural design in place incorporates a common anteroom for both hazardous and nonhazardous clean rooms). Anterooms are transition spaces, which ensure direction of airflow and help maintain the required pressure relationships. Nonhazardous clean rooms should be maintained at 0.02-in to 0.03-in positive pressure with respect to their anterooms, which, in turn, should be maintained at 0.02-in positive air pressure with respect to the adjoining circulation spaces. Hazardous clean rooms should be maintained at 0.02-inch negative pressure with respect to their anterooms, which, in turn, should be maintained at 0.02-inch positive air pressure with respect to the adjoining circulation spaces. Use of the anterooms prevents large swings in temperature. Each anteroom shall be equipped an automatic hand washing basin. Anteroom serving hazardous clean room should also be equipped with an eyewash station. For the hazardous clean rooms, anterooms can be used for storing the hazardous drugs so that the use of a dedicated storage room can be avoided.
3. Primary engineering control (PEC): This is an ISO Class 5 space or a device in which compounded sterile preparations (CSPs) take place. While the choice of the ISO 5 device is left to the discretion of the pharmacists using the facilities, the following four devices are recommended:
   a. Biological safety cabinets (BSC): Use of these cabinets is recommended for the hazardous clean rooms. These are vented cabinets meant of the protection of personnel, products, and environment. Air drawn by the BSC should be exhausted outdoors after passing through HEPA filters, integral or duct-mounted external, by a dedicated exhaust fan.
   b. Laminar airflow workstation (LAFW): Use of these devices is recommended for the nonhazardous clean rooms. These devises can be 100% recirculatory type.
   c. CAI (Compounding Aseptic Isolator): This is a form of isolator designed for maintaining aseptic environment within itself. Air exchange into and out of the isolator shall be done through HEPA filters.

   d. CACI (Compounding Aseptic Containment Isolator): This is a form of CAI, designed to provide worker protection from exposure to unacceptable levels to drug exposure. Hundred percent exhaust of the air is required while dealing with hazardous substances. Air exchange into and out of the isolator shall be done through HEPA filters.
4. Air lock: A small room or space ("pass-through" chamber or window) between two rooms of different air pressure, with interlocked doors (one tightly closed at all times) to prevent loss of pressure in the higher-pressure room.

The USP <797> describes three risk levels defined by the complexity of the pharmaceutical compounding process, namely, low-, medium-, and high-risk level compounding, all of which require that work involving the sterile pharmaceutical compounding shall take place under ISO Class 5 conditions within a buffer area that should be ISO Class 7 with appropriate air-conditioning and humidity controls in place in the buffer area environment. These standards are to be exemplified in every category. Class 5 environments require hundreds of air changes of HEPA-filtered air, stringent gowning and masking requirements, anteroom, etc. The Class 5 environment is achievable in four ways:

Option 1: Provide a Class 5 clean room.
Option 2: Provide a Class 5 environment in a PEC defined above. Locate this device in ISO Class 7 buffer room and protect the integrity of the clean-room requirement by providing an ISO Class 7 anteroom for the hazardous clean room, and an ISO Class 8 anteroom for the nonhazardous clean room.
Option 3: Perform all sterile pharmaceutical compounding within a CACI for low-risk levels.
Option 4: Consider use of a portable clean room.

C. Recommendations

1. Determine the risk level of compounding typically performed within the pharmacy (low, medium, or high) and the volume of work to be accomplished at peak periods. The medical centers can perform this essential task with guidance from the USP 797 Workgroup and Chief of Pharmacy. Consider Options 1 to 4 for their impact on ventilation and architectural issues:
   a. Option 1: ISO Class 5 clean rooms will be a very difficult option to follow, primarily because of the severe operational difficulties associated with gowning, masking, scrubbing, very high rate of air changes, and the high cost of the HVAC and architectural features. More importantly, if the air-handling system fails, it will not be possible to continue to use the space for sterile compounding until the system is back up again.
   b. Option 2: Class 7 clean rooms would be easier to construct and maintain than option 1 from an HVAC standpoint requiring on the order of minimum 30 air changes per hour which may include 15 air changes per hour from an ISO Class 5 air-recirculating device, and not hundreds. To simplify the HVAC system design, VA has opted to supply all 30 air changes per hour from the environmental air-handling unit and not use a secondary, dedicated air-circulating unit as stipulated in USP <797> pages 27–28. See the attached room data sheets for HVAC design parameters. The room, however, must be able to maintain the defined particle count during peak operations. Architectural features, however, will still apply such as monolithic, cleanable surfaces, with anteroom and gowning, masking scrubbing, etc. Also, if the air-handling system fails, it would still be possible to continue use the space to maintain ISO Class 5 environment within the operating PEC device.
   c. Option 3: The least impacted option could be the use of CACIs, where a surrounding clean-room environment and air lock and anteroom are not required. However, it may not be possible to perform all procedures in these enclosures.
   d. Option 4: A portable clean room would cost in the range of $40,000 to $80,000, but would be less than a total physical renovation or new addition of a space.
2. For the hazardous clean room, the ISO Class 5 PEC device should be BSC NSF Class II (laminar flow), type B2, with 100% exhaust to outside.
3. A DX (Direct Expansion) system for cooling should not be used. Use of chilled water is more effective in providing accurate environmental control. While it is preferable to provide emergency power for the heating, ventilating and air-conditioning system including all exhaust fans serving the clean rooms and support area, at least the dedicated exhaust fan serving the BSC cabinet, should be on emergency power.
4. Air locks and anterooms: The use of air locks and anterooms should be carefully planned. The medical center staff may consider provision of an air lock in addition to an anteroom where they expect a high volume of compounding in the clean room, otherwise use of an anteroom should be sufficient to maintain pressure in the clean room.
5. Pass-through chamber: Depending on the size and space availability in the clean room and volume of compounding done, the medical center may consider provision of a pass-through window to facilitate passing out of compounded drugs without having pharmacy personnel frequently go in and out of the clean room through an anteroom. The pass-through window should be big enough to facilitate the passage of compounded sterile products or materials and have a tight seal between the clean room and the pharmacy area and should have two access doors. To prevent direct exposure from the clean room to the pharmacy area, both doors should not open at the same time. Provide door interlocks limiting doors to being open.
6. HEPA with prefilters should be accessible for service from outside the clean room.
7. Location of outside air intake is critical. The intake should not be located near plumbing vents, animal room exhausts, generator exhausts, loading docks, automobile entrances, driveways, passenger drop offs, cooling towers, incinerator and boiler stacks, and any other item that may degrade the quality of air. There should be separation of at least 30 ft between the air intakes and exhaust air outlets. Perform a dispersion analysis based on the actual configuration of the pharmacy area, surrounding facilities, and prevailing wind directions, etc. to establish, if a separation of more than 30 ft is required.
8. Monitor room temperature, relative humidity, and pressure via monitoring devices in the clean rooms on a continuing basis.
9. Provide monolithic and cleanable walls, floors, and ceilings.
10. Do not provide floor drains and sinks in the clean room.
11. Operate the dedicated BSC exhaust system around the clock.

12. The external lens of any lighting fixture must be smooth and cleanable.
13. The doorway into the buffer zone or clean room must be of sufficient size to move LAFWs in and out of the buffer zone when required.
14. Seal all wall openings, slots, piping and electrical conduits, and other penetrations to minimize air leakage from the clean room.
15. Provide hand hygiene facilities in the anteroom and touch-less controls to the extent possible to avoid recontamination of hands. Consider items such as automatic controls for entrance door between the anteroom and the clean room. The controls should be on emergency power. Provide electronic devices or photo sensors with time delays for light switches and towel dispensers with electronic sensors. The electronic sensors should be in front of the faucets facing the user to allow water to be run long enough to come to temperature before immersing hands.
16. Provide clothing hooks in the anteroom on the way to the clean room.

Appendix: Air-Handling Unit

AHU Data Sheet

Air-handling unit type	• Variable air volume (VAV) • Note 1
Inside design conditions	Room data sheets
Minimum outside air	Minimum 20%
Minimum supply air changes per hour	Room data sheets
Return air	Room data sheets
Economizer cycle	ASHRAE 90.11—2007
Air balance	Room data sheets
Filtration	• Prefilters, MERV 8 rating • After filters, MERV 14 rating • Final filters, MERV 17 rating • Note 2
Cooling source	• Use chilled water from the central chiller plant • Note 3
Heating source	• Use high-pressure steam from the central boiler plant as the primary source for generating heating hot water and producing "clean steam" for winter humidification • Use medium-pressure steam from the central boiler plant for unit mounted preheat coils
General exhaust system(s)	Required
Special exhaust system(s)	Room data sheets
Heat recovery system	ASHRAE 90.1—2007
Additional energy conservation measures	To meet the mandated goal of 30% additional energy conservation above ASHRAE 90.1—2004, evaluate the use of desiccant dehumidification system to reduce the dew point temperature of the incoming outside air
Emergency power	Required

Nonhazardous Clean Room—Room Data Sheet

Description: The following introductory information is provided for the nonhazardous clean rooms. The room comprises three segments:

1. PEC is a device or a space that provides ISO Class 5 environment for compounding of drugs. Generally, a LAFW is used as the PEC device. The room air need not be exhausted outdoors. Note that USP <797> General Chapter allows the use of a CAI or CACI for low-risk level CSPs even without the use of Class 7 clean room, provided "nonhazardous and radiopharmaceutical CSPs pursuant to a physician's order for a specific patient may be prepared, and administration of such CSPs shall commence within 12 hours of preparation or as recommended by in the manufacturer's package insert whichever is less. See USP <797> for the low-risk conditions.
2. Buffer area is the space in which the PEC is physically located. This is the clean room where activities such as preparation and staging of components used for drug preparation take place. Buffer area is maintained at ISO Class 7 by supplying HEPA-filtered air in a unidirectional manner from the suspended ceiling.
3. Anteroom is an ISO Class 8 or better area, which serves as a transient place to maintain the integrity of buffer area. This space also handles personnel hygiene and garbing of the personnel. Physical separation between the anteroom and buffer area is a wall with doors. Only one set of doors will be able to open at any given time to avoid disruption of the air pressure gradient.

PEC and Buffer Room (Nonhazardous Clean Room)—Room Data Sheet

Inside design conditions	• Cooling mode: 68°F (20°C) dry-bulb temperature (maximum), 55% relative humidity • Heating mode: 68°F (20°C) dry-bulb temperature (minimum), 40% relative humidity (Room level humidity control is not required.)

(*Continued*)

Appendix: Air-Handling Unit (*Continued*)

Minimum supply air changes per hour	30—CV required (Air changes listed above must be able to limit the concentration of the airborne particles. Provide more air changer per hour, if required, to maintain ISO Class 7 particulate count.)
Return air	Permitted
Exhaust air	Not required with 100% recirculatory ISO Class 5. Specific configurations of the BSC cabinets may require exhaust from the room air to outdoors. Coordinate exhaust air volume and system configuration per manufacturer's recommendations.
Individual room temperature control	Required
Room air balance	Positive (+) with respect to the anteroom. (Provide outside air as required to maintain the specified pressure differential)
Room noise level	NC 40
Anteroom (Nonhazardous Clean Room)—Room Data Sheet	
Inside design conditions	• Cooling mode: 68°F (20°C) dry-bulb temperature (maximum), 55% relative humidity • Heating mode: 68°F (20°C)] dry-bulb temperature (minimum), 40% relative humidity. (Room level humidity control is not required.)
Minimum supply air changes per hour	20—CV required (Air changes listed above must be able to limit the concentration of the airborne particles. Provide more air changer per hour, if required, to maintain ISO Class 8 particulate count.)
Return air	Permitted
Exhaust air	Not required
Individual room temperature control	Required
Room air balance	• Positive (+) with respect to circulation space • Negative (−) with respect to buffer room
Room noise level	NC 40

Hazardous Clean Room—Room Data Sheet

Description: The following introductory information is provided for the hazardous clean rooms. The room comprises of three segments:

1. PEC is a device or a space that provides ISO Class 5 environment for compounding of drugs. Generally, a BSC Class II B2 is used as the PEC device through which the air is exhausted outdoors after passing over the duct-mounted HEPA filter. The HEPA is an integral to the BSC unit, and additional in duct HEPA is not needed.
2. Buffer area is the space in which the PEC is physically located. This is the clean room where activities such as preparation and staging of components used for drug preparation take place. Buffer area is maintained at ISO Class 7 by supplying HEPA-filtered air and establishing unidirectional flow.
3. This room can also be used to store hazardous drugs provided adequate storage space is available. Otherwise a separate room is required to store hazardous drugs. This room should be ventilated at minimum 12 air changes per hour with negative pressure. Exhaust from this room should be connected to the special exhaust system serving the buffer room and anteroom.
4. Anteroom is an ISO Class 7 or better area, which serves as a transient place to maintain the integrity of buffer area. This space also handles personnel hygiene and garbing of the personnel. Physical separation between the anteroom and buffer area is a wall with doors. Only one set of doors will be able to open at any given time to avoid disruption of the air pressure gradient.
5. See USP <797> for additional requirement for lighting and ceiling surfaces, caulking, etc.

PEC and Buffer Room (Hazardous Clean Room)—Room Data Sheet	
Inside design conditions	• Cooling mode: 68°F (20°C) dry-bulb temperature (maximum), 55% relative humidity • Heating mode: 68°F (20°C) dry-bulb temperature (minimum), 40% relative humidity. Room level humidity control is not required.
Minimum supply air changes per hour	30—CV Required
Return air	Not permitted
Exhaust air	100% (All air supplied to the buffer room shall be exhausted outdoors without in duct HEPA filters in a manner to avoid facility entrainment and building wake effect. BSC or equivalent ISO Class 5 device shall be served by a special exhaust system without additional in duct HEPA filters in accordance with the manufacturer's recommendations. Buffer area and anteroom below shall be exhausted outdoors through another special exhaust system but without HEPA filters.)
Individual room temperature control	Required
Room air pressure	Negative (−) with respect to the anteroom
Room noise level	NC 40

(*Continued*)

Appendix: Air-Handling Unit (*Continued*)

Anteroom (Hazardous Clean Room)—Room Data Sheet

Inside design conditions	• Cooling mode: 68°F (20°C) dry-bulb temperature (maximum), 55% Relative Humidity • Heating mode: 68°F (20°C) dry-bulb temperature (minimum), 40% relative humidity. (Room level humidity control is not required.)
Minimum supply air changes per hour	30—CV required
Return air	Not permitted
Exhaust air	100%, see buffer room above
Individual room temperature control	Required
Room air balance	Positive (+) with respect to hazardous clean room Positive (+) with respect to Circulation Space whose room pressure is assumed as neutral (0)
Room noise level	NC 40

Controlled Substance Vault and Secured Dispensing Receiving Area--Room Data Sheet

Inside Design Conditions	• Cooling mode: 70°F (21°C) dry-bulb temperature (maximum), 50% relative humidity • Heating Mode: 75°F (24°C) dry-bulb temperature (minimum), 35% Relative Humidity • 5°F (2.8°C) dead-band (Room level humidity control is not required. Room Humidity shall be 40% if this room is served by the same AHU serving the clean rooms above.)
Minimum supply air changes per hour	6—VAV permitted
Return air	Permitted
Exhaust air	Not required
Individual room temperature control	Required
Room air balance	Neutral (0)
Room noise level	NC 40

Dispensing, Prepacking and EXTEMP—Room Data Sheet

Inside design conditions	• Cooling mode: 70°F (21°C) dry-bulb temperature (maximum), 50% relative humidity • Heating mode: 75°F (24°C) dry-bulb temperature (minimum), 40% relative humidity • 5°F (2.8°C) dead-band (Room level humidity control is not required. Room Humidity shall be 40% if this room is served by the same AHU serving the clean rooms above.)
Minimum supply air changes per hour	6—VAV permitted
Return air	Permitted
Exhaust air	Not required
Individual room temperature control	Required
Room air balance	Neutral (0)
Room noise level	NC 40

Note 1: The HVAC system design criteria are based on the latest (December 2007) publication of the USP (The United States Pharmacopeial Convention) Revised Bulletin <797> Pharmaceutical Sterile Preparations. A dedicated air-handling unit is not required to serve the hazardous and/or nonhazardous clean rooms so long as any air-handling unit serving these spaces can meet all requirements outlined in the AHU data sheet and the room data sheets.
Note 2: Locate the final filters (third bed) on the downstream side of the individual air terminal units serving each hazardous and nonhazardous clean room. Oversize the final filters to minimize the pressure drop. For remaining rooms, terminal HEPA filters are not required.
Note 3: Dedicated chiller is required if chilled water is not available year-round.

13

Approved Excipients in Sterile Dosage Forms

Ingredient	Dosage Form	Qty	Unit
1,2-dimyristoyl-*sn*-glycero-3-[phospho-s-(1-glycerol)]	IV(infusion); suspension, injection	0.15	%
1,2-dioleoyl-*sn*-glycero-3-phosphocholine	Epidural; injection, suspension, liposomal	0.42	%
1,2-dipalmitoyl-*sn*-glycero-3-[phospho-rac-(1-glycerol)]	Epidural; injection, suspension, liposomal	0.09	%
1,2-distearoyl-*sn*-glycero-3-[phospho-rac-(1-glycerol)]	Intravenous; injection, powder, lyophilized, for liposomal suspsension	8.4	%
1,2-distearoyl-*sn*-glycero-3-phosphocholine	Intravenous; solution, liposome, injection	2.804	%
1-methyl-2-pyrrolidinone	Subcutaneous; injection	25.85	%
Acesulfame potassium	Dental; solution	0.12	%
Acetic acid	Intravenous; injectable	0.01	%
Acetic acid	Intramuscular; injection	0.02	%
Acetic acid	Ophthalmic; solution	0.043	%
Acetic acid	IV(infusion); injection	1	%
Acetic acid	Intravenous; injection	12.75	%
Acetic acid, glacial	Subcutaneous; liquid	0.0107	%
Acetic acid, glacial	Subcutaneous; powder, for injection solution, lyophilized	0.041	%
Acetic acid, glacial	Intravenous; injectable	0.046	%
Acetic acid, glacial	Intravenous; solution, injection	0.051	%
Acetic acid, glacial	Ophthalmic; solution, drops	0.09	%
Acetic acid, glacial	Subcutaneous; solution, injection	0.11	%
Acetic acid, glacial	IM–SC; injection	0.2	%
Acetic acid, glacial	IV–SC; injection	0.2	%
Acetic acid, glacial	IV–SC; liquid	0.2	%
Acetic acid, glacial	Ophthalmic; solution	0.2	%
Acetic acid, glacial	IM–IV; injection	0.25	%
Acetic acid, glacial	Intramuscular; injection	0.25	%
Acetic acid, glacial	IV(infusion); powder, for injection solution, lyophilized	0.27	%
Acetic acid, glacial	IM–IV–SC; injection	0.352	%
Acetic acid, glacial	Intravenous; injection	0.36	%
Acetic acid, glacial	IV(infusion); injection	0.44	%
Acetic acid, glacial	IV(infusion); solution, injection	0.715	%
Acetic acid, glacial	Auricular (otic); suspension, liquid	2.55	%
Acetone sodium bisulfite	Inhalation; solution	0.5003	%
Acetylcysteine	Inhalation; solution	0.5	%
Acetyltryptophan	Intravenous; injection	0.02	%
Adipic acid	Intramuscular; injection	1	%
Alanine	IV(infusion); solution, injection	21	%
Alanine	IV(infusion); injection	77	%

Ingredient	Dosage Form	Qty	Unit
Albumin aggregated	Intravenous; injection	0.15	%
Albumin colloidal	Intravenous; powder, for injection solution	0.1	%
Albumin human	Subcutaneous; injectable	0.1	%
Albumin human	Intravenous; injection	1	%
Albumin human	Intravenous; powder, for injection solution	1	%
Albumin human	IV(infusion); injection	1	%
Albumin human	IV(infusion); powder, for injection solution, lyophilized	80	%
Albumin microshere human serum	Intravenous; injection	0.5	%
Alcohol	Respiratory (inhalation); solution, for inhalation	0.081	%
Alcohol	Ophthalmic; solution	0.5	%
Alcohol	IV–SC; injection	0.945	%
Alcohol	Ophthalmic; solution, drops	1.4	%
Alcohol	IM–IV–SC; injection	6.1	%
Alcohol	IM–IV; solution, injection	10	%
Alcohol	Intramuscular; solution, injection	10	%
Alcohol	IM–IV; injection	11	%
Alcohol	Intramuscular; injection	12	%
Alcohol	Dental; solution	12.8	%
Alcohol	Inhalation; solution	25	%
Alcohol	IV(infusion); solution, injection	30	%
Alcohol	Inhalation; aerosol, spray	33	%
Alcohol	IV(infusion); injection	34.3	%
Alcohol	Intravenous; solution, injection	40	%
Alcohol	Intravenous; injection	49	%
Alcohol	Inhalation; aerosol, metered	95.89	%
Alcohol, dehydrated	IV(infusion); powder, for injection solution, lyophilized	0.0365	%
Alcohol, dehydrated	Ophthalmic; solution	0.5	%
Alcohol, dehydrated	Ophthalmic; solution, drops	0.5	%
Alcohol, dehydrated	Nasal; aerosol, metered	0.7	%
Alcohol, dehydrated	Nasal; aerosol	2	%
Alcohol, dehydrated	IM–IV–SC; injection	4.93	%
Alcohol, dehydrated	Extracorporeal; solution	5	%
Alcohol, dehydrated	Photopheresis; solution	5	%
Alcohol, dehydrated	IM–IV; injectable	10	%
Alcohol, dehydrated	IM–IV; solution, injection	10	%
Alcohol, dehydrated	Intramuscular; injection	10	%
Alcohol, dehydrated	Intramuscular; solution, injection	10	%
Alcohol, dehydrated	Respiratory (inhalation); aerosol, metered	10	%
Alcohol, dehydrated	Dental; solution	11.34	%
Alcohol, dehydrated	IM–IV; injection	20	%
Alcohol, dehydrated	Inhalation; aerosol, metered	34.548	%
Alcohol, dehydrated	Intravenous; solution, concentrate	39.46	%
Alcohol, dehydrated	Intravenous; injection	40	%

Ingredient	Dosage Form	Qty	Unit
Alcohol, dehydrated	IV(infusion); solution, injection	49.7	%
Alcohol, dehydrated	Intravesical; solution	50	%
Alcohol, dehydrated	IV(infusion); injection	80	%
Alcohol, denatured	Dental; gel	1.8	%
Alcohol, diluted	IM–IV; injection	10	%
Alfadex	Intracavitary; powder, for injection solution, lyophilized	0.129	%
Alginic acid	Ophthalmic; suppository, insert, controlled release	1	mg
Alpha-tocopherol	Intravenous; injection, powder, lyophilized, for liposomal suspension	0.064	%
DL-Alpha-tocopherol	Intravenous; solution, concentrate	0.075	%
Aluminum acetate	Auricular (otic); solution	0.79	%
Aluminum sulfate	Auricular (otic); solution	0.79	%
Amerchol-cab	Ophthalmic; ointment	0.002	%
Ammonium acetate	Intramuscular; injection	0.4	%
Ammonium acetate	Intravenous; injection	0.4	%
Ammonium acetate	IV(infusion); injection	0.4	%
Ammonium hydroxide	Intravenous; injection	0.219	%
Ammonium sulfate	Intravenous; injection, suspension, liposomal	0.2	%
Antipyrine	Ophthalmic; solution	0.1	%
Arginine	IV(infusion); solution, injection	29	%
Arginine	Intravenous; powder, for injection solution	78	%
Arginine	IV(infusion); injection	88	%
Ascorbic acid	Intravenous; powder, for injection solution, lyophilized	0.088	%
Ascorbic acid	Inhalation; aerosol, spray	0.1	%
Ascorbic acid	IM–IV; injection	0.2	%
Ascorbic acid	Intravenous; powder, for injection solution	0.2	%
Ascorbic acid	Intravenous; solution, injection	0.2	%
Ascorbic acid	Nerve block; injection	0.2	%
Ascorbic acid	IV(infusion); powder, for injection solution, lyophilized	0.5	%
Ascorbic acid	Intramuscular; injection	1	%
Ascorbic acid	Subcutaneous; injection	1	%
Ascorbic acid	Inhalation; solution	1.02	%
Ascorbic acid	IV(infusion); injection	50.4	%
Ascorbic acid	Intravenous; injection	62.5	%
Ascorbic acid	Inhalation; aerosol, metered	95.95	%
Aspartic acid	IV(infusion); injection	0.68	%
Barium sulfate	Intrauterine; suppository, insert, controlled release	10	mg
Benzalkonium chloride	Intraocular; solution	0.0052	%
Benzalkonium chloride	Ophthalmic; gel	0.008	%
Benzalkonium chloride	Auricular (otic); solution, drops	0.02	%
Benzalkonium chloride	Auricular (otic); suspension	0.02	%
Benzalkonium chloride	Ophthalmic; ointment	0.025	%
Benzalkonium chloride	Ophthalmic; suspension	0.025	%
Benzalkonium chloride	Ophthalmic; suspension, drops	0.025	%

Ingredient	Dosage Form	Qty	Unit
Benzalkonium chloride	Auricular (otic); solution	0.0275	%
Benzalkonium chloride	Nasal; spray, metered	0.1176	%
Benzalkonium chloride	Nasal; spray	0.119	%
Benzalkonium chloride	Ophthalmic; solution, drops	0.512	%
Benzalkonium chloride	Nasal; solution	1	%
Benzalkonium chloride	Ophthalmic; solution	8.8	%
Benzalkonium chloride	Inhalation; solution	20	%
Benzethonium chloride	IM–IV; injection	0.01	%
Benzethonium chloride	IV(infusion); injection	0.012	%
Benzethonium chloride	Auricular (otic); solution, drops	0.02	%
Benzethonium chloride	Nasal; spray, metered	0.02	%
Benzethonium chloride	Intravenous; powder, for injection solution	0.05	%
Benzethonium chloride	Auricular (otic); solution	0.1	%
Benzododecinium bromide	Ophthalmic; solution	0.012	%
Benzododecinium bromide	Ophthalmic; solution, gel forming, extended release	0.012	%
Benzoic acid	Irrigation; solution	0.024	%
Benzoic acid	Intramuscular; solution, injection	0.2	%
Benzoic acid	IM–IV; injection	5	%
Benzyl alcohol	Nasal; spray, metered	0.0366	%
Benzyl alcohol	Intravenous; emulsion, injection	0.1	%
Benzyl alcohol	Subcutaneous; liquid	0.225	%
Benzyl alcohol	Intrathecal; injection	0.45	%
Benzyl alcohol	Nasal; solution	0.5	%
Benzyl alcohol	Intracavitary; powder, for injection solution, lyophilized	0.84	%
Benzyl alcohol	Subcutaneous; solution, injection	0.885	%
Benzyl alcohol	Intra-arterial; injection	0.9	%
Benzyl alcohol	Intradermal; injection	0.9	%
Benzyl alcohol	Intratumor; injection	0.9	%
Benzyl alcohol	Intravenous; solution	0.9	%
Benzyl alcohol	N/A; liquid	0.9	%
Benzyl alcohol	Intralesional; suspension, injection	0.916	%
Benzyl alcohol	Intramuscular; suspension, injection	0.916	%
Benzyl alcohol	Intrasynovial; suspension, injection	0.916	%
Benzyl alcohol	Soft tissue; suspension, injection	0.916	%
Benzyl alcohol	Subconjunctival; injection	0.945	%
Benzyl alcohol	Epidural; injection	1	%
Benzyl alcohol	Extracorporeal; injection	1	%
Benzyl alcohol	IM–IV; injectable	1	%
Benzyl alcohol	Intrabursal; injection	1	%
Benzyl alcohol	Intralesional; injection	1	%
Benzyl alcohol	Intramuscular; injection, sustained action	1	%
Benzyl alcohol	Intrasynovial; injection	1	%
Benzyl alcohol	Soft tissue; injection	1	%

Ingredient	Dosage Form	Qty	Unit
Benzyl alcohol	IM–SC; injection, sustained action	1.2	%
Benzyl alcohol	Intra-articular; Injection	1.5	%
Benzyl alcohol	IV–SC; injection	1.5	%
Benzyl alcohol	Subcutaneous; injection	1.5	%
Benzyl alcohol	IM–IV–SC; injection	1.575	%
Benzyl alcohol	Intravenous; powder, for injection solution	1.8	%
Benzyl alcohol	IM–IV; solution, injection	2	%
Benzyl alcohol	IM–SC; injection	2	%
Benzyl alcohol	Intravenous; injectable	2.02	%
Benzyl alcohol	Intravenous; solution, injection	2.02	%
Benzyl alcohol	IV(infusion); solution, injection	2.02	%
Benzyl alcohol	IV(infusion); injection	3	%
Benzyl alcohol	Intramuscular; injectable	4	%
Benzyl alcohol	IM–IV; injection	5.21	%
Benzyl alcohol	IM–IV; powder, for injection solution	6.69	%
Benzyl alcohol	IV(infusion); powder, for injection solution	6.69	%
Benzyl alcohol	Auricular (otic); suspension, liquid	9	%
Benzyl alcohol	Intramuscular; solution, injection	10	%
Benzyl alcohol	Intravenous; injection	10.4	%
Benzyl alcohol	Intramuscular; injection	10.962	%
Benzyl alcohol	Dental; paste	25	mg
Benzyl benzoate	Intramuscular; solution, injection	15	%
Benzyl benzoate	Intramuscular; injectable	20	%
Benzyl benzoate	Intramuscular; injection	46	%
Benzyl chloride	Intravenous; injection	0.001	%
Bibapcitide	Intravenous; injection	0.01	%
Boric acid	Auricular (otic); solution	0.049	%
Boric acid	Ophthalmic; powder, for solution	0.06	%
Boric acid	Ophthalmic; solution, gel forming, extended release	0.3	%
Boric acid	Intravenous; solution, injection	0.319	%
Boric acid	Ophthalmic; suspension, drops	0.6	%
Boric acid	Ophthalmic; suspension	1	%
Boric acid	Ophthalmic; solution, drops	1.9	%
Boric acid	Ophthalmic; solution	37.2	%
Butylated hydroxyanisole	Nasal; spray, metered	0.0002	%
Butylated hydroxyanisole	IV(infusion); injection	0.0003	%
Butylated hydroxyanisole	Intramuscular; injection	0.03	%
Butylated hydroxyanisole	Nasal; solution	2	%
Butylated hydroxytoluene	IV(infusion); injection	0.001	%
Butylated hydroxytoluene	Intravenous; powder, for injection solution, lyophilized	0.0015	%
Butylated hydroxytoluene	Nasal; spray, metered	0.01	%
Butylated hydroxytoluene	Intramuscular; injection	0.03	%
Caffeine	Ophthalmic; solution	2	%

Ingredient	Dosage Form	Qty	Unit
Calcium	Intramuscular; injection	0.0012	%
Calcium carbonate	Auricular (otic); solution	0.382	%
Calcium carbonate	Respiratory (inhalation); solution, injection	4.024	%
Calcium chloride	Ophthalmic; solution, drops	0.006	%
Calcium chloride	Intravascular; injection	0.0074	%
Calcium chloride	Intravenous; solution, liposome, injection	0.028	%
Calcium chloride	AN, infiltration; injection	0.033	%
Calcium chloride	Caudal block; injection	0.033	%
Calcium chloride	Epidural; injection	0.033	%
Calcium chloride	Nerve block; injection	0.033	%
Calcium chloride	Subcutaneous; injectable	0.04	%
Calcium chloride	Intraocular; solution	0.048	%
Calcium chloride	Ophthalmic; powder, for solution	0.048	%
Calcium chloride	Subcutaneous; injection	0.053	%
Calcium chloride	Intravenous; injection	0.074	%
Calcium chloride	Intraperitoneal; solution	2.57	%
Calcium chloride	IM–IV; injection	4	%
Calcium chloride	Intramuscular; injection	4	%
Calcium gluceptate	Intravenous; injection	5	%
Calcium hydroxide	Intravenous; injection	0.37	%
Calteridol calcium	Intravenous; injection	0.023	%
Carbomer 1342	Ophthalmic; emulsion	0.05	%
Carbomer 934P	Ophthalmic; suspension, drops	0.45	%
Carbomer 940	Ophthalmic; gel	4	%
Carbomer 974P	Ophthalmic; suspension, drops	0.45	%
Carbomer 974P	Ophthalmic; suspension	0.5	%
Carbon dioxide	Inhalation; gas	95	%
Carboxymethylcellulose	Intra-articular; injection	0.2	%
Carboxymethylcellulose	Intramuscular; injection	0.9	%
Carboxymethylcellulose sodium	Intrasynovial; injection	0.1	%
Carboxymethylcellulose sodium	Nasal; spray, metered	0.15	%
Carboxymethylcellulose sodium	Dental; gel	0.4	%
Carboxymethylcellulose sodium	Intra-articular; injection	0.5	%
Carboxymethylcellulose sodium	Ophthalmic; solution, drops	0.5	%
Carboxymethylcellulose sodium	Soft tissue; injection	0.5	%
Carboxymethylcellulose sodium	Intramuscular; injection, microspheres	1	%
Carboxymethylcellulose sodium	Intramuscular; injection	3	%
Carboxymethylcellulose sodium	Intramuscular; powder, for injection solution, lyophilized	3	%
Carboxymethylcellulose sodium	Subcutaneous; implant	16	mg
Carboxymethylcellulose sodium	Dental; paste	174	mg
Castor oil	Ophthalmic; emulsion	1.25	%
Cellulose microcrystalline/carboxymethylcellulose sodium	Nasal; spray, metered	1.5	%
Cellulose microcrystalline/carboxymethylcellulose sodium	Nasal; spray	2	%

Ingredient	Dosage Form	Qty	Unit
Cellulose, microcrystalline	Intra-articular; injection	0.05	%
Cellulose, microcrystalline	Intramuscular; injection	0.05	%
Cellulose, microcrystalline	Nasal; spray, metered	0.15	%
Cellulose, microcrystalline	Intravitreal; implant	1.66	mg
Cellulose, microcrystalline	Intravenous; injection	14.9	%
Cetyl alcohol	Ophthalmic; suspension	0.5	%
Cetyl alcohol	Auricular (otic); suspension	1	%
Charcoal, activated	Intramuscular; injectable	0.3	%
Charcoal, activated	Intravenous; injectable	0.3	%
Chlorobutanol	Nasal; solution	0.05	%
Chlorobutanol	Ophthalmic; solution, drops	0.2	%
Chlorobutanol	Subcutaneous; injection	0.25	%
Chlorobutanol	AN, infiltration; injection	0.4	%
Chlorobutanol	IM–IV–SC; injection	0.5	%
Chlorobutanol	IM–IV; injection	0.5	%
Chlorobutanol	IM–SC; injection	0.5	%
Chlorobutanol	Inhalation; solution	0.5	%
Chlorobutanol	Nasal; spray	0.5	%
Chlorobutanol	Nasal; spray, metered	0.5	%
Chlorobutanol	Nerve block; injection	0.5	%
Chlorobutanol	Ophthalmic; solution	0.5	%
Chlorobutanol	Intramuscular; injectable	0.525	%
Chlorobutanol	Ophthalmic; powder, for solution	0.55	%
Chlorobutanol	IV(infusion); injection	0.6	%
Chlorobutanol	Ophthalmic; ointment	0.65	%
Chlorobutanol	Intramuscular; injection	5	%
Chlorobutanol hemihydrate	Intramuscular; injection	0.525	%
Chlorobutanol hemihydrate	Intravenous; solution, injection	0.525	%
Chlorobutanol, anhydrous	Intravenous; injection	0.5	%
Chlorobutanol, anhydrous	Ophthalmic; solution	0.5	%
Chlorobutanol, anhydrous	Intramuscular; injection	0.525	%
Chloroxylenol	Auricular (otic); solution	0.1	%
Cholesterol	Intravenous; injection, suspension, liposomal	0.319	%
Cholesterol	Epidural; injection, suspension, liposomal	0.33	%
Cholesterol	Intravenous; solution, liposome, injection	0.684	%
Cholesterol	Intravenous; injection, powder, lyophilized, for liposomal suspension	5.2	%
Citrate	Intravenous; injectable	0.72	%
Citric acid	Inhalation; aerosol, metered	0.0002	%
Citric acid	Intravenous; solution, concentrate	0.0025	%
Citric acid	AN, infiltration; injection	0.02	%
Citric acid	Epidural; injection	0.02	%
Citric acid	Nerve block; injection	0.0202	%
Citric acid	Intramuscular; powder, for injection solution	0.03	%

Ingredient	Dosage Form	Qty	Unit
Citric acid	Intrapleural; powder, for injection solution	0.03	%
Citric acid	Intrathecal; powder, for injection solution	0.03	%
Citric acid	Auricular (otic); solution, drops	0.04	%
Citric acid	IM–IV; injectable	0.05	%
Citric acid	Ophthalmic; solution, drops	0.05	%
Citric acid	Intravenous; solution, injection	0.075	%
Citric acid	IM–IV; solution, injection	0.08	%
Citric acid	Intracardiac; injection	0.2	%
Citric acid	IV(infusion); solution, injection	0.2	%
Citric acid	Ophthalmic; solution	0.2	%
Citric acid	IM–SC; injection	0.219	%
Citric acid	Nasal; spray	0.26	%
Citric acid	IM–IV; injection	0.33	%
Citric acid	Inhalation; solution	0.4404	%
Citric acid	Intravenous; solution	0.5017	%
Citric acid	Auricular (otic); solution	1	%
Citric acid	IM–IV–SC; injection	1.262	%
Citric acid	Intramuscular; injection	2	%
Citric acid	Nasal; spray, metered	3.5	%
Citric acid	IV(infusion); injection	5.1	%
Citric acid	IV(infusion); powder, for injection solution	6.92	%
Citric acid	Intravenous; powder, for injection solution, lyophilized	7.692	%
Citric acid	Intravenous; injection	20	%
Citric acid	Nasal; solution	20	%
Citric acid	Intravenous; injectable	41.36	%
Citric acid	Intravenous; powder, for injection solution	50	%
Citric acid monohydrate	IM–IV; injectable	0.05	%
Citric acid monohydrate	IM–IV; solution	0.05	%
Citric acid monohydrate	Intraocular; solution	0.05	%
Citric acid monohydrate	Ophthalmic; solution	0.05	%
Citric acid monohydrate	Ophthalmic; solution, drops	0.05	%
Citric acid monohydrate	Intravenous; injectable	0.052	%
Citric acid monohydrate	Intravenous; solution, injection	0.082	%
Citric acid monohydrate	IM–IV; solution, injection	0.0875	%
Citric acid monohydrate	IV(infusion); solution, injection	0.14	%
Citric acid monohydrate	Intravenous; solution	0.156	%
Citric acid monohydrate	AN, infiltration; injection	0.1613	%
Citric acid monohydrate	Nerve block; injection	0.1613	%
Citric acid monohydrate	Nasal; spray, metered	0.17	%
Citric acid monohydrate	IM–IV; injection	0.361	%
Citric acid monohydrate	Nasal; solution	0.42	%
Citric acid monohydrate	Intramuscular; injectable	0.5	%
Citric acid monohydrate	Intracardiac; injection	1.05	%

Ingredient	Dosage Form	Qty	Unit
Citric acid monohydrate	IV(infusion); injection	1.05	%
Citric acid monohydrate	IM–IV–SC; injection	1.26	%
Citric acid monohydrate	Intravenous; powder, for injection solution	21.9	%
Citric acid monohydrate	Intravenous; powder, for injection solution, lyophilized	41.36	%
Citric acid monohydrate	Intravenous; injection	52.5	%
Citric acid, hydrous	IV(infusion); injection	0.0032	%
Citric acid, hydrous	IM–IV–SC; injection	1.26	%
Citric acid, hydrous	Intravenous; injection	10.5	%
Cottonseed oil	Intramuscular; injection	87.46	%
Creatinine	Ophthalmic; solution, drops	0.2	%
Creatinine	Auricular (otic); solution	0.5	%
Creatinine	Intramuscular; injection	0.5	%
Creatinine	Ophthalmic; solution	0.5	%
Creatinine	IM–IV; injection	0.8	%
Creatinine	Intra-articular; injection	0.8	%
Creatinine	Intralesional; injection	0.8	%
Creatinine	Intrasynovial; injection	0.8	%
Creatinine	Soft Tissue; injection	0.8	%
M-Cresol	IM–IV–SC; injection	0.1	%
M-Cresol	IV(infusion); injection	0.1	%
M-Cresol	Intradermal; injection	0.16	%
M-Cresol	Subcutaneous; suspension, injection	0.172	%
M-Cresol	Subcutaneous; solution, injection	0.22	%
M-Cresol	IM–SC; injection	0.25	%
M-Cresol	Intramuscular; powder, for injection solution, lyophilized	0.3	%
M-Cresol	Subcutaneous; powder, for injection solution, lyophilized	0.3	%
M-Cresol	Subcutaneous; injectable	0.315	%
M-Cresol	Subcutaneous; injection	0.45	%
Croscarmellose sodium	Intramuscular; injection	1	%
Crospovidone	Intra-articular; injection	0.02	%
Crospovidone	Intramuscular; injection	0.02	%
Crospovidone	Implantation; pellet	2	mg
Cysteine	IM–SC; injection, sustained action	0.1	%
Cysteine	IV(infusion); solution, injection	2	%
Cysteine	Intravenous; powder, for injection solution, lyophilized	2.6	%
Cysteine hydrochloride	Intravenous; powder, for injection solution	0.1	%
Cysteine hydrochloride	IV(infusion); powder, for injection solution, lyophilized	1.5	%
Cysteine hydrochloride	IV(infusion); injection	2	%
D&C Red No. 33	Dental; solution	0.0007	%
D&C Yellow No. 10	Dental; gel	0.003	%
Dextran 40	Intravenous; powder, for injection solution, lyophilized	30	%
Dextrose	Intramuscular; injection	4.4	%
Dextrose	IM–IV; injection	5	%

Ingredient	Dosage Form	Qty	Unit
Dextrose	IM–IV; powder, for injection solution	5	%
Dextrose	Intraspinal; injection	5	%
Dextrose	Intravenous; injectable	5	%
Dextrose	Intravenous; powder, for injection solution	5	%
Dextrose	Intravenous; solution, injection	5	%
Dextrose	IV(infusion); powder, for injection solution	5	%
Dextrose	Nasal; spray	5	%
Dextrose	Nasal; spray, metered	5	%
Dextrose	IV(infusion); solution, injection	5.17	%
Dextrose	IV(infusion); injection	5.6	%
Dextrose	Spinal; injection	7.5	%
Dextrose	Intravenous; injection	30	%
Dextrose solution	IV(infusion); powder, for injection solution	5	%
Dextrose, anhydrous	Nasal; spray	0.275	%
Dextrose, anhydrous	Nasal; spray, metered	0.5	%
Dextrose, anhydrous	Intravenous; kit	1.11	gm
Dextrose, anhydrous	IM–SC; injection	3.75	%
Dextrose, anhydrous	Intravenous; injection	4.7	%
Dextrose, anhydrous	IV(infusion); solution, injection	4.7	%
Dextrose, anhydrous	IM–IV; injectable	5	%
Dextrose, anhydrous	Intramuscular; injection	5	%
Dextrose, anhydrous	Intravenous; solution, injection	5	%
Dextrose, anhydrous	IV(infusion); injection	5.43	%
Dextrose, anhydrous	Spinal; injection	8.25	%
Diatrizoic acid	Intramuscular; injection	59.7	%
Diatrizoic acid	Intravenous; injection	59.7	%
Dichlorodifluoromethane	Nasal; aerosol, metered	1.72	%
Dichlorodifluoromethane	Inhalation; aerosol, metered	74.029	%
Dichlorotetrafluoroethane	Nasal; aerosol, metered	0.86	%
Dichlorotetrafluoroethane	Inhalation; aerosol, metered	51.12	%
Diethanolamine	IV(infusion); injection	1.5	%
Dimethyl sulfoxide	Subcutaneous; implant	104	mg
Dimethylsiloxane/methylvinylsiloxane copolymer	Implantation; pellet, implant	142	mg
Dimethylsiloxane/methylvinylsiloxane copolymer	Implantation; rod	142	mg
Dimyristoyl lecithin	IV(infusion); suspension, injection	0.34	%
Dimyristoyl lecithin	Intravenous; powder, for injection solution, lyophilized	7.05	%
Dioctylphthalate	Ophthalmic; suppository, insert, controlled release	2	mg
Disodium sulfosalicylate	IV(infusion); powder, for injection solution, lyophilized	0.032	%
Disofenin	IV(infusion); injection	2	%
Divinylbenzene styrene copolymer	Ophthalmic; suspension, drops	0.75	%
Docusate sodium	Intramuscular; injection	0.015	%
Edamine	Intravenous; injection	0.3755	%
Edamine	IV(infusion); injection	0.392	%

Ingredient	Dosage Form	Qty	Unit
Edetate calcium disodium	Intramuscular; powder, for injection solution	0.005	%
Edetate calcium disodium	Intraperitoneal; powder, for injection solution	0.005	%
Edetate calcium disodium	IV(infusion); injection	0.005	%
Edetate calcium disodium	IV(infusion); powder, for injection solution	0.005	%
Edetate calcium disodium	Nerve block; injection	0.01	%
Edetate calcium disodium	Intra-arterial; injection	0.048	%
Edetate calcium disodium	Intramuscular; injection	0.048	%
Edetate calcium disodium	Subcutaneous; injection	0.17	%
Edetate calcium disodium	Intrathecal; injection	0.216	%
Edetate calcium disodium	Intravenous; injection	0.48	%
Edetate calcium disodium	Intravascular; injection	10	%
Edetate disodium	Intravenous; emulsion, injection	0.005	%
Edetate disodium	Intrabursal; injection	0.01	%
Edetate disodium	Intravenous; infusion	0.01	%
Edetate disodium	Intravenous; injectable	0.01	%
Edetate disodium	Ophthalmic; gel	0.01	%
Edetate disodium	AN, infiltration; injection	0.0111	%
Edetate disodium	Epidural; injection	0.0111	%
Edetate disodium	Nerve block; injection	0.0111	%
Edetate disodium	Respiratory (inhalation); solution, for inhalation	0.03	%
Edetate disodium	Intravascular; injection	0.04	%
Edetate disodium	IV(infusion); solution, injection	0.04	%
Edetate disodium	IM–IV; injectable	0.05	%
Edetate disodium	Intra-articular; injection	0.05	%
Edetate disodium	Intralesional; injection	0.05	%
Edetate disodium	Intravenous; solution	0.05	%
Edetate disodium	Soft tissue; injection	0.05	%
Edetate disodium	IV(infusion); powder, for injection suspension, lyophilized	0.0801	%
Edetate disodium	Auricular (otic); solution	0.1	%
Edetate disodium	Auricular (otic); solution, drops	0.1	%
Edetate disodium	Intramuscular; solution, injection	0.1	%
Edetate disodium	Nasal; spray	0.1	%
Edetate disodium	Ophthalmic; suspension, drops	0.1	%
Edetate disodium	Subcutaneous; injectable	0.1	%
Edetate disodium	Intravenous; solution, injection	0.11	%
Edetate disodium	Ophthalmic; suspension	0.13	%
Edetate disodium	Intravenous; powder, for injection solution, lyophilized	0.15	%
Edetate disodium	IM–IV–SC; injection	0.2	%
Edetate disodium	IM–SC; injection	0.2	%
Edetate disodium	Subcutaneous; injection	0.2	%
Edetate disodium	Ophthalmic; solution, drops	0.3	%
Edetate disodium	Nasal; spray, metered	0.5	%
Edetate disodium	IV(infusion); injection	1	%

Ingredient	Dosage Form	Qty	Unit
Edetate disodium	Inhalation; solution	5	%
Edetate disodium	Nasal; solution	5	%
Edetate disodium	IM–IV; injection	10	%
Edetate disodium	Intramuscular; injection	10	%
Edetate disodium	Intravenous; injection	10	%
Edetate disodium	Ophthalmic; solution	10	%
Edetate disodium, anhydrous	Intramuscular; injection	0.01	%
Edetate disodium, anhydrous	Intravenous; injectable	0.01	%
Edetate disodium, anhydrous	IV(infusion); injection	0.01	%
Edetate disodium, anhydrous	Intravenous; injection	0.025	%
Edetate disodium, anhydrous	Ophthalmic; solution, drops	0.1	%
Edetate sodium	Intramuscular; injection	0.01	%
Edetate sodium	Inhalation; solution	0.02	%
Edetate sodium	Ophthalmic; suspension	0.02	%
Edetate sodium	IV(infusion); solution, injection	0.04	%
Edetate sodium	Ophthalmic; solution	0.1	%
Edetate sodium	IM–IV–SC; injection	0.2	%
Edetic acid	Auricular (otic); suspension	0.001	%
Egg yolk phosphatides	Intravenous; emulsion, injection	1.2	%
Egg yolk phosphatides	Intravenous; injection	1.2	%
Egg yolk phosphatides	IV(infusion); injection	1.8	%
Ethanolamine hydrochloride	Intravenous; injection	0.15	%
Ethylene vinyl acetate copolymer	Ophthalmic; suppository, insert, controlled release	14	mg
Ethylene vinyl acetate copolymer	Periodontal; film, controlled release	51	mg
Ethylene vinyl acetate copolymer	Implantation; rod	61	mg
Ethylene vinyl acetate copolymer	Subcutaneous; rod	61	mg
Ethylene vinyl acetate copolymer	Intrauterine; suppository, insert, controlled release	160	mg
FD&C Blue No. 1	Dental; solution	0.01	%
FD&C Green No. 3	Dental; gel	0.0033	%
FD&C Red No. 40	Dental; solution	0.0006	%
Ferric chloride	Intravenous; injection	6.05	%
Flavor 89-186	Dental; solution	0.08	%
Flavor DF-1530	Dental; gel	0.77	%
Flavor NNS DZ-03226	Nasal; spray, metered	1	%
Flavor peppermint stick FMC 16170	Dental; solution	4.5	%
Fructose	IV(infusion); powder, for injection solution, lyophilized	5	%
Fused sodium ash	Ophthalmic; solution, drops	0.005	%
Gamma-cyclodextrin	Intravenous; injection	5	%
Gelatin	Intramuscular; injection, microspheres	0.13	%
Gelatin	Intramuscular; injection	0.26	%
Gelatin	IM–IV–SC; powder, for injection solution	1.4	%
Gelatin	IV(infusion); injection	2	%
Gelatin	Intravenous; solution	3.48	%

Ingredient	Dosage Form	Qty	Unit
Gelatin	IM–SC; injection	16	%
Gelatin	IM–SC; injection, sustained action	16	%
Gelatin	Dental; paste	180	mg
Gellan gum	Ophthalmic; solution	0.6	%
Gentisic acid	Intravenous; injection	0.056	%
Gentisic acid ethanolamide	IV(infusion); injection	2	%
Gluceptate sodium	Intravenous; injection	7.5	%
Gluceptate sodium	Intravenous; powder, for injection solution	20	%
Gluceptate sodium dihydrate	Intravenous; injection	7.5	%
Glutathione	Intramuscular; injection, sustained action	0.5	%
Glycerin	Auricular (otic); suspension	0.05	%
Glycerin	Nasal; spray, metered	0.223	%
Glycerin	IM–IV–SC; powder, for injection solution	1.2	%
Glycerin	IV–SC; injection	1.2	%
Glycerin	IM–SC; injection	1.6	%
Glycerin	Intradermal; injection	1.6	%
Glycerin	Subcutaneous; suspension, injection	1.6	%
Glycerin	Intramuscular; injectable	1.7814	%
Glycerin	Subcutaneous; injectable	2	%
Glycerin	Ophthalmic; emulsion	2.2	%
Glycerin	Intravenous; emulsion, injection	2.25	%
Glycerin	Intravenous; injectable	2.25	%
Glycerin	IV(infusion); injection	2.5	%
Glycerin	Nasal; solution	2.5	%
Glycerin	Ophthalmic; suspension	2.5	%
Glycerin	Ophthalmic; suspension, drops	2.5	%
Glycerin	Perfusion, biliary; liquid	2.5	%
Glycerin	Ophthalmic; solution, drops	2.6	%
Glycerin	Ophthalmic; solution	3	%
Glycerin	Intramuscular; injection	5.9367	%
Glycerin	Inhalation; solution	7.3	%
Glycerin	Intravenous; injection	12.62	%
Glycerin	Dental; solution	15	%
Glycerin	IM–IV; injection	15	%
Glycerin	IM–IV–SC; injection	15.36	%
Glycerin	IV(infusion); emulsion, injection	22.5	%
Glycerin	Subcutaneous; injection	32.5	%
Glycerin	Auricular (otic); solution	60	%
Glycerin	Auricular (otic); solution, drops	63.6373	%
Glyceryl stearate	Auricular (otic); suspension	0.5	%
Glyceryl stearate	Ophthalmic; suspension	0.5	%
Glyceryl stearate	Dental; paste	64	mg
Glycine	Respiratory (inhalation); powder, for inhalation	0.013	%

Ingredient	Dosage Form	Qty	Unit
Glycine	Subcutaneous; injectable	0.136	%
Glycine	Intravenous; solution, liposome, injection	0.376	%
Glycine	IV(infusion); powder, for injection solution	0.376	%
Glycine	Intramuscular; injection	1.126	%
Glycine	Intramuscular; injectable	2.252	%
Glycine	Subcutaneous; powder, for injection solution	2.4	%
Glycine	Intramuscular; powder, for injection solution, lyophilized	2.76	%
Glycine	Subcutaneous; powder, for injection solution, lyophilized	2.76	%
Glycine	Intramuscular; powder, for injection solution	4	%
Glycine	Intravenous; powder, for injection solution, lyophilized	25	%
Glycine	IV(infusion); solution, injection	42	%
Glycine	IV(infusion); injection	90	%
Glycocholic acid	Intravenous; powder, for injection solution, lyophilized	14	%
Guanidine hydrochloride	Intravenous; injection	0.25	%
Hetastarch	Intravenous; powder, for injection solution	7.36	%
Histidine	Subcutaneous; solution, injection	0.11	%
Histidine	Intravenous; injection, suspension, liposomal	0.155	%
Histidine	IV(infusion); solution, injection	8.5	%
Histidine	IV(infusion); injection	37.2	%
Hydrochloric acid	IM–IV; injectable	0.0249	%
Hydrochloric acid	Auricular (otic); suspension	0.044	%
Hydrochloric acid	Auricular (otic); solution, drops	0.06	%
Hydrochloric acid	Ophthalmic; solution, drops	0.17	%
Hydrochloric acid	Subcutaneous; injection	0.17	%
Hydrochloric acid	Subcutaneous; suspension, injection	0.22	%
Hydrochloric acid	Auricular (otic); solution	0.37	%
Hydrochloric acid	AN, infiltration; injection	0.64	%
Hydrochloric acid	Nerve block; injection	0.64	%
Hydrochloric acid	IV(infusion); powder, for injection suspension, lyophilized	0.834	%
Hydrochloric acid	Ophthalmic; solution	1.06	%
Hydrochloric acid	IV(infusion); injection	1.44	%
Hydrochloric acid	Inhalation; aerosol, metered	1.72	%
Hydrochloric acid	Intravenous; solution	1.825	%
Hydrochloric acid	Inhalation; solution	3.5	%
Hydrochloric acid	Intramuscular; injectable	8	%
Hydrochloric acid	Intravenous; injectable	8	%
Hydrochloric acid	Intravenous; injection	10	%
Hydrochloric acid	IV(infusion); solution, injection	12.7	%
Hydrochloric acid	Intravenous; powder, for injection solution, lyophilized	14.11	%
Hydrochloric acid	Nasal; solution	24.7	%
Hydrochloric acid, diluted	AN, infiltration; injection	1.36	%
Hydrochloric acid, diluted	Nerve block; injection	1.36	%
Hydrocortisone	Auricular (otic); solution	5.5007	%

Ingredient	Dosage Form	Qty	Unit
Hydroxyethyl cellulose	Auricular (otic); solution	0.25	%
Hydroxyethyl cellulose	Ophthalmic; suspension	0.25	%
Hydroxyethyl cellulose	Ophthalmic; solution	0.35	%
Hydroxyethyl cellulose	Ophthalmic; suspension, drops	0.35	%
Hydroxyethyl cellulose	Ophthalmic; solution, drops	0.5	%
Hydroxypropyl methylcellulose 2906	Ophthalmic; solution, drops	0.5	%
Hydroxypropyl methylcellulose 2910	Nasal; spray, metered	0.1	%
Hydroxypropyl methylcellulose 2910	Ophthalmic; solution	0.5	%
Hydroxypropyl methylcellulose 2910	Ophthalmic; suspension	0.5	%
Hydroxypropyl methylcellulose 2910	Ophthalmic; suspension, drops	0.5	%
Hydroxypropyl-*b*-cyclodextrin	IV(infusion); injection	0.4	%
Insulin beef	Subcutaneous; injection	0.1	%
Insulin pork	Subcutaneous; injection	0.1	%
Iodoxamic acid	Intravenous; infusion	7.61	%
Iodoxamic acid	Intravenous; injection	31	%
Isoleucine	IV(infusion); solution, injection	21	%
Isoleucine	IV(infusion); injection	90	%
Isopropyl myristate	Auricular (otic); suspension	0.024	%
Isotonic sodium chloride solution	Intravenous; injection	0.9	%
Lactic acid	IM–IV–SC; injection	0.012	%
Lactic acid	Intracardiac; injection	0.012	%
Lactic acid	AN, infiltration; injection	0.1184	%
Lactic acid	Nerve block; injection	0.1184	%
Lactic acid	IV(infusion); solution, injection	0.119	%
Lactic acid	Subcutaneous; injection	0.34	%
Lactic acid	Intravenous; injectable	0.413	%
Lactic acid	Intravenous; injection	0.71	%
Lactic acid	IM–IV; injection	1.1578	%
Lactic acid	IV(infusion); injection	32.2	%
DL-Lactic acid	IV(infusion); injection	2.82	%
L-Lactic acid	Intravenous; injection	0.3	%
L-Lactic acid	Subcutaneous; injection	0.3	%
L-Lactic acid	Intravenous; injectable	0.4	%
Lactose	IV(infusion); solution, injection	0.45	%
Lactose	Subcutaneous; powder, for injection solution, lyophilized	0.5	%
Lactose	Intramuscular; powder, for injection solution, lyophilized	1	%
Lactose	Intravenous; powder, for injection solution, lyophilized	1	%
Lactose	Intramuscular; powder, for injection solution	2	%
Lactose	Subcutaneous; powder, for injection solution	2	%
Lactose	Intravenous; powder, for injection solution	5	%
Lactose	Inhalation; powder	9	%
Lactose	IM–IV–SC; powder, for injection solution	13.3	%
Lactose	Intracavitary; powder, for injection solution, lyophilized	19.38	%

Ingredient	Dosage Form	Qty	Unit
Lactose	Inhalation; capsule	20	mg
Lactose	Inhalation; capsule, hard gelatin	25	mg
Lactose	Intravenous; injection	50	%
Lactose monohydrate	Respiratory (inhalation); powder, for inhalation	2	%
Lactose monohydrate	IM–SC; injection	2.1	%
Lactose monohydrate	IM–IV; powder	2.75	%
Lactose monohydrate	Intracavitary; powder, for injection solution, lyophilized	4.54	%
Lactose monohydrate	IV–SC; injection	4.9	%
Lactose monohydrate	Intramuscular; injection	5	%
Lactose monohydrate	IM–IV–SC; powder, for injection solution, lyophilized	10.7	%
Lactose monohydrate	IV(infusion); powder, for injection solution	20	%
Lactose monohydrate	Respiratory (inhalation); capsule	25	mg
Lactose monohydrate	Intravenous; powder, for injection solution, lyophilized	69	%
Lactose monohydrate	IV(infusion); powder, for injection solution, lyophilized	90	%
Lactose, anhydrous	IM–IV; injectable	2.5	%
Lactose, anhydrous	IM–IV; powder, for injection solution	2.5	%
Lactose, anhydrous	IV(infusion); powder, for injection solution	2.5	%
Lactose, anhydrous	Intracavitary; powder, for injection solution, lyophilized	4.75	%
Lactose, hydrous	Intramuscular; powder, for injection solution, lyophilized	1.05	%
Lactose, hydrous	IM–IV; injection	2.5	%
Lactose, hydrous	IM–IV; powder, for injection solution	2.5	%
Lactose, hydrous	IV(infusion); powder, for injection solution	20	%
Lactose, hydrous	Intravenous; injection	25	%
Lactose, hydrous	Intravenous; powder, for injection solution	75	%
Lanolin	Ophthalmic; ointment	2	%
Lanolin alcohols	Ophthalmic; ointment	10	%
Lanolin, anhydrous	Ophthalmic; ointment	3	%
Lauralkonium chloride	Ophthalmic; solution, drops	0.005	%
Lecithin	Inhalation; aerosol, metered	0.0002	%
Lecithin	Intramuscular; injection	2.3	%
Lecithin, egg	Intravenous; emulsion, injection	1.2	%
Lecithin, egg	Intravenous; injectable	1.2	%
Lecithin, hydrogenated	Auricular (otic); suspension, liquid	1.5	%
Lecithin, hydrogenated soy	Inhalation; aerosol, metered	0.28	%
Lecithin, hydrogenated soy	Intravenous; injection, suspension, liposomal	0.958	%
Lecithin, hydrogenated soy	Intravenous; injection, powder, lyophilized, for liposomal suspension	21.3	%
Lecithin, soybean	Inhalation; aerosol, metered	0.1	%
Lecithin, soybean	Intravenous; powder, for injection solution, lyophilized	11.25	%
Leucine	IV(infusion); solution, injection	27	%
Leucine	IV(infusion); injection	52.6	%
Lysine	IV(infusion); solution, injection	22	%
Lysine	IV(infusion); injection	61	%
Lysine acetate	IV(infusion); injection	0.756	%

Ingredient	Dosage Form	Qty	Unit
Lysine acetate	IV(infusion); solution, injection	31	%
Magnesium chloride	Ophthalmic; solution, drops	0.0065	%
Magnesium chloride	Intraocular; solution	0.03	%
Magnesium chloride	Ophthalmic; powder, for solution	0.03	%
Magnesium chloride	Subcutaneous; powder, for injection solution, lyophilized	0.125	%
Magnesium chloride	Intraperitoneal; solution	0.508	%
Magnesium chloride	IV(infusion); injection	10.2	%
Magnesium stearate	Implantation; injection	0.0015	%
Magnesium stearate	Intravitreal; injection	0.0015	%
Magnesium stearate	Intravitreal; implant	0.0048	mg
Magnesium stearate	Subcutaneous; implant	0.5	mg
Mannitol	Respiratory (inhalation); powder, for inhalation	0.051	%
Mannitol	IM–SC; powder, for injection solution	2	%
Mannitol	Ophthalmic; suspension	2.4	%
Mannitol	IM–IV; injection	2.5	%
Mannitol	Intramuscular; powder, for injection solution, lyophilized, with additives	3.6	%
Mannitol	Subcutaneous; injectable	3.6	%
Mannitol	Subcutaneous; suspension, injection	3.64	%
Mannitol	Ophthalmic; suspension, drops	4	%
Mannitol	Subcutaneous; powder, for injection solution, lyophilized, with additives	4	%
Mannitol	Intravenous; solution	4.15	%
Mannitol	Subcutaneous; solution, injection	4.3	%
Mannitol	Ophthalmic; solution, gel forming, extended release	4.35	%
Mannitol	Subcutaneous; injection	4.5	%
Mannitol	Ophthalmic; solution, drops	4.6	%
Mannitol	IV(infusion); solution, injection	4.7	%
Mannitol	Intravenous; solution, injection	4.95	%
Mannitol	Intramuscular; powder, for injection suspension, lyophilized	5.19	%
Mannitol	Ophthalmic; powder, for solution	5.6	%
Mannitol	Intravenous; liquid, concentrate, injection	6.13	%
Mannitol	IV(infusion); powder, for injection solution, lyophilized, with additives	7.5	%
Mannitol	Intramuscular; powder, for injection solution, lyophilized	8.5	%
Mannitol	Subcutaneous; powder, for injection solution	9	%
Mannitol	Subcutaneous; powder, for injection suspension, lyophilized	10	%
Mannitol	Intramuscular; injection	10.66	%
Mannitol	Intramuscular; powder, for injection solution	11.9292	%
Mannitol	Intravenous; injection	13	%
Mannitol	Intramuscular; injection, microspheres	13.49	%
Mannitol	Subcutaneous; powder, for injection solution, lyophilized	16.44	%
Mannitol	IV(infusion); injection	20	%
Mannitol	Ophthalmic; solution	23	%
Mannitol	IM–IV; powder, for injection solution	30	%
Mannitol	Intravenous; powder, for injection solution	34	%

Ingredient	Dosage Form	Qty	Unit
Mannitol	Intravenous; injectable	45	%
Mannitol	Intravenous; powder	45	%
Mannitol	Intravenous; powder, for injection solution, lyophilized	45	%
Mannitol	IV(infusion); powder, for injection solution, lyophilized	50	%
Mannitol	IV(infusion); powder, for injection solution	75	%
Medronate disodium	Intravenous; powder, for injection solution	0.01	%
Medronate disodium	Intravenous; injection	1	%
Medronic acid	Intravenous; powder, for injection solution	1	%
Medronic acid	Intravenous; injection	2.5	%
Meglumine	Intravenous; infusion	2.3	%
Meglumine	IV(infusion); injection	7.238	%
Meglumine	Intramuscular; injection	15.924	%
Meglumine	Intravenous; injection	15.924	%
Menthol	Inhalation; aerosol, metered	0.0502	%
Metaphosphoric acid	IV(infusion); injection	0.13	%
Methanesulfonic acid	IV(infusion); powder, for injection solution, lyophilized	8.07	%
Methionine	Intrathecal; injectable	0.005	%
Methionine	Subcutaneous; powder, for injection solution, lyophilized	0.01	%
Methionine	Subcutaneous; injection	0.015	%
Methionine	Intramuscular; solution, injection	0.0443	%
Methionine	Subcutaneous; solution, injection	0.0443	%
Methionine	Subcutaneous; suspension, injection	0.15	%
Methionine	Intravenous; injection	0.3	%
Methionine	IV(infusion); solution, injection	16	%
Methionine	IV(infusion); injection	49.2	%
Methyl boronic acid	Intravenous; injection	0.2	%
Methylcellulose	Intra-articular; injection	0.1	%
Methylcellulose	Intramuscular; injection	0.1	%
Methylcellulose	Ophthalmic; solution	0.1641	%
Methylcellulose 4000	Ophthalmic; solution	0.5	%
Methylene blue	Intravenous; injection	1	%
Methylparaben	Auricular (otic); suspension	0.0014	%
Methylparaben	Nasal; solution	0.033	%
Methylparaben	Ophthalmic; ointment	0.05	%
Methylparaben	Ophthalmic; solution	0.05	%
Methylparaben	Ophthalmic; solution, drops	0.05	%
Methylparaben	Ophthalmic; suspension	0.05	%
Methylparaben	Ophthalmic; suspension, drops	0.05	%
Methylparaben	Inhalation; solution	0.07	%
Methylparaben	AN, infiltration; injection	0.1	%
Methylparaben	Caudal block; injection	0.1	%
Methylparaben	Epidural; injection	0.1	%
Methylparaben	Intradermal; injection	0.1	%

Ingredient	Dosage Form	Qty	Unit
Methylparaben	IV(infusion); powder, for injection solution	0.1	%
Methylparaben	Nerve block; injection	0.1	%
Methylparaben	Peridural; injection	0.1	%
Methylparaben	IM–IV; injectable	0.12	%
Methylparaben	N/A; liquid	0.12	%
Methylparaben	IM–IV; solution	0.126	%
Methylparaben	Intralesional; injection	0.15	%
Methylparaben	Soft tissue; injection	0.15	%
Methylparaben	Subcutaneous; suspension, injection	0.16	%
Methylparaben	IM–SC; injection	0.18	%
Methylparaben	Intrabursal; injection	0.18	%
Methylparaben	Intravenous; injectable	0.18	%
Methylparaben	IV–SC; injection	0.18	%
Methylparaben	Subcutaneous; injection	0.18	%
Methylparaben	Intra-articular; injection	0.24	%
Methylparaben	Intramuscular; injection	0.24	%
Methylparaben	IM–IV–SC; injection	0.44	%
Methylparaben	IV(infusion); injection	0.44	%
Methylparaben	N/A; not applicable	0.45	mg
Methylparaben	Nasal; spray, metered	0.7	%
Methylparaben	IM–IV; injection	0.75	%
Methylparaben	Intravenous; powder, for injection solution	1.5	%
Methylparaben	Intravenous; injection	1.8	%
Methylparaben	Irrigation; solution	2	%
Mineral oil	Ophthalmic; suspension	0.1	%
Mineral oil	Auricular (otic); suspension	0.5	%
Mineral oil	Ophthalmic; ointment	59.5	%
Mineral oil	Dental; paste	457.95	mg
Myristyl-gamma-picolinium chloride	Intra-articular; injection	0.019	%
Myristyl-gamma-picolinium chloride	Intralesional; injection	0.019	%
Myristyl-gamma-picolinium chloride	Intramuscular; injection	0.019	%
Myristyl-gamma-picolinium chloride	Soft tissue; injection	0.019	%
Myristyl-gamma-picolinium chloride	Intralesional; injection, sustained action	0.0195	%
Myristyl-gamma-picolinium chloride	Intramuscular; injection, sustained action	0.0195	%
Myristyl-gamma-picolinium chloride	Intrasynovial; injection, sustained action	0.0195	%
Myristyl-gamma-picolinium chloride	Soft tissue; injection, sustained action	0.0195	%
N-(carbamoyl-methoxy PEG-40)-1,2-distearoyl-cephalin sodium	Intravenous; injection, suspension, liposomal	0.319	%
N, N-dimethylacetamide	Intravenous; injection	1.8	%
Niacinamide	IM–IV; injection	2.5	%
Nioxime	Intravenous; injection	0.2	%
Nitric acid	Inhalation; aerosol, metered	1.67	%
N-lauroylsarcosine	Ophthalmic; suspension, drops	0.03	%
nonoxynol-9	Ophthalmic; solution	0.125	%

Ingredient	Dosage Form	Qty	Unit
Norflurane	Inhalation; aerosol, metered	7.5	%
Norflurane	Respiratory (inhalation); aerosol, metered	89.76	%
Octanoic acid	Intravenous; injection	0.012	%
Octoxynol-40	Ophthalmic; solution	0.01	%
Oleic acid	Respiratory (inhalation); aerosol, metered	0.0003	%
Oleic acid	Nasal; aerosol, metered	0.132	%
Oleic acid	Inhalation; inhalant	0.16	%
Oleic acid	Inhalation; aerosol, metered	0.267	%
Oxidronate sodium	Intravenous; injection	0.2	%
Oxyquinoline	Intravenous; injection	0.005	%
Pectin	Dental; paste	180	mg
PEG vegetable oil	IV(infusion); injection	5	%
PEG vegetable oil	IM–SC; injection	7	%
PEG-40 sorbitan diisostearate	Dental; solution	2.4	%
Pentetate pentasodium	Intravenous; injection	0.5	%
Pentetic acid	Intravenous; injection	0.2	%
Peppermint	Dental; solution	0.5	%
Peppermint oil	Dental; solution	0.525	%
Petrolatum	Ophthalmic; ointment	85	%
Petrolatum, white	Dental; paste	64	mg
Petrolatum, white	Ophthalmic; ointment	89	%
Phenethyl alcohol	Nasal; solution	0.2	%
Phenethyl alcohol	Auricular (otic); solution	0.25	%
Phenethyl alcohol	Nasal; spray, metered	0.254	%
Phenethyl alcohol	Ophthalmic; solution	0.5	%
Phenol	Subcutaneous; suspension, injection	0.15	%
Phenol	Subcutaneous; injectable	0.18	%
Phenol	Intradermal; injection	0.25	%
Phenol	IM–IV–SC; injection	0.45	%
Phenol	Intramuscular; solution, injection	0.45	%
Phenol	IM–SC; injection	0.5	%
Phenol	IM–SC; injection, sustained action	0.5	%
Phenol	Intra-articular; injection	0.5	%
Phenol	Intralesional; injection	0.5	%
Phenol	Intramuscular; injectable	0.5	%
Phenol	Intramuscular; injection, sustained action	0.5	%
Phenol	Intrasynovial; injection	0.5	%
Phenol	Intravenous; injectable	0.5	%
Phenol	Intravenous; injection	0.5	%
Phenol	Subcutaneous; injection	0.5	%
Phenol	Subcutaneous; solution, injection	0.5	%
Phenol	IM–IV; injection	1	%
Phenol	IV(infusion); injection	1	%

Ingredient	Dosage Form	Qty	Unit
Phenol	Intramuscular; injection	1.3333	%
Phenol, liquefied	Subcutaneous; injection	0.065	%
Phenol, liquefied	Subcutaneous; suspension, injection	0.073	%
Phenol, liquefied	IM–SC; injection	0.2	%
Phenol, liquefied	Intravenous; injection	0.28	%
Phenol, liquefied	IM–IV; injection	0.5	%
Phenol, liquefied	IV–SC; liquid	0.5	%
Phenylalanine	IV(infusion); solution, injection	17	%
Phenylalanine	IV(infusion); injection	52.6	%
Phenylmercuric acetate	Ophthalmic; ointment	0.0008	%
Phenylmercuric nitrate	Ophthalmic; ointment	0.002	%
Phenylmercuric nitrate	Ophthalmic; solution	0.002	%
Phosphatidyl glycerol, egg	Intravenous; powder, for injection solution, lyophilized	4.875	%
Phospholipid	IV(infusion); injection	1.2	%
Phospholipid	IV(infusion); emulsion, injection	12	%
Phospholipid, egg	IV(infusion); injection	1.2	%
Phosphoric acid	Subcutaneous; powder, for injection solution, lyophilized, with additives	0.1398	%
Phosphoric acid	Subcutaneous; injection	0.205	%
Phosphoric acid	Intramuscular; powder, for injection solution, lyophilized	0.233	%
Phosphoric acid	Subcutaneous; powder, for injection solution, lyophilized	0.233	%
Phosphoric acid	IV(infusion); injection	11.5	%
Plastibase-50W	Dental; paste	549	mg
Poloxamer 188	Subcutaneous; injection	0.015	%
Poloxamer 188	Ophthalmic; solution	0.1	%
Poloxamer 188	Ophthalmic; solution, drops	0.1	%
Poloxamer 188	Intravenous; powder, for injection solution	0.22	%
Poloxamer 188	Subcutaneous; solution, injection	0.3	%
Poloxamer 188	Intravenous; injection	0.6	%
Poloxamer 407	Ophthalmic; solution, drops	0.16	%
Poloxamer 407	Ophthalmic; solution	0.2	%
Poly(bis(*p*-carboxyphenoxy)propane anhydride): sebacic acid	Implantation; wafer	192.3	mg
Polycarbophil	Ophthalmic; solution	0.9	%
Polyethylene	Dental; paste	40	mg
Polyethylene glycol 1540	Dental; gel	5	%
Polyethylene glycol 200	Intramuscular; injection	30	%
Polyethylene glycol 300	IM–IV; injection	50	%
Polyethylene glycol 300	Intramuscular; injection	50	%
Polyethylene glycol 300	Intravenous; injection	65	%
Polyethylene glycol 300	IV(infusion); injection	65	%
Polyethylene glycol 3350	Nasal; spray, metered	1.5	%
Polyethylene glycol 3350	Subcutaneous; suspension, injection	2.875	%
Polyethylene glycol 3350	Intralesional; injection, sustained action	2.9	%

Ingredient	Dosage Form	Qty	Unit
Polyethylene glycol 3350	Intramuscular; injection, sustained action	2.9	%
Polyethylene glycol 3350	Intrasynovial; injection, sustained action	2.9	%
Polyethylene glycol 3350	Soft tissue; injection, sustained action	2.9	%
Polyethylene glycol 3350	Intralesional; suspension, injection	2.91	%
Polyethylene glycol 3350	Intramuscular; suspension, injection	2.91	%
Polyethylene glycol 3350	Intrasynovial; suspension, injection	2.91	%
Polyethylene glycol 3350	Soft tissue; suspension, injection	2.91	%
Polyethylene glycol 3350	Intra-articular; injection	3	%
Polyethylene glycol 3350	Intralesional; injection	3	%
Polyethylene glycol 3350	Intramuscular; injection	3	%
Polyethylene glycol 3350	Intrasynovial; injection	3	%
Polyethylene glycol 3350	Soft tissue; injection	3	%
Polyethylene glycol 400	Ophthalmic; ointment	4.997	%
Polyethylene glycol 400	Intravenous; injection	11.25	%
Polyethylene glycol 400	IV(infusion); injection	11.25	%
Polyethylene glycol 400	IM–IV; solution, injection	18	%
Polyethylene glycol 400	Nasal; spray, metered	20	%
Polyethylene glycol 400	IM–IV; injection	20.3	%
Polyethylene glycol 4000	Intra-articular; injection	3	%
Polyethylene glycol 4000	Intralesional; injection	3	%
Polyethylene glycol 4000	Intramuscular; injection	3	%
Polyethylene glycol 4000	Intrasynovial; injection	3	%
Polyethylene glycol 600	Intravenous; injection	5	%
Polyethylene glycol 600	Intravenous; solution, injection	5	%
Polyethylene glycol 8000	Ophthalmic; solution	2	%
Polyglactin	Subcutaneous; powder, for injection suspension	13.26	%
Polyglactin	Intramuscular; injection	14.5	%
Polyglactin	Intramuscular; powder, for injection solution, lyophilized	17	%
Polyglactin	Subcutaneous; injection	21.15	%
Polyglactin	Implantation; pellet, implant	25.2	mg
Polyglactin	Subcutaneous; pellet, implant	25.2	mg
Polyglactin	Intramuscular; injection, microspheres	56.64	%
Polylactide	Intramuscular; powder, for injection suspension, lyophilized	26.48	%
Polyols	Dental; gel	65.82	%
Polyoxyethylene fatty acid esters	IM–SC; injection	7	%
Polyoxyl 35 castor oil	Ophthalmic; solution	5	%
Polyoxyl 35 castor oil	Intravesical; solution	50	%
Polyoxyl 35 castor oil	IV(infusion); solution, injection	52.75	%
Polyoxyl 35 castor oil	IV(infusion); injection	65	%
Polyoxyl 40 castor oil	IM–SC; injection	7	%
Polyoxyl 40 hydrogenated castor oil	Ophthalmic; solution, drops	0.5	%
Polyoxyl 40 hydrogenated castor oil	Dental; solution	1	%
Polyoxyl 40 stearate	Ophthalmic; suspension	0.5	%

Ingredient	Dosage Form	Qty	Unit
Polyoxyl 40 stearate	Auricular (otic); suspension	1	%
Polyoxyl 40 stearate	Ophthalmic; solution	7	%
Polyoxyl 400 stearate	Nasal; spray, metered	15	%
Polyoxyl 60 castor oil	IV(infusion); injection	20	%
Polyoxyl stearate	Auricular (otic); suspension	0.006	%
Polypropylene glycol	Ophthalmic; solution	15	%
Polypropylene glycol	IM–IV; injectable	40	%
Polyquaternium-1	Ophthalmic; solution, drops	0.0005	%
Polysorbate 20	IM–SC; injection	0.0005	%
Polysorbate 20	Subcutaneous; injection	0.001	%
Polysorbate 20	Subcutaneous; injectable	0.002	%
Polysorbate 20	Intramuscular; powder, for injection solution, lyophilized	0.01	%
Polysorbate 20	Subcutaneous; powder, for injection solution, lyophilized	0.01	%
Polysorbate 20	Intramuscular; solution, injection	0.0177	%
Polysorbate 20	Ophthalmic; suspension	0.05	%
Polysorbate 20	Subcutaneous; liquid	0.05	%
Polysorbate 20	Intravenous; injection	0.4	%
Polysorbate 20	Intravenous; solution, injection	0.4	%
Polysorbate 20	Subcutaneous; solution, injection	0.4	%
Polysorbate 20	Auricular (otic); suspension, liquid	1	%
Polysorbate 20	IV(infusion); injection	2.4	%
Polysorbate 20	Nasal; spray, metered	2.5	%
Polysorbate 60	Ophthalmic; ointment	15	%
Polysorbate 80	Nasal; spray	0.004	%
Polysorbate 80	Ophthalmic; solution, gel forming, extended release	0.05	%
Polysorbate 80	Auricular (otic); solution, drops	0.1	%
Polysorbate 80	Intramuscular; injection, microspheres	0.1	%
Polysorbate 80	Nasal; solution	0.1	%
Polysorbate 80	Ophthalmic; suspension	0.1	%
Polysorbate 80	Ophthalmic; suspension, drops	0.1	%
Polysorbate 80	Intralesional; suspension, injection	0.194	%
Polysorbate 80	Intramuscular; suspension, injection	0.194	%
Polysorbate 80	Intrasynovial; suspension, injection	0.194	%
Polysorbate 80	Soft tissue; suspension, injection	0.194	%
Polysorbate 80	Auricular (otic); solution	0.2	%
Polysorbate 80	Intralesional; injection	0.2	%
Polysorbate 80	Intramuscular; powder, for injection solution, lyophilized	0.2	%
Polysorbate 80	Intrasynovial; injection	0.2	%
Polysorbate 80	Ophthalmic; solution	0.2	%
Polysorbate 80	Soft tissue; injection	0.2	%
Polysorbate 80	Subcutaneous; suspension, injection	0.3	%
Polysorbate 80	Intra-articular; injection	0.4	%
Polysorbate 80	Ophthalmic; emulsion	1	%

Ingredient	Dosage Form	Qty	Unit
Polysorbate 80	Ophthalmic; solution, drops	1	%
Polysorbate 80	Intravenous; powder, for injection solution, lyophilized	2.5	%
Polysorbate 80	Auricular (otic); suspension	5	%
Polysorbate 80	Intramuscular; solution, injection	5	%
Polysorbate 80	IV(infusion); injection	8	%
Polysorbate 80	Intravenous; injectable	10	%
Polysorbate 80	Intravenous; injection	10	%
Polysorbate 80	Intravenous; solution, injection	10	%
Polysorbate 80	IV(infusion); solution, injection	10	%
Polysorbate 80	Nasal; spray, metered	10	%
Polysorbate 80	Intramuscular; injection	12	%
Polysorbate 80	IV(infusion); powder, for injection solution, lyophilized	12.5	%
Polyvinyl alcohol	Intravitreal; implant	0.119	mg
Polyvinyl alcohol	Intraocular; solution	1.4	%
Polyvinyl alcohol	Ophthalmic; solution	1.4	%
Polyvinyl alcohol	Ophthalmic; solution, drops	1.4	%
Polyvinyl alcohol	Ophthalmic; suspension	1.4	%
Polyvinyl alcohol	Ophthalmic; suspension, drops	1.4	%
Polyvinyl alcohol	Auricular (otic); suspension, liquid	20	%
Potassium acetate	Ophthalmic; powder, for solution	4	%
Potassium chloride	AN, infiltration; injection	0.03	%
Potassium chloride	Caudal block; injection	0.03	%
Potassium chloride	Epidural; injection	0.03	%
Potassium chloride	Nerve block; injection	0.03	%
Potassium chloride	Intraocular; solution	0.075	%
Potassium chloride	Ophthalmic; powder, for solution	0.075	%
Potassium chloride	Ophthalmic; solution, drops	0.14	%
Potassium chloride	Intravenous; solution, injection	0.382	%
Potassium chloride	Ophthalmic; solution	22.2	%
Potassium metabisulfite	IV(infusion); injection	0.06	%
Potassium metabisulfite	Auricular (otic); solution, drops	0.1	%
Potassium metabisulfite	IM–IV; injection	0.1	%
Potassium metabisulfite	Auricular (otic); solution	0.11	%
Potassium metabisulfite	IV(infusion); solution, injection	5	%
Potassium phosphate, dibasic	Subcutaneous; powder, for injection solution, lyophilized	0.192	%
Potassium phosphate, dibasic	Intra-articular; injection	0.6	%
Potassium phosphate, dibasic	Intramuscular; injection	0.6	%
Potassium phosphate, dibasic	Subcutaneous; injection	1.36	%
Potassium phosphate, dibasic	IV(infusion); injection	55.2	%
Potassium phosphate, monobasic	Intravenous; injection	0.0153	%
Potassium phosphate, monobasic	Ophthalmic; solution, drops	0.065	%
Potassium phosphate, monobasic	IM–IV; injection	0.096	%
Potassium phosphate, monobasic	Intramuscular; injectable	0.096	%

Ingredient	Dosage Form	Qty	Unit
Potassium phosphate, monobasic	Intravenous; injectable	0.096	%
Potassium phosphate, monobasic	Subcutaneous; powder, for injection solution, lyophilized	0.122	%
Potassium phosphate, monobasic	Nasal; spray	0.14	%
Potassium phosphate, monobasic	Auricular (otic); solution	0.2	%
Potassium phosphate, monobasic	Ophthalmic; solution	0.2	%
Potassium phosphate, monobasic	Intra-articular; injection	0.3	%
Potassium phosphate, monobasic	Intramuscular; injection	0.3	%
Potassium phosphate, monobasic	Ophthalmic; suspension	0.44	%
Potassium phosphate, monobasic	IV(infusion); solution, injection	1.361	%
Potassium phosphate, monobasic	AN, infiltration; injection	2.7218	%
Potassium phosphate, monobasic	Nerve block; injection	2.7218	%
Potassium sorbate	Nasal; spray, metered	0.0084	%
Potassium sorbate	Ophthalmic; solution	0.47	%
Povidone K17	Subcutaneous; suspension, injection	0.5	%
Povidone K29-32	Ophthalmic; solution	1.8	%
Povidone K30	Ophthalmic; suspension	0.6	%
Povidone K90	Ophthalmic; solution, drops	1.2	%
Proline	IV(infusion); solution, injection	34	%
Proline	IV(infusion); injection	80	%
Propylene glycol	Ophthalmic; solution, drops	0.75	%
Propylene glycol	Ophthalmic; suspension, drops	1	%
Propylene glycol	Dental; solution	2	%
Propylene glycol	Extracorporeal; solution	5	%
Propylene glycol	Ophthalmic; suspension	5	%
Propylene glycol	Photopheresis; solution	5	%
Propylene glycol	Auricular (otic); suspension	10	%
Propylene glycol	Ophthalmic; solution	10	%
Propylene glycol	Nasal; spray, metered	20	%
Propylene glycol	Inhalation; solution	25	%
Propylene glycol	Intravenous; injectable	30	%
Propylene glycol	Intravenous; solution, injection	30	%
Propylene glycol	IV(infusion); solution, injection	30	%
Propylene glycol	Intramuscular; injection	40	%
Propylene glycol	Intramuscular; solution, injection	40	%
Propylene glycol	IM–IV; solution, injection	41.6	%
Propylene glycol	Intravenous; injection	50	%
Propylene glycol	Intravenous; solution, concentrate	50.3325	%
Propylene glycol	IV(infusion); injection	51.8	%
Propylene glycol	Auricular (otic); solution, drops	80	%
Propylene glycol	IM–IV; injection	82.043	%
Propylene glycol	Auricular (otic); solution	94.925	%
Propylene glycol diacetate	Auricular (otic); solution, drops	3	%
Propylene glycol diacetate	Auricular (otic); solution	65	%

Ingredient	Dosage Form	Qty	Unit
Propylparaben	Auricular (otic); suspension	0.0006	%
Propylparaben	AN, infiltration; injection	0.01	%
Propylparaben	Ophthalmic; ointment	0.01	%
Propylparaben	Ophthalmic; suspension	0.01	%
Propylparaben	Ophthalmic; suspension, drops	0.01	%
Propylparaben	N/A; liquid	0.012	%
Propylparaben	IM–IV; injectable	0.015	%
Propylparaben	Ophthalmic; solution	0.015	%
Propylparaben	Ophthalmic; solution, drops	0.015	%
Propylparaben	Subcutaneous; suspension, injection	0.015	%
Propylparaben	IM–IV; solution	0.0158	%
Propylparaben	Nasal; solution	0.017	%
Propylparaben	IM–SC; injection	0.02	%
Propylparaben	Intrabursal; injection	0.02	%
Propylparaben	Intralesional; injection	0.02	%
Propylparaben	Intravenous; injectable	0.02	%
Propylparaben	IV–SC; injection	0.02	%
Propylparaben	Soft tissue; injection	0.02	%
Propylparaben	Subcutaneous; injection	0.02	%
Propylparaben	Nerve block; injection	0.035	%
Propylparaben	Inhalation; solution	0.0375	%
Propylparaben	IV(infusion); injection	0.056	%
Propylparaben	N/A; not applicable	0.06	mg
Propylparaben	Intravenous; powder, for injection solution	0.08	%
Propylparaben	Intra-articular; injection	0.16	%
Propylparaben	Intramuscular; injection	0.16	%
Propylparaben	IM–IV; injection	0.2	%
Propylparaben	Intravenous; injection	0.2	%
Propylparaben	Nasal; spray, metered	0.3	%
Propylparaben	IM–IV–SC; injection	20	%
Protamine sulfate	Subcutaneous; suspension, injection	0.033	%
Protamine sulfate	Subcutaneous; injection	0.036	%
Protamine sulfate	Intradermal; injection	0.125	%
Saccharin	Inhalation; aerosol, metered	0.1127	%
Saccharin sodium	Inhalation; aerosol, metered	0.045	%
Saccharin sodium	IM–IV; injection	0.09	%
Saccharin sodium	Intramuscular; injection	0.09	%
Saccharin sodium	Intravenous; injection	0.09	%
Saccharin sodium	IV(infusion); injection	0.09	%
Saccharin sodium	Dental; solution	0.15	%
Saccharin sodium	Dental; gel	0.3	%
Saccharin sodium, anhydrous	IM–IV; injection	0.09	%
Saccharin sodium, anhydrous	IV(infusion); injection	0.09	%

Ingredient	Dosage Form	Qty	Unit
Serine	IV(infusion); solution, injection	18	%
Serine	IV(infusion); injection	50	%
Sesame oil	Intramuscular; injection	70	%
Silastic brand medical grade tubing	Implantation; rod	13	mg
Silastic medical adhesive, silicone type A	Implantation; pellet, implant	13	mg
Silicon dioxide	Dental; gel	19	%
Silicon dioxide, colloidal	Endocervical; gel	8	%
Silicone	Intrauterine; suppository, insert, controlled release	60	mg
Sodium acetate	Intravenous; solution, injection	0.0204	%
Sodium acetate	Auricular (otic); solution, drops	0.0267	%
Sodium acetate	Auricular (otic); suspension	0.042	%
Sodium acetate	Intravenous; injectable	0.05	%
Sodium acetate	Auricular (otic); solution	0.075	%
Sodium acetate	Subcutaneous; injection	0.14	%
Sodium acetate	Subcutaneous; liquid	0.1455	%
Sodium acetate	Subcutaneous; solution, injection	0.1592	%
Sodium acetate	Intradermal; injection	0.16	%
Sodium acetate	Extracorporeal; solution	0.175	%
Sodium acetate	Photopheresis; solution	0.175	%
Sodium acetate	IM–SC; injection	0.2	%
Sodium acetate	IV–SC; injection	0.2	%
Sodium acetate	IV–SC; liquid	0.2	%
Sodium acetate	Ophthalmic; solution	0.35	%
Sodium acetate	Intraocular; solution	0.39	%
Sodium acetate	Ophthalmic; powder, for solution	0.39	%
Sodium acetate	Intramuscular; injection	0.4	%
Sodium acetate	IM–IV–SC; injection	0.65	%
Sodium acetate	IM–IV; injection	0.969	%
Sodium acetate	Ophthalmic; solution, drops	1.279	%
Sodium acetate	IV(infusion); solution, injection	1.7	%
Sodium acetate	Auricular (otic); suspension, liquid	6.8	%
Sodium acetate	Intravenous; injection	12.25	%
Sodium acetate	IV(infusion); injection	59.4	%
Sodium acetate, anhydrous	Intravenous; injectable	0.005	%
Sodium acetate, anhydrous	Subcutaneous; powder, for injection solution, lyophilized	0.01	%
Sodium acetate, anhydrous	IM–SC; injection	0.07	%
Sodium acetate, anhydrous	Subcutaneous; injection	0.16	%
Sodium acetate, anhydrous	Intramuscular; injection	0.471	%
Sodium acetate, anhydrous	IV(infusion); injection	6.25	%
Sodium acetate, anhydrous	Intravenous; solution	17.7	%
Sodium ascorbate	Intravenous; injection	1	%
Sodium ascorbate	Intravenous; solution, injection	1	%
Sodium benzoate	Intravenous; injectable	0.07	%

Ingredient	Dosage Form	Qty	Unit
Sodium benzoate	Dental; gel	0.08	%
Sodium benzoate	Intramuscular; solution, injection	4.8	%
Sodium benzoate	Intramuscular; injection	5	%
Sodium benzoate	IV(infusion); injection	5	%
Sodium benzoate	IM–IV; injection	10	%
Sodium bicarbonate	Intrathecal; injection	0.005	%
Sodium bicarbonate	Intravenous; injection	0.005	%
Sodium bicarbonate	Subcutaneous; powder, for injection solution	0.016	%
Sodium bicarbonate	Intravitreal; injection	0.178	%
Sodium bicarbonate	IV(infusion); powder, for injection solution, lyophilized	0.18	%
Sodium bicarbonate	Intravenous; powder, for injection solution	2.1	%
Sodium bicarbonate	Intramuscular; powder, for injection solution	3	%
Sodium bicarbonate	Intramuscular; injection	3.5	%
Sodium bicarbonate	Intraperitoneal; powder, for injection solution	60	%
Sodium bicarbonate	IM–IV; powder, for injection solution, lyophilized	61.9	%
Sodium bicarbonate	IV(infusion); powder, for injection solution	81.94	%
Sodium bicarbonate	IV(infusion); injection	83	%
Sodium bisulfate	Inhalation; solution	0.011	%
Sodium bisulfate	IM–IV–SC; injection	0.1	%
Sodium bisulfate	IM–IV; injection	0.32	%
Sodium bisulfite	Auricular (otic); suspension	0.001	%
Sodium bisulfite	IV(infusion); solution, injection	0.024	%
Sodium bisulfite	Ophthalmic; suspension	0.06	%
Sodium bisulfite	Inhalation; inhalant	0.075	%
Sodium bisulfite	Auricular (otic); solution	0.1	%
Sodium bisulfite	Auricular (otic); solution, drops	0.1	%
Sodium bisulfite	Intracardiac; injection	0.1	%
Sodium bisulfite	Ophthalmic; solution	0.1	%
Sodium bisulfite	Ophthalmic; solution, drops	0.1	%
Sodium bisulfite	Soft tissue; injection	0.1	%
Sodium bisulfite	Subcutaneous; injection	0.15	%
Sodium bisulfite	AN, infiltration; injection	0.2	%
Sodium bisulfite	Inhalation; solution	0.2	%
Sodium bisulfite	Intra-articular; injection	0.32	%
Sodium bisulfite	Intralesional; injection	0.32	%
Sodium bisulfite	Intrasynovial; injection	0.32	%
Sodium bisulfite	IM–IV–SC; injection	0.5	%
Sodium bisulfite	IM–IV; injection	0.66	%
Sodium bisulfite	Irrigation; injection	0.66	%
Sodium bisulfite	Intramuscular; injection	1.35	%
Sodium bisulfite	Intraperitoneal; injection	1.35	%
Sodium bisulfite	Nerve block; injection	2.2	%
Sodium bisulfite	Intravenous; injection	5	%

Ingredient	Dosage Form	Qty	Unit
Sodium bisulfite	Intravenous; solution, injection	5	%
Sodium bisulfite	IM–IV; powder, for injection solution	5.18	%
Sodium bisulfite	IV(infusion); injection	10	%
Sodium borate	Ophthalmic; suspension, drops	0.0285	%
Sodium borate	Auricular (otic); solution	0.3	%
Sodium borate	Ophthalmic; solution	0.543	%
Sodium borate	Ophthalmic; solution, drops	1.1	%
Sodium borate decahydrate	Ophthalmic; solution, drops	0.084	%
Sodium borate decahydrate	Ophthalmic; solution	0.15	%
Sodium carbonate	Intravitreal; injection	0.0082	%
Sodium carbonate	Intravenous; injection	0.046	%
Sodium carbonate	IV(infusion); powder, for injection solution, lyophilized	0.177	%
Sodium carbonate	Ophthalmic; solution	1	%
Sodium carbonate	IM–IV; injection	1.64	%
Sodium carbonate	IV(infusion); injection	24.1	%
Sodium carbonate	IV(infusion); powder, for injection solution	63	%
Sodium carbonate	IM–IV; powder, for injection solution	70.8	%
Sodium carbonate decahydrate	Intravenous; injection	12.428	%
Sodium chlorate	IV(infusion); injection	15.4	%
Sodium chloride	Intratracheal; suspension	0.088	%
Sodium chloride	Intra-arterial; powder, for injection solution	0.135	%
Sodium chloride	Intrathecal; powder, for injection solution	0.135	%
Sodium chloride	Subcutaneous; liquid	0.146	%
Sodium chloride	Intravascular; injection	0.187	%
Sodium chloride	Intralesional; suspension, injection	0.22	%
Sodium chloride	Intramuscular; suspension, injection	0.22	%
Sodium chloride	Intrasynovial; suspension, injection	0.22	%
Sodium chloride	Soft tissue; suspension, injection	0.22	%
Sodium chloride	Intramuscular; powder, for injection solution, lyophilized, with additives	0.24	%
Sodium chloride	AN, sympathetic NBLK; injection	0.3	%
Sodium chloride	Intrabursal; injection	0.32	%
Sodium chloride	Auricular (otic); solution, drops	0.362	%
Sodium chloride	Dental; injection	0.6	%
Sodium chloride	Nasal; solution	0.668	%
Sodium chloride	IV–SC; powder, for injection solution	0.68	%
Sodium chloride	Ophthalmic; suspension, drops	0.68	%
Sodium chloride	Intracardiac; injection	0.7	%
Sodium chloride	Intradermal; injection	0.7	%
Sodium chloride	Intraocular; solution	0.7	%
Sodium chloride	IV–SC; liquid	0.7	%
Sodium chloride	IM–IV; solution, injection	0.75	%
Sodium chloride	Intravitreal; injection	0.774	%
Sodium chloride	AN, CNBLK intrathecal; injection	0.8	%

Ingredient	Dosage Form	Qty	Unit
Sodium chloride	Extracorporeal; solution	0.8	%
Sodium chloride	Subcutaneous; suspension, injection	0.8	%
Sodium chloride	Photopheresis; solution	0.8	%
Sodium chloride	Peridural; injection	0.807	%
Sodium chloride	Intracavitary; injection	0.82	%
Sodium chloride	Infiltration; solution, injection	0.85	%
Sodium chloride	Intralesional; injection	0.85	%
Sodium chloride	Ophthalmic; suspension	0.85	%
Sodium chloride	Soft tissue; injection	0.85	%
Sodium chloride	Subcutaneous; injectable	0.85	%
Sodium chloride	AN, infiltration; injection	0.855	%
Sodium chloride	Caudal block; injection	0.9	%
Sodium chloride	Epidural; injection	0.9	%
Sodium chloride	Epidural; solution, injection	0.9	%
Sodium chloride	Extracorporeal; injection	0.9	%
Sodium chloride	IM–IV–SC; injection	0.9	%
Sodium chloride	IM–IV; injectable	0.9	%
Sodium chloride	IM–IV; solution	0.9	%
Sodium chloride	IM–SC; injection	0.9	%
Sodium chloride	Intra-arterial; solution	0.9	%
Sodium chloride	Intra-articular; injection	0.9	%
Sodium chloride	Intralesional; injection, sustained action	0.9	%
Sodium chloride	Intramuscular; injection, sustained action	0.9	%
Sodium chloride	Intramuscular; solution, injection	0.9	%
Sodium chloride	Intrasynovial; injection	0.9	%
Sodium chloride	Intrasynovial; injection, sustained action	0.9	%
Sodium chloride	Intrathecal; injectable	0.9	%
Sodium chloride	Intrathecal; solution, injection	0.9	%
Sodium chloride	Intravenous bolus; solution, injection	0.9	%
Sodium chloride	Intravenous; injectable	0.9	%
Sodium chloride	Intravenous; solution	0.9	%
Sodium chloride	Intravenous; solution, injection	0.9	%
Sodium chloride	Intravitreal; injectable	0.9	%
Sodium chloride	IV(infusion); solution, injection	0.9	%
Sodium chloride	IV(infusion); suspension, injection	0.9	%
Sodium chloride	Nasal; spray	0.9	%
Sodium chloride	Nerve block; injection	0.9	%
Sodium chloride	Nerve block; solution, injection	0.9	%
Sodium chloride	Ophthalmic; powder, for solution	0.9	%
Sodium chloride	Ophthalmic; solution, drops	0.9	%
Sodium chloride	Soft tissue; injection, sustained action	0.9	%
Sodium chloride	Subarachnoid; solution, injection	0.9	%
Sodium chloride	Subcutaneous; injection	0.9	%

Ingredient	Dosage Form	Qty	Unit
Sodium chloride	IV–SC; injection	1	%
Sodium chloride	Respiratory (inhalation); solution, aerosol, for inhalation	1.125	%
Sodium chloride	Intratracheal; injection	1.2	%
Sodium chloride	Intratumor; injection	1.2	%
Sodium chloride	Nasal; spray, metered	1.9	%
Sodium chloride	Respiratory (inhalation); solution	2.7	%
Sodium chloride	Respiratory (inhalation); solution, for inhalation	2.7	%
Sodium chloride	Inhalation; solution	3.16	%
Sodium chloride	Intramuscular; injection	4.5	%
Sodium chloride	Subcutaneous; solution, injection	4.5	%
Sodium chloride	Intratracheal; powder, for suspension	4.676	%
Sodium chloride	Intra-arterial; injection	4.9	%
Sodium chloride	Intrathecal; injection	4.9	%
Sodium chloride	Auricular (otic); solution	9	%
Sodium chloride	Auricular (otic); suspension, liquid	9	%
Sodium chloride	IM–IV; powder, for injection solution	9	%
Sodium chloride	Intrathecal; injection, suspension, liposomal	9	%
Sodium chloride	Submucosal; solution, injection	16	%
Sodium chloride	IM–IV; powder, for injection solution, lyophilized	18	%
Sodium chloride	Intramuscular; powder, for injection solution	22.6	%
Sodium chloride	Intraperitoneal; powder, for injection solution	22.6	%
Sodium chloride	Intrapleural; powder, for injection solution	22.6	%
Sodium chloride	Intravenous; powder, for injection solution, lyophilized	45	%
Sodium chloride	IV(infusion); powder, for injection solution	45	%
Sodium chloride	Intravenous; powder, for injection solution	45.2	%
Sodium chloride	Intraperitoneal; solution	53.5	%
Sodium chloride	Ophthalmic; solution	55	%
Sodium chloride	Subcutaneous; implant	77	mg
Sodium chloride	IM–IV; injection	90	%
Sodium chloride	Intravenous; injection	90	%
Sodium chloride	IV(infusion); injection	90	%
Sodium chlorite	Ophthalmic; solution, drops	0.005	%
Sodium cholesteryl sulfate	IV(infusion); powder, for injection suspension, lyophilized	5.676	%
Sodium citrate	Intracavitary; powder, for injection solution, lyophilized	0.0053	%
Sodium citrate	IM–IV; solution	0.025	%
Sodium citrate	Intravenous; injectable	0.025	%
Sodium citrate	Nasal; spray, metered	0.032	%
Sodium citrate	AN, infiltration; injection	0.0395	%
Sodium citrate	Nerve block; injection	0.0395	%
Sodium citrate	Intravenous; solution, injection	0.065	%
Sodium citrate	Respiratory (inhalation); powder, for inhalation	0.138	%
Sodium citrate	Intracavitary; injection	0.15	%
Sodium citrate	Ophthalmic; powder, for solution	0.17	%

Ingredient	Dosage Form	Qty	Unit
Sodium citrate	IM–SC; injection	0.228	%
Sodium citrate	Ophthalmic; suspension	0.3	%
Sodium citrate	Intravascular; injection	0.32	%
Sodium citrate	Intraocular; solution	0.4	%
Sodium citrate	Nasal; spray	0.44	%
Sodium citrate	Ophthalmic; suspension, drops	0.45	%
Sodium citrate	Inhalation; solution	0.6	%
Sodium citrate	IV(infusion); solution, injection	0.6	%
Sodium citrate	Intramuscular; injectable	0.6214	%
Sodium citrate	Intramuscular; powder, for injection solution, lyophilized	0.645	%
Sodium citrate	Subcutaneous; powder, for injection solution, lyophilized	0.645	%
Sodium citrate	Intracardiac; injection	0.8	%
Sodium citrate	Intravenous; solution	0.8295	%
Sodium citrate	IM–IV–SC; injection	0.94	%
Sodium citrate	Intralesional; injection	1	%
Sodium citrate	Intrasynovial; injection	1	%
Sodium citrate	Soft tissue; injection	1	%
Sodium citrate	Intramuscular; solution, injection	1.301	%
Sodium citrate	Subcutaneous; solution, injection	1.301	%
Sodium citrate	IM–IV; injectable	1.35	%
Sodium citrate	Auricular (otic); solution	2	%
Sodium citrate	Ophthalmic; solution	2	%
Sodium citrate	Epidural; injection	2.2	%
Sodium citrate	Intra-articular; injection	2.2	%
Sodium citrate	Irrigation; injection	2.2	%
Sodium citrate	Ophthalmic; solution, drops	2.2	%
Sodium citrate	Intramuscular; powder, for injection solution	4.62	%
Sodium citrate	Intrapleural; powder, for injection solution	4.62	%
Sodium citrate	Intrathecal; powder, for injection solution	4.62	%
Sodium citrate	Intramuscular; injection	6.6	%
Sodium citrate	Intraperitoneal; injection	6.6	%
Sodium citrate	IV(infusion); powder, for injection solution	8	%
Sodium citrate	IV(infusion); powder, for injection solution, lyophilized	14	%
Sodium citrate	Intravenous; powder, for injection solution, lyophilized	16.35	%
Sodium citrate	Intravenous; powder, for injection solution	16.4	%
Sodium citrate	Intravenous; injection	30	%
Sodium citrate	IM–IV; injection	40	%
Sodium citrate	IV(infusion); injection	40	%
Sodium citrate	Nasal; solution	70	%
Sodium citrate, anhydrous	Nasal; spray, metered	0.0007	%
Sodium citrate, anhydrous	Intra-articular; injection	1	%
Sodium citrate, anhydrous	Intrabursal; injection	1	%
Sodium citrate, anhydrous	Intravenous; powder, for injection solution	6.99	%

Ingredient	Dosage Form	Qty	Unit
Sodium citrate, anhydrous	IM–IV; injection	16	%
Sodium citrate, anhydrous	IV(infusion); injection	16	%
Sodium desoxycholate	IV(infusion); powder, for injection solution	4.1	%
Sodium dithionite	IM–IV–SC; injection	0.1	%
Sodium dithionite	IV(infusion); injection	2	%
Sodium dithionite	Intravenous; injection	3	%
Sodium formaldehyde sulfoxylate	IM–IV; injection	0.1	%
Sodium formaldehyde sulfoxylate	IM–SC; injection	0.1	%
Sodium formaldehyde sulfoxylate	Intramuscular; injection	0.2	%
Sodium formaldehyde sulfoxylate	IV(infusion); injection	1.1	%
Sodium gluconate	IV(infusion); powder, for injection solution, lyophilized	0.1	%
Sodium gluconate	Intravenous; injection	2.3	%
Sodium hydroxide	Nasal; spray, metered	0.004	%
Sodium hydroxide	Intravenous; solution, injection	0.035	%
Sodium hydroxide	AN, infiltration; injection	0.0706	%
Sodium hydroxide	Nerve block; injection	0.0706	%
Sodium hydroxide	Ophthalmic; solution	0.1	%
Sodium hydroxide	IM–IV; solution, injection	0.134	%
Sodium hydroxide	Subcutaneous; suspension, injection	0.22	%
Sodium hydroxide	Ophthalmic; emulsion	0.397	%
Sodium hydroxide	Subcutaneous; injectable	0.42	%
Sodium hydroxide	IM–IV; powder, for injection solution	0.701	%
Sodium hydroxide	Auricular (otic); solution	0.8	%
Sodium hydroxide	IV(infusion); powder, for injection solution, lyophilized	1.565	%
Sodium hydroxide	IV(infusion); solution, injection	2.83	%
Sodium hydroxide	Intramuscular; injection	3.145	%
Sodium hydroxide	Subcutaneous; injection	3.145	%
Sodium hydroxide	Inhalation; solution	8	%
Sodium hydroxide	IV(infusion); powder, for injection solution	9	%
Sodium hydroxide	Intravenous; injection	10	%
Sodium hydroxide	IM–IV; injection	10.68	%
Sodium hydroxide	IV(infusion); injection	13	%
Sodium hydroxide	Intravenous; powder, for injection solution	13.655	%
Sodium hydroxide	Intravenous; powder, for injection solution, lyophilized	19.27	%
Sodium hypochlorite	IV(infusion); injection	1	%
Sodium iodide	Intravenous; injection	1	%
Sodium iodide	Intravenous; powder, for injection solution	5	%
Sodium lactate	Caudal block; injection	0.0001	%
Sodium lactate	Intravenous; injection	0.17	%
Sodium lactate	Nerve block; injection	0.17	%
Sodium lactate	Intravenous; powder, for injection solution, lyophilized	1.87	%
Sodium lactate	Intraperitoneal; solution	44.8	%
L-Sodium lactate	IM–IV–SC; injection	0.18	%

Ingredient	Dosage Form	Qty	Unit
L-Sodium lactate	Intracardiac; injection	0.18	%
L-Sodium lactate	IV(infusion); injection	0.18	%
Sodium lauryl sulfate	Dental; gel	1.47	%
Sodium metabisulfite	Intravenous; emulsion, injection	0.025	%
Sodium metabisulfite	Intravenous; solution, injection	0.05	%
Sodium metabisulfite	Intracardiac; injection	0.09	%
Sodium metabisulfite	Ophthalmic; suspension, drops	0.1	%
Sodium metabisulfite	IM–IV–SC; injection	0.15	%
Sodium metabisulfite	Caudal block; injection	0.183	%
Sodium metabisulfite	Epidural; injection	0.183	%
Sodium metabisulfite	Intra-articular; injection	0.2	%
Sodium metabisulfite	Intrabursal; injection	0.2	%
Sodium metabisulfite	Ophthalmic; solution	0.2	%
Sodium metabisulfite	Ophthalmic; solution, drops	0.25	%
Sodium metabisulfite	Subcutaneous; injection	0.3016	%
Sodium metabisulfite	Intravenous; injection	0.32	%
Sodium metabisulfite	AN, infiltration; injection	0.5	%
Sodium metabisulfite	Nerve block; injection	0.5	%
Sodium metabisulfite	Intraperitoneal; injection	0.66	%
Sodium metabisulfite	Inhalation; solution	1	%
Sodium metabisulfite	IV(infusion); injection	1.1	%
Sodium metabisulfite	Submucosal; solution, injection	5	%
Sodium metabisulfite	IV(infusion); solution, injection	22	%
Sodium metabisulfite	IM–IV; injection	27.5	%
Sodium metabisulfite	Intramuscular; injection	27.5	%
Sodium nitrate	Ophthalmic; solution	1.18	%
Sodium phosphate	Nerve block; injection	0.02	%
Sodium phosphate	Intramuscular; powder, for injection solution	0.1	%
Sodium phosphate	IM–IV; solution, injection	0.17	%
Sodium phosphate	Nasal; solution	0.189	%
Sodium phosphate	Intradermal; injection	0.2	%
Sodium phosphate	Ophthalmic; suspension	0.2	%
Sodium phosphate	Ophthalmic; solution, drops	0.29	%
Sodium phosphate	IM–IV; injection	0.3	%
Sodium phosphate	Subcutaneous; injection	0.378	%
Sodium phosphate	Intramuscular; injection	0.425	%
Sodium phosphate	IV(infusion); injection	0.79	%
Sodium phosphate	Ophthalmic; solution	0.81	%
Sodium phosphate	Intravenous; powder, for injection solution	1	%
Sodium phosphate	Intravenous; injection	1.6	%
Sodium phosphate	IM–IV; powder, for injection solution	2.475	%
Sodium phosphate dihydrate	Ophthalmic; solution	0.03	%
Sodium phosphate dihydrate	Subcutaneous; powder, for injection solution, lyophilized	0.13	%

Ingredient	Dosage Form	Qty	Unit
Sodium phosphate dihydrate	Subcutaneous; injection	0.24	%
Sodium phosphate, dibasic	Subcutaneous; suspension, injection	0.0588	%
Sodium phosphate, dibasic	Intralesional; suspension, injection	0.142	%
Sodium phosphate, dibasic	Intramuscular; suspension, injection	0.142	%
Sodium phosphate, dibasic	Intrasynovial; suspension, injection	0.142	%
Sodium phosphate, dibasic	Soft tissue; suspension, injection	0.142	%
Sodium phosphate, dibasic	Intradermal; injection	0.2	%
Sodium phosphate, dibasic	Ophthalmic; solution	0.29	%
Sodium phosphate, dibasic	Subcutaneous; powder, for injection solution, lyophilized	0.298	%
Sodium phosphate, dibasic	Ophthalmic; suspension	0.43	%
Sodium phosphate, dibasic	Intravenous; injection	0.76	%
Sodium phosphate, dibasic	IM–IV; injectable	1.74	%
Sodium phosphate, dibasic, anhydrous	Nasal; spray	0.011	%
Sodium phosphate, dibasic, anhydrous	Intramuscular; powder, for injection solution, lyophilized	0.03	%
Sodium phosphate, dibasic, anhydrous	Subcutaneous; powder, for injection solution, lyophilized	0.03	%
Sodium phosphate, dibasic, anhydrous	Subcutaneous; injectable	0.104	%
Sodium phosphate, dibasic, anhydrous	Intramuscular; injectable	0.24	%
Sodium phosphate, dibasic, anhydrous	Intravenous; injectable	0.24	%
Sodium phosphate, dibasic, anhydrous	Ophthalmic; suspension	0.25	%
Sodium phosphate, dibasic, anhydrous	Intramuscular; injection	0.29	%
Sodium phosphate, dibasic, anhydrous	Intravenous; solution, injection	0.76	%
Sodium phosphate, dibasic, anhydrous	Auricular (otic); solution, drops	0.7954	%
Sodium phosphate, dibasic, anhydrous	Ophthalmic; solution	1.28	%
Sodium phosphate, dibasic, anhydrous	Ophthalmic; solution, drops	1.4	%
Sodium phosphate, dibasic, anhydrous	Intravenous; powder, for injection solution, lyophilized	1.5	%
Sodium phosphate, dibasic, anhydrous	IM–IV; injectable	1.746	%
Sodium phosphate, dibasic, anhydrous	IV(infusion); injection	4	%
Sodium phosphate, dibasic, anhydrous	IM–IV; injection	13.92	%
Sodium phosphate, dibasic, anhydrous	IM–IV; powder, for injection solution	13.92	%
Sodium phosphate, dibasic, anhydrous	IV(Infusion); powder, for injection solution	13.92	%
Sodium phosphate, dibasic, anhydrous	Intravenous; injection	21.3	%
Sodium phosphate, dibasic, dihydrate	Subcutaneous; powder, for injection solution, lyophilized	0.111	%
Sodium phosphate, dibasic, dihydrate	Subcutaneous; injection	0.1665	%
Sodium phosphate, dibasic, dihydrate	Subcutaneous; injectable	0.18	%
Sodium phosphate, dibasic, dihydrate	Nasal; spray, metered	0.3	%
Sodium phosphate, dibasic, dihydrate	Ophthalmic; solution	1.081	%
Sodium phosphate, dibasic, dihydrate	Ophthalmic; solution, drops	1.201	%
Sodium phosphate, dibasic, dodecahydrate	Nasal; spray, metered	14.3	%
Sodium phosphate, dibasic, heptahydrate	AN, infiltration; injection	0.02	%
Sodium phosphate, dibasic, heptahydrate	Nerve block; injection	0.02	%
Sodium phosphate, dibasic, heptahydrate	IM–SC; injection	0.0268	%
Sodium phosphate, dibasic, heptahydrate	Nasal; solution	0.0452	%
Sodium phosphate, dibasic, heptahydrate	Intramuscular; injection, sustained action	0.067	%

Ingredient	Dosage Form	Qty	Unit
Sodium phosphate, dibasic, heptahydrate	Intravitreal; injectable	0.12	%
Sodium phosphate, dibasic, heptahydrate	Subcutaneous; injectable	0.188	%
Sodium phosphate, dibasic, heptahydrate	Subcutaneous; powder, for injection solution, lyophilized	0.209	%
Sodium phosphate, dibasic, heptahydrate	Subcutaneous; injection	0.378	%
Sodium phosphate, dibasic, heptahydrate	Subcutaneous; suspension, injection	0.378	%
Sodium phosphate, dibasic, heptahydrate	Intravenous; injection	0.43	%
Sodium phosphate, dibasic, heptahydrate	Ophthalmic; suspension, drops	0.431	%
Sodium phosphate, dibasic, heptahydrate	Nasal; spray, metered	0.486	%
Sodium phosphate, dibasic, heptahydrate	Auricular (otic); solution	0.5	%
Sodium phosphate, dibasic, heptahydrate	Intramuscular; powder, for injection solution	0.543	%
Sodium phosphate, dibasic, heptahydrate	Subcutaneous; powder, for injection solution	0.543	%
Sodium phosphate, dibasic, heptahydrate	IM–IV; solution, injection	0.566	%
Sodium phosphate, dibasic, heptahydrate	Ophthalmic; suspension	0.866	%
Sodium phosphate, dibasic, heptahydrate	Ophthalmic; solution	1.206	%
Sodium phosphate, dibasic, heptahydrate	IV(infusion); powder, for injection solution	1.58	%
Sodium phosphate, dibasic, heptahydrate	Ophthalmic; solution, drops	2.5	%
Sodium phosphate, dibasic, heptahydrate	Intravenous; powder, for injection solution	2.9	%
Sodium phosphate, dibasic, heptahydrate	IM–IV; powder	3.627	%
Sodium phosphate, dibasic, heptahydrate	Intramuscular; powder, for injection solution, lyophilized	4.8	%
Sodium phosphate, dibasic, heptahydrate	IM–IV; injection	6.96	%
Sodium phosphate, dibasic, heptahydrate	IV(infusion); injection	10.3	%
Sodium phosphate, dibasic, heptahydrate	IM–IV; powder, for injection solution	27.927	%
Sodium phosphate, monobasic	Ophthalmic; solution, drops	0.01	%
Sodium phosphate, monobasic	Subcutaneous; powder, for injection solution, lyophilized	0.022	%
Sodium phosphate, monobasic	Subcutaneous; suspension, injection	0.0694	%
Sodium phosphate, monobasic	IM–IV; injectable	0.16	%
Sodium phosphate, monobasic	Ophthalmic; solution	0.19	%
Sodium phosphate, monobasic	Intramuscular; injection	0.5747	%
Sodium phosphate, monobasic	Intralesional; suspension, injection	0.68	%
Sodium phosphate, monobasic	Intramuscular; suspension, injection	0.68	%
Sodium phosphate, monobasic	Intrasynovial; suspension, injection	0.68	%
Sodium phosphate, monobasic	Soft tissue; suspension, injection	0.68	%
Sodium phosphate, monobasic	IV(infusion); powder, for injection solution	1.32	%
Sodium phosphate, monobasic	IM–IV; injection	1.472	%
Sodium phosphate, monobasic, anhydrous	Intravascular; injection	0.0125	%
Sodium phosphate, monobasic, anhydrous	Nasal; spray, metered	0.019	%
Sodium phosphate, monobasic, anhydrous	Ophthalmic; suspension, drops	0.056	%
Sodium phosphate, monobasic, anhydrous	Subcutaneous; powder, for injection solution	0.08	%
Sodium phosphate, monobasic, anhydrous	Subcutaneous; powder, for injection solution, lyophilized	0.11	%
Sodium phosphate, monobasic, anhydrous	Auricular (otic); solution, drops	0.128	%
Sodium phosphate, monobasic, anhydrous	Intramuscular; injection	0.5	%
Sodium phosphate, monobasic, anhydrous	Intramuscular; powder, for injection solution	0.5	%
Sodium phosphate, monobasic, anhydrous	Intravenous; injection	0.5	%
Sodium phosphate, monobasic, anhydrous	IV(infusion); injection	0.5	%

Ingredient	Dosage Form	Qty	Unit
Sodium phosphate, monobasic, anhydrous	IM–IV; solution, injection	0.62	%
Sodium phosphate, monobasic, anhydrous	Ophthalmic; suspension	0.65	%
Sodium phosphate, monobasic, anhydrous	Intravenous; powder, for injection solution	0.71	%
Sodium phosphate, monobasic, anhydrous	Ophthalmic; solution	0.725	%
Sodium phosphate, monobasic, anhydrous	Ophthalmic; solution, drops	0.78	%
Sodium phosphate, monobasic, anhydrous	Intramuscular; powder, for injection solution, lyophilized	1.2	%
Sodium phosphate, monobasic, anhydrous	IM–IV; injection	1.28	%
Sodium phosphate, monobasic, anhydrous	IM–IV; powder, for injection solution	1.28	%
Sodium phosphate, monobasic, anhydrous	IV(infusion); powder, for injection solution	1.28	%
Sodium phosphate, monobasic, anhydrous	Subcutaneous; injection	3.31	%
Sodium phosphate, monobasic, anhydrous	Intravenous; solution	4	%
Sodium phosphate, monobasic, dihydrate	Subcutaneous; powder, for injection solution, lyophilized	0.045	%
Sodium phosphate, monobasic, dihydrate	IV(infusion); powder, for injection solution	0.16	%
Sodium phosphate, monobasic, dihydrate	Intravenous; injection	0.76	%
Sodium phosphate, monobasic, dihydrate	Ophthalmic; solution, drops	1.053	%
Sodium phosphate, monobasic, dihydrate	Ophthalmic; solution	1.158	%
Sodium phosphate, monobasic, dihydrate	Nasal; spray, metered	4.2	%
Sodium phosphate, monobasic, monohydrate	Subcutaneous; injectable	0.036	%
Sodium phosphate, monobasic, monohydrate	Intravenous; powder, for injection solution	0.0495	%
Sodium phosphate, monobasic, monohydrate	Subcutaneous; injection	0.0675	%
Sodium phosphate, monobasic, monohydrate	Intravitreal; injectable	0.077	%
Sodium phosphate, monobasic, monohydrate	Intravenous; solution, injection	0.18	%
Sodium phosphate, monobasic, monohydrate	IM–IV; powder	0.202	%
Sodium phosphate, monobasic, monohydrate	IM–IV; injection	0.5	%
Sodium phosphate, monobasic, monohydrate	IV(infusion); injection	0.5	%
Sodium phosphate, monobasic, monohydrate	Ophthalmic; suspension	0.538	%
Sodium phosphate, monobasic, monohydrate	Ophthalmic; solution	0.54	%
Sodium phosphate, monobasic, monohydrate	Ophthalmic; solution, drops	0.721	%
Sodium phosphate, monobasic, monohydrate	IV(infusion); powder, for injection solution	1.3606	%
Sodium phosphate, monobasic, monohydrate	IM–IV; powder, for injection solution	1.555	%
Sodium phosphate, monobasic, monohydrate	Intravenous; injection	6.21	%
Sodium phosphate, monobasic, monohydrate	N/A; not applicable	600	mg
Sodium pyrophosphate	Intravenous; injection	1.2	%
Sodium succinate	Intravenous; injection, powder, lyophilized, for liposomal suspension	2.7	%
Sodium sulfate	Ophthalmic; solution	0.226	%
Sodium sulfate	Ophthalmic; suspension	1.2	%
Sodium sulfate decahydrate	Ophthalmic; solution, drops	0.09	%
Sodium sulfate, anhydrous	Inhalation; solution	0.025	%
Sodium sulfate, anhydrous	Ophthalmic; solution	0.152	%
Sodium sulfate, anhydrous	Ophthalmic; solution, drops	0.17	%
Sodium sulfate, anhydrous	Ophthalmic; suspension	1.2	%
Sodium sulfite	Auricular (otic); solution	0.02	%
Sodium sulfite	Intramuscular; injection	0.05	%
Sodium sulfite	Subcutaneous; injection	0.09	%

Ingredient	Dosage Form	Qty	Unit
Sodium sulfite	Epidural; injection	0.1	%
Sodium sulfite	Inhalation; solution	0.1	%
Sodium sulfite	Intra-articular; injection	0.1	%
Sodium sulfite	Intravenous; injection	0.1	%
Sodium sulfite	IM–IV; injection	0.2	%
Sodium sulfite	Ophthalmic; solution, drops	0.2	%
Sodium tartrate	IM–IV; injection	1.2	%
Sodium tartrate	Intravenous; injection	1.2	%
Sodium tartrate	IV(infusion); injection	1.2	%
Sodium tartrate	Intramuscular; injection	1.41	%
Sodium thioglycolate	Subcutaneous; injection	0.66	%
Sodium thiosulfate	Ophthalmic; solution, drops	0.31	%
Sodium thiosulfate	Ophthalmic; suspension, drops	0.314	%
Sodium thiosulfate	Ophthalmic; suspension	0.32	%
Sodium thiosulfate	Ophthalmic; solution	5	%
Sodium thiosulfate, anhydrous	Intravenous; solution	0.19	%
Sorbic acid	Ophthalmic; solution	0.2	%
Sorbitan trioleate	Nasal; aerosol, metered	0.0175	%
Sorbitan trioleate	Inhalation; aerosol, metered	0.0694	%
Sorbitol	Ophthalmic; solution, drops	0.25	%
Sorbitol	Nasal; solution	2.5	%
Sorbitol	Nasal; spray, metered	2.86	%
Sorbitol	Intravenous; solution, injection	7.14	%
Sorbitol	IV(infusion); solution, injection	7.14	%
Sorbitol	Intravenous; injection	30	%
Sorbitol	Intra-articular; injection	45	%
Sorbitol	Intralesional; injection	45	%
Sorbitol	Intrasynovial; injection	45	%
Sorbitol solution	Intravenous; injection	7.14	%
Sorbitol solution	Intravenous; solution, injection	7.14	%
Sorbitol solution	IV(infusion); solution, injection	7.14	%
Sorbitol solution	Intramuscular; injection	25	%
Sorbitol solution	Ophthalmic; solution, drops	39.9996	%
Soybean oil	Intravenous; emulsion, injection	10	%
Soybean oil	Intravenous; injectable	10	%
Stannous chloride	IV(infusion); powder, for injection solution, lyophilized	0.003	%
Stannous chloride	Intravenous; powder, for injection solution	0.025	%
Stannous chloride	IV(infusion); injection	0.05	%
Stannous chloride	Intravenous; injection	0.34	%
Stannous chloride, anhydrous	Intravenous; injection	0.005	%
Stannous fluoride	Intravenous; injection	0.073	%
Stannous tartrate	Intravenous; injection	0.008	%
Starch	Intramuscular; injection	0.6	%

Ingredient	Dosage Form	Qty	Unit
Stearic acid	Implantation; pellet	0.2	mg
Stearic acid	Subcutaneous; implant	1.04	mg
Sucrose	Subcutaneous; powder, for injection solution, lyophilized, with additives	4.104	%
Sucrose	Intramuscular; solution, injection	4.425	%
Sucrose	Subcutaneous; solution, injection	4.425	%
Sucrose	IV(infusion); powder, for injection solution, lyophilized	5.4	%
Sucrose	Intramuscular; powder, for injection solution, lyophilized	6.84	%
Sucrose	Subcutaneous; powder, for injection solution, lyophilized	6.84	%
Sucrose	Intravenous; powder, for injection solution, lyophilized	7.78	%
Sucrose	Intravenous; solution, liposome, injection	8.5	%
Sucrose	Subcutaneous; injection	9	%
Sucrose	Intravenous; injection, suspension, liposomal	9.4	%
Sucrose	Intravenous; injection	19.5	%
Sucrose	Intravenous; injection, powder, lyophilized, for liposomal suspension	90	%
Sulfur dioxide	IV(infusion); solution, injection	0.15	%
Sulfuric acid	Ophthalmic; solution, drops	0.02	%
Sulfuric acid	Auricular (otic); suspension	0.023	%
Sulfuric acid	Nasal; spray	0.4	%
Sulfuric acid	Intramuscular; injection	2.098	%
Sulfuric acid	Intravenous; injection	2.098	%
Sulfuric acid	IV(infusion); injection	2.12	%
Sulfuric acid	Inhalation; solution	12.5	%
Sulfuric acid	IM–IV; injection	56.6	%
Tartaric acid	Intravenous; injection	0.2	%
Tartaric acid	Intravenous; solution, injection	0.2	%
Tartaric acid	Intramuscular; injection	0.35	%
Tartaric acid	IV(infusion); powder, for injection solution, lyophilized	2	%
Tetrofosmin	IV(infusion); powder, for injection solution, lyophilized	0.023	%
Theophylline, anhydrous	Intravenous; injection	1.973	%
Theophylline, anhydrous	IV(infusion); injection	2.053	%
Thimerosal	Intramuscular; injection, sustained action	0.002	%
Thimerosal	Ophthalmic; suspension	0.004	%
Thimerosal	Intramuscular; injection	0.0084	%
Thimerosal	Auricular (otic); suspension	0.01	%
Thimerosal	Ophthalmic; solution	0.01	%
Thimerosal	Ophthalmic; solution, drops	0.01	%
Thimerosal	Subcutaneous; injection	0.01	%
Thimerosal	Ophthalmic; suspension, drops	1	%
Thioglycerol	Nerve block; injection	0.0001	%
Thioglycerol	IM–IV; injection	0.5	%
Thioglycerol	Intramuscular; injection	1	%
Thioglycerol	Intravenous; injection	1	%
Threonine	IV(infusion); solution, injection	12	%

Ingredient	Dosage Form	Qty	Unit
Threonine	IV(infusion); injection	45	%
Thymol	Inhalation; liquid	0.01	%
Tin	Intravenous; injection	0.0083	%
Titanium dioxide	Ophthalmic; suppository, insert, controlled release	0.4	mg
Titanium dioxide	Intrauterine; suppository, insert, controlled release	1	mg
Tocophersolan	Ophthalmic; solution, drops	0.5	%
Tricaprylin	Epidural; injection, suspension, liposomal	0.03	%
Trichloromonofluoromethane	Nasal; aerosol, metered	0.9	%
Trichloromonofluoromethane	Inhalation; aerosol, metered	33.831	%
Triolein	Epidural; injection, suspension, liposomal	0.01	%
Trisodium citrate dihydrate	Intravenous; injectable	0.023	%
Trisodium citrate dihydrate	IM–IV; injectable	0.025	%
Trisodium citrate dihydrate	IM–IV; solution	0.025	%
Trisodium citrate dihydrate	Ophthalmic; solution	0.14	%
Tromethamine	IV(infusion); injection	0.005	%
Tromethamine	Respiratory (inhalation); solution, for inhalation	0.0121	%
Tromethamine	Intramuscular; injection	0.1	%
Tromethamine	Intra-arterial; injection	0.242	%
Tromethamine	Ophthalmic; solution, drops	0.5	%
Tromethamine	Subcutaneous; injection	0.6	%
Tromethamine	Ophthalmic; solution, gel forming, extended release	0.8	%
Tromethamine	Ophthalmic; solution	0.936	%
Tromethamine	Intravascular; injection	1	%
Tromethamine	Intravenous; injection	1	%
Tromethamine	IM–IV; injectable	1.1	%
Tromethamine	IM–IV; injection, solution	1.211	%
Tromethamine	IV(infusion); powder, for injection suspension, lyophilized	1.213	%
Tryptophan	IV(infusion); solution, injection	4.6	%
Tryptophan	IV(infusion); injection	15.2	%
Tyloxapol	Ophthalmic; solution	0.1	%
Tyloxapol	Ophthalmic; solution, drops	0.1	%
Tyloxapol	Ophthalmic; suspension	0.3	%
Tyloxapol	Ophthalmic; suspension, drops	0.3	%
Tyrosine	IV(infusion); injection	3.4	%
Valine	IV(infusion); solution, injection	20	%
Valine	IV(infusion); injection	84	%
Versetamide	Intravenous; injection	2.54	%
Xanthan gum	Ophthalmic; solution, gel forming, extended release	0.6	%
Zinc	Subcutaneous; injectable	0.0065	%
Zinc	Subcutaneous; injection	0.015	%
Zinc	Subcutaneous; suspension, injection	3.27	%
Zinc acetate	Subcutaneous; powder, for injection suspension	0.23	%
Zinc carbonate	Subcutaneous; powder, for injection suspension	0.16	%

Ingredient	Dosage Form	Qty	Unit
Zinc chloride	Ophthalmic; solution, drops	0.0025	%
Zinc chloride	Subcutaneous; injectable	0.0063	%
Zinc chloride	Subcutaneous; injection	0.015	%
Zinc chloride	Intradermal; injection	0.04	%
Zinc oxide	Subcutaneous; injectable	0.002	%
Zinc oxide	Subcutaneous; suspension, injection	0.0025	%
Zinc oxide	Subcutaneous; injection	0.019	%
Zinc oxide	Respiratory (inhalation); solution, injection	3.114	%

Part II

Manufacturing Formulations

Abciximab Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Abciximab	2.00	g
0.01	M	2	Sodium phosphate	0.01	M
0.15	M	3	Sodium chloride	0.15	M
0.001	%	4	Polysorbate 80	0.001	%
QS	mL	5	Water for injection	QS to 1.00	L

Manufacturing Directions

1. Abciximab is the Fab fragment of the chimeric human-murine monoclonal antibody 7E3.
2. Abciximab binds to the glycoprotein (GP) IIb/IIIa receptor of human platelets and inhibits platelet aggregation. Abciximab also binds to the vitronectin ($alpha_v beta_3$) receptor found on platelets and vessel wall endothelial and smooth muscle cells.
3. The chimeric 7E3 antibody is produced by continuous perfusion in mammalian cell culture. The 47615 Da Fab fragment is purified from cell culture supernatant by a series of steps involving specific viral inactivation and removal procedures, digestion with papain, and column chromatography.
4. It is a clear, colorless sterile nonpyrogenic solution for intravenous (IV) use (pH 7.2). No preservatives are added.

Acetazolamide Injection

Bill of Materials					
Scale/Vial		Item	Material	Qty	UOM
500.00	mg	1	Acetazolamide sodium	500.00	mg
QS	mL	2	Sodium hydroxide[a]	QS	mL
QS	mL	3	Hydrochloric acid[a]	QS	mL

[a] For pH adjustment.

Description

Supplied as a sterile powder requiring reconstitution. The bulk solution is adjusted to pH 9.2 prior to lyophilization.

Acetylcholine Chloride Intraocular Solution

Bill of Materials for Lower Chamber					
Scale/Vial		Item	Material	Qty	UOM
20.00	mg	1	Acetylcholine chloride	20.00	mg
56.00	mg	2	Mannitol	56.00	mg

Description

Acetylcholine chloride intraocular solution is a parasympathomimetic preparation for intraocular use packaged in a vial of two compartments. The reconstituted liquid will be a sterile isotonic solution (275–330 mOsm/kg) containing 20 mg acetylcholine chloride (1:100 solution) and 2.8% mannitol. The pH range is 5.0 to 8.2. Mannitol is used in the process of lyophilizing acetylcholine chloride and is not considered an active ingredient. Diluet includes sodium acetate trihydrate, potassium chloride, magnesium chloride hexahydrate, calcium chloride in sterile water for injection.

Acyclovir Sodium Injection

Bill of Materials per Vial (10 mL)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Acyclovir	500.00	mg
4.90	mg	2	Sodium	49.00	mg
QS	mL	3	Sterile water for injection, USP (for reconstitution)	10.00	mL

Description

Acyclovir sodium for injection is a sterile lyophilized powder for IV administration only. The pH of the reconstituted solution is ca. 11. Further dilution in any appropriate IV solution must be performed before infusion.

Adenosine 5′ Monophosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Adenosine 5′ monophosphate	200.00	g
1.50	%	2	Benzyl alcohol, NF	1.50	%
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Sodium hydroxide for pH adjustment	QS	mL

Adenosine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3.00	mg	1	Adenosine	3.00	g
9.00	mg	2	Sodium chloride	9.00	g
QS	mL	3	Water for injection	QS to 1.00	L

Adjust pH to 4.7 to 5.0.

Adrenal Cortex Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Adrenal cortex equivalent to 200 mg hydrocortisone reference standard, USP	200.00	mg
1:20,000	—	2	Thimerosal as preservative	1:20,000	—
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Sodium acetate for buffering	QS	mL
QS	mL	5	Acetic acid for buffering	QS	mL

Adrenaline Tartarate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.80	mg	1	Adrenaline bitartrate (1:1000)[a]	1.80	g
1.00	mg	2	Sodium metabisulfite	1.00	g
8.00	mg	3	Sodium chloride NF	8.00	g
QS	L	4	Water for injection, USP	QS to 1.00	L

[a] Contains not less than 0.09% and not more than 0.115% w/v of adrenaline.

Manufacturing Directions

1. Boil item 4 and allow to cool to room temperature; check for suitability by pH and electrical conductivity.
2. Add and mix items 1, 2, and 3 and stir to dissolve all ingredients.
3. Check and record pH 2.9 to 3.6. Sample.
4. Filter through 0.22-μm filter.
5. Fill 1.1 mL into amber ampoules.
6. Heat-sterilize at 121°C for 30 minutes. Sample.
7. Check for clarity. Sample.

Alatrofloxacin Mesylate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
7.86	mg	1	Alatrofloxacin mesylate	7.86	g
QS	mL	2	Hydrochloric acid for pH adjustment	QS	mL
QS	mL	3	Sodium hydroxide for pH adjustment	QS	mL
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take 0.9 L of item 4 and dissolve item 1 in it.
2. Check and adjust pH to 4.0 (3.7–4.1) by item 2 or 3.

An isotonic form of the above is obtained as follows.

3. Filter and fill 30 mL into a 40-mL vial or ampoule.
4. Autoclave at 115°C for 15 minutes.
5. Finish and sample.

Alatrofloxacin Mesylate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3.14	mg	1	Alatrofloxacin mesylate	3.14	g
5.00	mg	2	Dextrose, USP	5.00	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	mL
QS	mL	4	Sodium hydroxide for pH adjustment	QS	mL
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take 0.9 L of item 5 and dissolve items 1 and 2 in it.
2. Check and adjust pH to 4.0 (3.7–4.1) by item 3 or 4.

A lyophilized form of the above is obtained as follows:

3. Filter and fill 30 mL into a 40-mL vial.
4. Autoclave at 115°C for 15 minutes.
5. Finish and sample. Final concentration is 3.14 mg/mL.

Alatrofloxacin Mesylate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3.14	mg	1	Alatrofloxacin mesylate	3.14	g
5.00	mg	2	Lactose, USP	5.00	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	mL
QS	mL	4	Sodium hydroxide for pH adjustment	QS	mL
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take 0.9 L of item 5 and dissolve items 1 and 2 in it.
2. Check and adjust pH to 4.0 (3.7–4.1) by item 3 or 4.
3. Filter and fill 30 mL into a 40-mL vial.
4. Lyophilize for 24 hours under a 0.1-atm vacuum.
5. Autoclave at 115°C for 15 minutes.
6. Finish and sample. Final concentration is 3.14 mg/mL.

Alatrofloxacin Mesylate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Trovafloxacin, use alatrofloxacin mesylate	5.00	g
QS	mL	2	Sodium hydroxide[a]	QS	mL
QS	mL	3	Hydrochloric acid[a]	QS	mL
QS	mL	4	Water for injection	QS to 1.00	L

[a] For pH adjustment.

Description

Available in 40- and 60-mL single-use vials as a sterile, preservative-free aqueous concentrate intended for dilution prior to IV administration of doses of 200 or 300 mg of trovafloxacin, respectively. The pH range for the 5 mg/mL aqueous concentrate is 3.5 to 4.3.

Albumin (Human)

Albumin (human), USP, is made from pooled human venous plasma by using the Cohn cold ethanol fractionation process. The approximate sodium content of the product is 145 mEq/L. It contains no preservative. Each 1: 5% vial is heat treated at 60°C for 10 hours against the possibility of transmitting the hepatitis viruses. The product is available in 50- and 100-mL rubber-stoppered single-dose vials.

Albumin 5% Solution

Bill of Materials (Batch Size 1 L)					
Scale/100 mL		Item	Material	Qty	UOM
5.00	g	1	Albumin	50.00	g
QS	mL	2	Sodium caprylate (0.004 M)[a]	QS	mL
QS	mL	3	Sodium *N*-acetyl tryptophanate (0.004 M)[a]	QS	mL
QS	mL	4	Sodium bicarbonate[b]	QS	mL
QS	mL	5	Water for injection	QS to 1.00	L

[a] For stabilization.
[b] For pH adjustment.

Albumin 20% Solution

Bill of Materials (Batch Size 1 L)					
Scale/100 mL		Item	Material	Qty	UOM
20.00	g	1	Albumin	200.00	g
QS	mL	2	Sodium caprylate (0.016 M)	QS	mL
QS	mL	3	Sodium *N*-acetyl tryptophanate (0.016 M)[a]	QS	mL
QS	mL	4	Sodium bicarbonate[b]	QS	mL
QS	mL	5	Water for injection	QS to 1.00	L

[a] For stabilization.
[b] For pH adjustment.

Albumin 25% Solution

Bill of Materials (Batch Size 1 L)					
Scale/100 mL		Item	Material	Qty	UOM
25.00	g	1	Albumin	250.00	g
QS	mL	2	Sodium caprylate (0.02 M)[a]	QS	mL
QS	mL	3	Sodium *N*-acetyl tryptophanate (0.02 M)[a]	QS	mL
QS	mL	4	Sodium bicarbonate[b]	QS	mL
QS	mL	5	Water for injection	QS to 1.00	L

[a] For stabilization.
[b] For pH adjustment 6.9 $\pm$ 0.5.

Albuterol Sulfate Inhalation Solution

Bill of Materials (Batch Size 1 L)					
Scale/3 mL		Item	Material	Qty	UOM
0.63 0.75	mg mg	1	Albuterol use albuterol sulfate	210.00	mg
QS	mg	2	Sodium chloride	QS	mg
QS	mL	3	Sulfuric acid	QS	mL
QS	mL	4	Sterile water for injection	QS to 1.00	L

Adjust pH to 3.5.

Aldesleukin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.10	mg	1	Aldesleukin (18 million IU)	1.10	g
50.00	mg	2	Mannitol	50.00	g
0.18	mg	3	Sodium dodecyl sulfate	0.18	g
0.17	mg	4	Sodium phosphate monobasic	0.17	g
0.89	mg	5	Sodium phosphate dibasic	0.89	g

Note: Each milliliter of product requires 1.2 mL sterile water for injection for reconstitution.

Alemtuzumab Injection

Bill of Materials (Batch Size 1 L)					
Scale/3 mL		Item	Material	Qty	UOM
30.00	mg	1	Alemtuzumab	10.00	g
24.00	mg	2	Sodium chloride	8.00	g
3.50	mg	3	Sodium phosphate dibasic	1.167	g
0.60	mg	4	Potassium chloride	200.00	mg
0.60	mg	5	Potassium phosphate monobasic	200.00	mg
0.30	mg	6	Polysorbate 80	100.00	mg
0.056	mg	7	Disodium edetate	18.667	mg

Alpha-Tocopherol (Vitamin E) Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Alpha-tocopherol (Vitamin E)[a]	200.00	g
20.00	mg	2	Benzyl alcohol	20.00	g
QS	mg	3	Sesame oil refined	QS to 1.00	L

[a] Vitamin E is a form of alpha-tocopherol ($C_{29}H_{50}O_2$). It includes the following: *d*- or *dl*-alpha-tocopherol ($C_{29}H_{50}O_2$); *d*- or *dl*-alpha-tocopheryl acetate ($C_{31}H_{52}O_3$); *d*- or *dl*-alpha-tocopheryl acid succinate ($C_{33}H_{54}O_5$). It contains 96% to 102% of $C_{29}H_{50}O_2$, $C_{31}H_{52}O_3$, or $C_{33}H_{54}O_5$.

Alprostadil for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.40	mg	1	Alprostadil	5.40	mg
172.00	mg	2	Lactose	172.00	g
47.00	mg	3	Sodium citrate	47.00	mg
8.40	mg	4	Benzyl alcohol	8.40	mg
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Extra quantity of item 1 to compensate for losses due to adsorption to vial and syringe. Lyophilized powder given is the concentration after reconstitution.

Alteplase Recombinant Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
58 MM	IU	1	Alteplase	100.00	g
3.50	g	2	L-Arginine	3.50	kg
1.00	g	3	Phosphoric acid	1.00	kg
11.00	mg	4	Polysorbate 80	11.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: The specific activity of alteplase is 580,000 IU/mg; 200-mg strength under vacuum.

Amikacin Sulfate Injection (50 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.70	mg	1	Sodium citrate	5.70	g
1.20	mg	2	Sodium metabisulfite	1.20	g
15.60	mg	3	Sulfuric acid for pH adjustment	15.60	g
50.00	mg	4	Amikacin, USP	50.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Nitrogen gas, NF	QS	cy

Amikacin Sulfate Injection (250 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
28.50	mg	1	Sodium citrate	28.50	g
6.00	mg	2	Sodium metabisulfite	6.00	g
73.60	mg	3	Sulfuric acid for pH adjustment	73.60	g
250.00	mg	4	Amikacin, USP	250.00	g
QS	L	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Nitrogen gas, NF	QS	cy

Manufacturing Directions

1. Prepare the solution in a glass-lined or 316 or higher temper-grade stainless steel tank. Protect solution with item 6 throughout the process.
2. Collect ca. 110% of the batch size of item 5 into the tank, heat it to not less than 70°C, then cool to 25°C (20–30°C) while sparging with filtered item 6. Bubble for not less than 30 minutes.
3. Transfer ca. 40% of item 5 from step 2 item into another tank for use in the QS step. Protect tank headspace with filtered item 6.
4. Continue sparging N_2 while adding and dissolving items 1 to 4 one at a time and slowly.
5. Check pH to 4.5 (4–5); adjust if necessary with item 4.
6. Make up volume with item 5 set aside in step 3.
7. Sample for testing.
8. Filter solution through a 0.45-mm or finer membrane into a glass-lined or 316 or higher temper-grade stainless steel tank. Protect solution with item 6.
9. Prior to filling, filter through a 0.22-mm or finer membrane filter.
10. Fill container, protect headspace with item 6, and sterilize using an approved cycle.

Amikacin Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
250.00	mg	1	Amikacin, use amikacin sulfate, 33% excess	333.75	g
6.60	mg	2	Sodium metabisulfite (sodium disulfite)	6.60	g
25.00	mg	3	Sodium citrate monohydrate	25.00	g
QS	mL	4	Water for injection	QS to 1.00	L
QS	ft^3	5	Nitrogen gas	QS	
QS	mL	6	Sulfuric acid as buffering agent	QS	
QS	mL	7	Sodium hydroxide, reagent-grade pellets for buffering	QS	

Note: Quantity of amikacin sulfate per liter = 333.75 ∞ 100/% assay (as is basis).

Manufacturing Directions

Important: For general requirements for tests, assays, and equipment, refer to USP.

1. Preparation of water. Check item 4 to be used for solution preparation and verify that it meets a conductivity limit of NMT 1.0 mS/cm and pH range of 5 to 7.
2. Preparation of solution.
   a. Put 700 mL of item 4 into the preparation vessel and bubble N_2 gas to expel dissolved oxygen gas. Monitor the O_2 sensor display (O_2% limit = NMT 1).
   b. Add and dissolve item 1 into the step 2a preparation vessel. Mix well by stirring to make clear solution.
   c. Add and dissolve items 2 and 3 into the solution of step 2b, mix well, and make clear solution.
   d. Check pH (4–5).
   e. Adjust pH by 2 N H_2SO_4/1 N NaOH solution (4–5).
   f. After adjustment of pH, make up volume to 1 L by item 4 and mix during bubbling item 5 until O_2% is less than 1.
   g. Check final pH (4.0–5.2).
3. Preparation of filtration assembly and machine parts for production. Clean and sterilize filtration assembly and machine parts using autoclave as per USP.
4. Prefiltration.
   a. Before starting the primary filtration, check the integrity of filter cartridge.
   b. Integrity test results of filter cartridge by the bubble point test:
      Before filtration bubble point mbar
      After filtration bubble point mbar
      Minimum acceptable bubble point mbar
   c. Transfer the solution from the preparation vessel to mobile vessel through filtration assembly, containing 0.2-mm filter cartridge.
   d. After filtration transfer mobile vessel to solution room.
5. Preparation of ampoules. Use type I 2-mL clear glass ampoules, USP.
   a. Wash the ampoules in the washing machine as per the following parameters and their limits:
      DI water pressure: 2 bar/min
      WFI pressure: 2 bar/min
      Compressed air pressure: 6 bar
      Compressed air pressure after regulator: 2 bar
      Machine speed: 100%
   b. Set the temperature to 330°C (as per latest validation studies).
   c. Sterilize the ampoules by dry heat.
6. Final filtration.
   a. Before starting the final filtration, check the integrity of filter cartridge.
   b. Integrity test results of filter cartridge by the bubble point test:
      Before filtration bubble point mbar
      After filtration bubble point mbar
      Minimum acceptable bubble point mbar
   c. Aseptically connect the N_2 line through sterile N_2 filter to the inlet of mobile vessel. Check the validity of N_2 filter.
   d. Aseptically connect one end of previously sterilized filtration assembly with 0.22-mm pore size filtration cartridge to the outlet of mobile vessel and other end to buffer holding tank on the ampoules filling machine parts.
   e. Filter the solution.
7. Aseptic filling.
   a. Operate previously sterilized ampoules filling machine as per following parameters:
      Adjust the volume to 2.15 mL; O_2 pressure: 4.0 bar; N_2 pressure: 0.4 bar; LPG pressure: 0.4 bar; machine speed (100% max).
   b. Fill 2.15 mL (range 2.1–2.2 mL) amikacin solution from the bulk into each sterile dry clean ampoule and seal it.
8. Terminal sterilization and leak test. Load the inverted ampoules inside the autoclave chamber, run the cycle as per the following parameters:
   Sterilization temperature: 121.1°C
   Exposure time: 20 minutes
9. Optical checking. Check the ampoules under the optical checking machine.

Packaging Material Specifications

Ampoule, 2 mL, flint glass type I.

Amino Acid Parenteral Nutrition Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.10	mg	1	Isoleucine, USP	5.61	g
6.60	mg	2	Leucine, USP	8.50	g
5.10	mg	3	Lysine, use lysine acetate, USP	12.59	g
2.80	mg	4	Methionine, USP	1.46	g
3.10	mg	5	Phenylalanine, USP	2.53	g
3.70	mg	6	Threonine, USP	3.40	g
1.20	mg	7	Tryptophan, USP	1.70	g
5.60	mg	8	Valine, USP	4.25	g
0.44	mg	9	*N*-Acetyl-L-tyrosine	2.30	g
9.00	mg	10	Alanine, USP	8.44	g
6.90	mg	11	Arginine, USP	8.65	g
9.00	mg	12	Glycine, USP	4.25	g
6.10	mg	13	Proline, USP	6.14	g
2.10	mg	14	Histidine base, USP	2.55	g
3.00	mg	15	Serine, USP	4.50	g
0.60	mg	16	Potassium metabisulfite	6.27	g
0.042	mg	17	Glacial acetic acid	5.95	g
QS	mL	18	Water for injection, USP	QS to 1.00	L
QS	mL	19	Nitrogen gas, NF	QS	mL

Manufacturing Directions

1. This solution must be prepared in a glass-lined or 316 or higher temper-grade stainless steel tank.
2. If using the volume method, add item 18 to ca. 85% of the final volume; if using weight method, add all the item 18 at the point of use.
3. Heat item 18 to not less than 70°C, bubble item 19 during the entire manufacturing process.
4. Stop steam supply and begin dissolving amino acids in the following order: arginine, leucine, isoleucine, phenylalanine, histidine, methionine, serine, threonine, valine, proline, lysine acetate, alanine, glycine, and *N*-acetyl-L-tyrosine.
5. Mix until all ingredients are dissolved and solution is uniform.
6. Sample for pH check and adjust to 5.8 (range 5.6–6.2) with item 17.
7. Add and dissolve potassium metabisulfite and tryptophan with mixing.
8. Cool to and maintain temperature of the solution in the mixing tank at 40°C (25–45°C) throughout the remaining process.
9. If using volume method, QS with item 18 to final volume; if using weight method, check final weight of product, add item 18 if necessary to bring specific weight. Mix until solution is uniform.
10. Check and record pH (range 5.6–6.2); again adjust with 20% solution of item 10 if necessary.
11. Prefilter solution through a prefilter unit prepared with approved filter—one prefiltration and one bulk tank microbial sample are taken at this stage for biological test. The size of sample should be large enough for statistical significance.
12. Prior to filling, filter solution through a 0.45-mm or finer membrane connected in a series to a prefilter. Check filtered solution for clarity. Protect product with filtered item 19 in the container headspace during the filling operation.
13. Fill into appropriate containers (250–1000 mL) and seal. During filling pull samples for volume check, develop a statistical sample plan to allow sampling throughout the batch.
14. Maintain N_2 headspace.
15. Autoclave at approved cycle.
16. Sample for final testing.

Amino Acid Parenteral Nutrition Solution (8.5%)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.61	mg	1	Isoleucine, USP	5.61	g
8.50	mg	2	Leucine, USP	8.50	g
8.93	mg	3	Lysine, use lysine acetate, USP	12.59	g
1.46	mg	4	Methionine, USP	1.46	g
2.53	mg	5	Phenylalanine, USP	2.53	g
3.40	mg	6	Threonine, USP	3.40	g
1.70	mg	7	Tryptophan, USP	1.70	g
4.25	mg	8	Valine, USP	4.25	g
2.30	mg	9	*N*-Acetyl-L-tyrosine	2.30	g
8.44	mg	10	Alanine, USP	8.44	g
8.65	mg	11	Arginine, USP	8.65	g
4.25	mg	12	Glycine, USP	4.25	g
6.14	mg	13	Proline, USP	6.14	g
2.55	mg	14	Histidine base, USP	2.55	g
4.50	mg	15	Serine, USP	4.50	g
6.27	mg	16	L-Glutamic acid	6.27	g
5.95	mg	17	L-Aspartic acid	5.95	g
0.20	mg	18	Sodium hydrosulfite, CP	0.20	g
QS		19	Sodium hydroxide pellets for pH adjustment	QS	
QS	mL	20	Water for injection, USP	QS to 1.00	L
QS		21	Nitrogen gas, NF	QS	

Amino Acid Parenteral Nutrition Solution: 10%

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
6.60	mg	1	Isoleucine, USP	6.60	g
10.00	mg	2	Leucine, USP	10.00	g
10.50	mg	3	Lysine, use lysine acetate, USP	14.80	g
1.72	mg	4	Methionine, USP	1.72	g
2.98	mg	5	Phenylalanine, USP	2.98	g
4.00	mg	6	Threonine, USP	4.00	g
2.00	mg	7	Tryptophan, USP	2.00	g
5.00	mg	8	Valine, USP	5.00	g
2.70	mg	9	*N*-Acetyl-L-tyrosine	2.70	g
9.93	mg	10	Alanine, USP	9.93	g
10.18	mg	11	Arginine, USP	10.18	g
5.00	mg	12	Glycine, USP	5.00	g
7.22	mg	13	Proline, USP	7.22	g
3.00	mg	14	Histidine base, USP	3.00	g
5.30	mg	15	Serine, USP	5.30	g
7.38	mg	16	L-Glutamic acid	7.38	g
7.00	mg	17	L-Aspartic acid	7.00	g
0.20	mg	18	Sodium hydrosulfite, CP	0.20	g
QS		19	Sodium hydroxide Pellets for pH adjustment	QS	
QS	mL	20	Water for injection, USP	QS to 1.00	L
QS		21	Nitrogen gas, NF		

Manufacturing Directions

1. Prepare this solution in a glass-lined or 316 or higher temper-grade stainless steel tank.
2. If using the volume method, add item 20 to ca. 85% of the final volume; if using weight method, add all the item 20 at the point of use.
3. Heat item 20 to not less than 70°C; bubble item 21 during the entire manufacturing process.
4. Add items 16 and 17 to the heated item 20 and mix.
5. Stop steam supply and begin dissolving amino acids in the following order: arginine, leucine, isoleucine, phenylalanine, histidine, methionine, serine, threonine, valine, proline, lysine acetate, alanine, glycine, and *N*-acetyl-L-tyrosine.
6. Mix until all ingredients are dissolved and solution is uniform.
7. Sample for pH check and adjust to 5.8 (range 5.6–6.2) with 20% solution of item 19.
8. Add and dissolve sodium hydrosulfite and tryptophan with mixing.
9. Cool to and maintain temperature of the solution in the mixing tank at 40°C (25–45°C) throughout the remaining process.
10. If using volume method, QS with item 20 to final volume; if using weight method, check final weight of product, add item 20 if necessary to bring specific weight. Mix until solution is uniform.
11. Check and record pH (range 5.6–6.2); again adjust with 20% solution of item 10 if necessary.
12. Prefilter solution through a prefilter unit prepared with approved filter—one prefiltration and one bulk tank microbial sample is taken at this stage for biological test. The size of sample should be large enough for statistical significance.
13. Prior to filling, filter solution through 0.45-μm or finer membrane connected in a series to a prefilter. Check filtered solution for clarity. Protect product with filtered item 21 in the container headspace during the filling operation.
14. Fill into appropriate containers (250–1000 mL) and seal. During filling pull samples for volume check, develop a statistical sample plan to allow sampling throughout the batch.
15. Maintain N_2 headspace.
16. Autoclave at approved cycle.
17. Sample for final testing.

Amino Acid Parenteral Injection

Bill of Materials	
Isoleucine	4.0–5.5 g/L
Leucine	8.0–10.0 g/L
Lysine	6.0–8.0 g/L
Methionine	4.0–6.0 g/L
Phenylalanine	4.0–6.0 g/L
Threonine	4.0–6.0 g/L
Tryptophan	1.0–2.0 g/L
Valine	6.0–8.0 g/L
Arginine	10.0–12.0 g/L
Histidine	1.5–3.5 g/L
Alanine	9.0–12.0 g/L
Aminoacetic Acid (Glycine)	11.0–16.0 g/L
Asparagine	0–1.0 g/L
Aspartic Acid	5.5–8.0 g/L
Acetylcysteine	0–2.5 g/L
Glutamic Acid	6.0–10.0 g/L
Ornithine	0–1.0 g/L
Proline	4.0–6.0 g/L
Serine	1.0–3.0 g/L
Tyrosine	0.1–0.5 g/L
(as Acetyltyrosine)	0–2.0 g/L
Taurine	0–4.0 g/L

Aminohippurate Sodium for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Aminohippurate sodium	200.00	g
QS	mL	2	Sodium hydroxide for pH adjustment		
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 6.7 to 7.6 with item 2.

Aminophylline Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Aminophylline, USP, anhydrous	25.00	g
QS		2	Ethylenediamine, USP, for pH adjustment[a]	QS	
QS		3	Nitrogen gas, NF	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

[a] For pH adjustment to a maximum of 0.5 mg/mL.

Manufacturing Directions

1. The product must be manufactured in a glass-lined or stainless steel 316 or higher temper-grade tank.
2. Add item 4 to ca. 110% of the final volume into the tank.
3. Bring to boiling and keep it boiling for 10 minutes as a minimum. Begin bubbling item 3 through the solution.
4. Transfer ca. 20% of the final volume of item 4 from step 2 into another glass-lined or stainless steel tank under item 3 protection and cool to 75°C to 85°C.
5. To 90% of the final volume of item 4 at 75°C to 85°C, add and dissolve item 1 with mixing. Avoid vortex formation; maintain item 3 cover throughout.
6. Check and record pH. Add item 2 to solution with mixing to adjust pH to 8.6 to 9.0. Record pH and amount of item 2 used.
7. Bring to volume with boiled N_2-protected item 4 and mix until ingredients are dissolved and solution is uniform.
8. Check and record pH again and again adjust pH with item 2 to 8.6 to 9.0. Record amount used.
9. Cool solution to 20°C to 30°C.
10. Filter solution using an approved 0.45-μm or finer membrane filter with a prefilter into a glass-lined or stainless steel holding tank flushed and under N_2 protection.
11. Sample for testing and adjust batch composition accordingly.
12. Preflush the ampoules with item 3 prior to filling.
13. Fill nominal volume into each ampoule and N_2 flush the headspace.
14. Terminal sterilization: F_0 equal to 8.0 for the coolest container and the hottest container to not exceed an F_0 of 18.0; temperature of the sterilizer chamber to be 115°C during the process dwell period; water spray cooling until 45°C or lower.
15. Sample and test for final specifications.

Amiodarone Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.80	mg	1	Amiodarone	1.80	g
0.02	mL	2	Lactic acid[a], 20%	20.00	mL
45.46	mg	3	Dextrose anhydrous, USP	45.46	g
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

[a] Prepared by heat treatment of a dilute 90% lactic acid concentrate to hydrolyze lactic acid dimer.

Manufacturing Directions

1. In a suitable size jacketed tank, add 0.4 L of item 5.
2. Add to this item 2.
3. Heat the mixture to 55°C.
4. Add item 1 to the above solution, mix, and dissolve.
5. Add another 0.4 L of item 5, mix, and allow to cool to 30°C.
6. Add item 3. Mix with agitation to dissolve.
7. Check and adjust pH with item 4 to 3.5 (3.4–3.6).
8. Make up the volume with item 5.

Amiodarone Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Amiodarone hydrochloride	50.00	g
20.20	mg	2	Benzyl alcohol	20.20	g
100.00	mg	3	Polysorbate 80	100.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Fill 3 mL per ampoule.

Amoxicillin Lyophilisate for Injection (250 mg)

Formulation

Amoxicillin sodium, 6.25 g; Kollidon 12 PF [1], 7.50 g; water for injections, add 100.00 mL.

Manufacturing Directions

Dissolve the active ingredient in the well-stirred solution of Kollidon 12 PF and after freeze-drying, fill 500-mg portions of the dry lyophilizate into ampoules. Prior to administration, the dry content of an ampoule is mixed with 1.9 mL of water to give a clear injection solution.

Amoxicillin–Clavulanic Acid Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
1.00	g	1	Amoxicillin as sterile amoxicillin sodium[a]	1.225	kg
200.00	mg	2	Clavulanic acid as sterile potassium clavulanate[b]	269.00	g

[a] Quantity of sterile amoxicillin sodium is calculated on the basis of assay 85% of amoxicillin ($C_{16}H_{19}N_3O_5S$) on the anhydrous basis and 4.0% for water compensation.
[b] Quantity of sterile potassium clavulanate is calculated on the basis of assay 75.5% of clavulanic acid ($C_8H_9NO_5$) on the anhydrous basis and 1.5% for water compensation.

Manufacturing Directions

1. Clean the vials and rubber closure in automatic machine.
2. Clean the filling accessories related to filling machine.
3. Sterilize and depyrogenize the clean, empty vials using sterilizer.
4. Sterilize the stopper and filling equipment.
5. Mix aseptically amoxicillin sodium sterile powder and clavulanate potassium sterile powder in a suitable mixer.
6. Aseptically fill the mixed powder into the vials automatically with purging of N_2 gas, to get labeled amount of active ingredient per vial.
7. Close the vials and cap with flip-off cap.

Amoxicillin Powder for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
250.00	mg	1	Amoxicillin as sodium amoxicillin equivalent[a] (276.88 ∞ 4), 3% excess	1107.53	g

[a] For 500 mg, use 553.76 g; for 1000 mg, use 1107.53 g. Actual weight (adjusted according to potency) = weight above $\times$ 930/potency.

Manufacturing Directions

Caution: Amoxicillin sodium is sensitive to moisture. This powder is sterile and must be handled aseptically in a dry, dust-free atmosphere. RH NMT 25% at 27°C.

1. Preparation. Wipe outer surface of each bottle with 3A alcohol and deliver immediately to sterile area.
2. Preparation of vials.
   a. Wash and dry type I 20- or 10-mL (for 500 and 250 mg, respectively) glass vials and load in appropriate containers for sterilization.
   b. Sterilize by dry heat at 200°C (–0, +50°C) bottle temperature, for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for the duration of the cycle (or an equivalent heat input).
   c. Deliver to the sterile filling area.
3. Preparation of stoppers.
   a. Wash west compound 888 stoppers by using rubber cycle (slow tumbling) with Triton X-100 detergent.
   b. Dry in dryer at 55°C. Rack, inspect, and wrap the stoppers for autoclaving.
   c. Sterilize in an autoclave for 1 hour at 121°C and vacuum dry with heat for a minimum of 4 hours at a temperature not exceeding 90°C.
   d. Deliver to sterile area for filling.
4. Filling.
   a. Sterile-fill required gram of powder (see formula in table) equivalent to labeled amount of amoxicillin into each clean, dry sterile vial. Check fill weight of vials at ca. 5-minute intervals.
   b. Insert sterile stopper and apply sterile overcap.
   c. Remove from sterile area and pack into bulk containers and label each container with product lot number.
   d. Sample for testing.
5. Finishing. Sample for testing.

Amphotericin B Cholesteryl Sulfate Complex for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Amphotericin B	50.00	g
26.40	mg	2	Sodium cholesteryl sulfate	26.40	g
5.64	mg	3	Tromethamine	5.64	g
0.372	mg	4	Disodium edetate dihydrate	0.372	g
950.00	mg	5	Lactose monohydrate	950.00	g
QS	mL	6	Hydrochloric acid for pH adjustment	QS	

Note: This is a 1:1 molar ratio complex of amphotericin B and cholesteryl sulfate. For 100-mg dose, use 52.8 mg of cholesteryl sulfate, lyophilized powder.

Amphotericin B Injection

Bill of Materials (Batch Size 15 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Amphotericin B, USP	150.00	g
8.20	mg	2	Sodium desoxycholate	123.00	g
4.04	mg	3	Monobasic sodium phosphate, USP (anhydrous)	60.60	g
QS		4	Sodium hydroxide, NF, as 4% solution for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 15.00	L

Manufacturing Directions

Caution: Do not inhale amphotericin. Avoid skin contact. Adjust amount of amphotericin on assay and sodium desoxycholate and monobasic sodium phosphate on moisture level.

1. Prepare a 4% sodium hydroxide solution by dissolving 20 g of sodium hydroxide, NF, in enough water for injection to make 500 mL; cool to less than 20°C before using.
2. Prepare a 2% (w/v) monobasic sodium phosphate solution by dissolving weighed amount (as calculated) in enough water for injection, USP, to make 3030 mL.
3. In a suitable compounding tank, collect ca. 10 L of cold (lower than 20°C) water for injection.
4. Add the sodium desoxycholate and mix to dissolve.
5. Add 4% sodium hydroxide solution and mix to adjust pH between 12.5 and 12.6. Cool solution to less than 20°C and maintain it at this temperature.
6. Add amphotericin B, USP, and mix to form a clear amber solution. Cover tank while mixing.
7. Check and record pH. Immediately after all drug has dissolved, slowly add 2% sodium phosphate monobasic solution in 100-mL portions to adjust pH to 7.6 (range 7.5–7.7). *Note*: pH must not drop less than 7.2. Add 3030 mL of sodium phosphate monobasic solution; use 4% sodium hydroxide to further adjust pH.
8. QS to 15 L with cold (lower than 20°C) water for injection and mix thoroughly for at least 10 minutes. Keep tank covered. Sample and keep solution cool until QC approval.
9. Aseptically filter the solution through a 0.22-mm filter system into a suitable sterile receiving vessel.
10. Aseptically fill and lyophilize.
11. Load the filled vials into lyophilizer. Place thermocouples as per current SOPs; turn freezer on. When at least four thermocouples reach –30°C or less, hold for at least 30 minutes. Turn condenser on. After condenser temperature reaches –40°C or less, turn vacuum on.
12. When the vacuum reading is less than 250 mm, adjust the shelf temperature to 0°C and dry the product with full vacuum.
13. When at least four product thermocouples reach −8°C (±5°C), raise the shelf temperature to +3°C or higher to maintain the product temperature at 25°C (± 5°C) and dry with full vacuum when at least four product temperature probes reach 25°C (±5°C) for at least 2 more hours.
14. Break the vacuum by bleeding N_2 and check the moisture of three representative samples. Close chamber and pull vacuum.
15. If the moisture content of any of the three samples is more than 6%, pull vacuum and dry for at least two more hours. Withdraw three more samples and repeat.
16. If the moisture is satisfactory, bleed the chamber with sterile N_2, stopper the vials with the door closed, and terminate cycle.
17. Finish. Sample.

Amphotericin B Lipid Complex Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Amphotericin B	5.00	g
3.40	mg	2	L-(alpha)-dimyristoylphosphatidylcholine (DMPC)	3.40	g
1.50	mg	3	L-(alpha)-dimyristoylphosphatidylglycerol (DMPG)	1.50	g
9.00	mg	4	Sodium chloride	9.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: pH 5.0 to 7.0; fill 10 or 20 mL.

Amphotericin B Liposome for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
50.00	mg	1	Amphotericin B	50.00	g
213.00	mg	2	Hydrogenated soy phosphatidylcholine	213.00	g
84.00	mg	3	Distearoylphosphatidylglycerol	84.00	g
0.64	mg	4	Alpha-tocopherol	0.64	g
52.00	mg	5	Cholesterol	52.00	g
900.00	mg	6	Sucrose	900.00	g
27.00	mg	7	Disodium succinate hexahydrate	27.00	g
QS	mL	8[a]	Water for injection, USP	QS	

[a] For reconstitution; pH after reconstitution 5.0 to 6.0.

Antazoline Sulfate and Xylometazoline Hydrochloride Ophthalmic Drops

Bill of Materials (Batch Size 1 L)					
Scale/5 mL		Item	Material	Qty	UOM
5.00	mg	1	Antazoline sulfate	5.00	g
0.50	mg	2	Xylometazoline hydrochloride, USP	0.50	g
1.50	mg	3	Hydroxypropyl methylcellulose 2910, USP, 4000 cps	1.50	g
0.10	mg	4	Benzalkonium chloride 0.1 g, use benzalkonium chloride solution, USP, 17%, 7% excess or benzalkonium chloride solution (50% w/v), BP, 7% excess	0.637 0.214	mL mL
1.00	mg	5	Disodium edetate, USP/BP	1.00	g
8.43	mg	6	Sodium chloride, USP/BP	8.43	g
QS	mL	7	Water purified, USP	QS to 1.00	L

Manufacturing Directions

Equipment

Thoroughly clean and rinse equipment used before proceeding. Use steam-jacketed, glass-lined, or stainless steel (No. 304 or better). The tank must be equipped with an agitator (preferably with speed control) and a cover to prevent at all times during the manufacturing process except when ingredients are being added or samples being taken.

Foaming

Benzalkonium chloride markedly lowers the surface tension. During severe agitation or turbulent flow, substantial foaming will occur. This condition often exists in the processing equipment and in the overflow system of vacuum filling machines. This item tends to concentrate in the foam. If the foam is not dissipated quickly, and if allowed to accumulate, a substantial excess of it may result near the surface of the liquid after the foam condenses. It is therefore advisable to design the processing and filling systems in such a way as to minimize foaming and ensure rapid dissipation of any unavoidable foaming.

1. Preparation of bulk solution.
   a. Charge mixing tank to 90% of final volume with item 7.

b. Heat water to 90°C and while agitating, add and dissolve item 3 by slowly sprinkling onto the surface of the water. It must be dispersed evenly over a period of time to ensure complete wetting and dispersion. Adjust agitation rate to avoid excessive foaming. Allow 15 minutes for hydration before cooling.
c. Discontinue heating and cool solution to ca. 40°C.
d. While agitating, add and dissolve items 1, 2, 4, 5, and 6.
e. Continue cooling to 25°C.
f. Turn off agitator and QS to final volume. Mix well. Sample.

2. Prefiltration. *Note*: Methylcellulose solutions filter slowly.
   a. Recirculate the solution through filter assembly until clear.
   b. Transfer clean solution into a holding or sterilization tank.
3. Sterilization and filling.
   a. Use only recommended filters for sterile filtration.
   b. Prepare and steam-sterilize the recommended filter unit.
   c. Aseptically fill sterile solution into sterilized container and apply sterile closure component and sample.

Antipyrine, Phenylephrine, and Pyrilamine Maleate Ophthalmic Drops

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
		1	Water purified (distilled), USP	40.00	L
12.000	mg	2	Boric acid, NF	540.00	g
4.600	mg	3	Sodium citrate dihydrate, USP	207.00	g
0.548	mg	4	Sodium metabisulfite, NF	24.65	g
1.000	mg	5	Antipyrine, USP	45.00	g
1.320	mg	6	Phenylephrine hydrochloride, USP (10% overage)	59.40	g
1.100	mg	7	Pyrilamine maleate, USP (10% overage)	49.50	g
0.127	mg	8	Disodium edetate, USP	5.70	g
0.040	mL	9	Benzalkonium chloride, NF (use 10% solution)	18.00[a]	mL
QS	mL	10	Water purified (distilled), USP	QS to 45.00	L

[a] The amount of benzalkonium chloride, 10% solution, to be added must be calculated on the basis of the assay of the raw material lot used as per the following formula: 18.0 mL × 10.0% = mL of benzalkonium chloride, 10% solution, required.

Manufacturing Directions

1. Measure 40 L of item 1 into a suitable plastic mixing tank. Add items 2 to 9, in order, allowing each to dissolve before adding the next.
2. QS to 45 L with item 10 and mix well for 15 minutes. Sterile filtration.
3. Sterilize for 1 hour (range 45–60 minutes) at 121°C (–0, +5°C) in autoclave at 15 psi, the Sartorius mini cartridge, filter, and a stainless steel pressure vessel.
4. Mix the product for at least 10 minutes before filtration. Before sterile filtration to the 100-L pressure vessel, perform the bubble point test at NLT 46 psi.
5. After completion of product filtration, flush the sterilizing filter with at least 20 L of water purified (distilled). Sample.
6. Aseptically fill sterile solution through sintered glass into sterilized containers. Perform the bubble point test on a 0.22-μm inline gas filter before and after filtration at 18 psi.

Antipyrine, Phenylephrine, and Sodium Thiosulfate Ophthalmic Solution

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Qty	UOM
Part I					
		1	Water purified (distilled), USP, ca.	10.00	L
14.00	mg	2	Polyvinyl alcohol, 20–90	630.00	g
Part II					
		3	Water purified (distilled), USP, ca.	30.00	L
6.70[a]	mg	4	Sodium phosphate dibasic heptahydrate, USP[a]	301.50	g
3.45	mg	5	Sodium phosphate monobasic, USP	155.25	g
0.0127	mg	6	Disodium edetate, USP	0.57	g
7.35[b]	mg	7	Sodium acetate trihydrate USP[b]	330.75	g
1.00	mg	8	Antipyrine, USP	45.00	g
0.04	mg	9	Benzalkonium chloride, NF (use 10% solution)[c]	18.00[c]	mL
		10	1 N hydrochloric acid, NF	QS	mL
		11	1 N sodium hydroxide, NF	QS	mL
1.57	mg	12	Sodium thiosulfate, pentahydrate, USP	70.65	g
1.32	mg	13	Phenylephrine hydrochloride, USP (10% overage)	59.40	g
QS	mL	14	Water purified (distilled), USP	QS to 45.00	L

[a] Equivalent to 3.55 mg/mL sodium phosphate dibasic anhydrous.
[b] Equivalent to 4.43 mg/mL sodium acetate anhydrous.
[c] The amount of benzalkonium chloride, 10% solution, to be added must be calculated on the basis of the assay value of the raw material lot(s) used.
Assay value: (mL)
Formula: 18.0 mL × 10.0% = mL of benzalkonium chloride, 10% solution, required.
Assay value (%)
Calculation: 18.0 mL × 10.0% = mL of benzalkonium chloride, 10% solution, ____ (%) required.

Manufacturing Directions

Part I

1. Measure out ca. 10 L of item 1 into a stainless steel-jacketed pressure vessel. Begin mixing with a suitable mixer. Heat to 85°C to 90°C.
2. When the temperature reaches 85°C to 90°C, turn off the heat source. Add item 2 slowly to the vortex. Mix for at least 90 minutes until dissolved. Cool to room temperature, with force cooling.

Part II

1. Measure out ca. 30 L of item 3 into a mixing tank suitably calibrated for a final QS of 45 L.
2. Add items 4 to 9, in order, allowing each to dissolve before adding the next.
3. Check pH (range 6.7–6.9). If necessary, adjust the pH to 6.7 to 6.9 with item 10 or 11.
4. After pH is within the specified range, add item 12. Mix until dissolved.
5. Add item 13. Mix until dissolved.
6. Add part I to part II, while mixing part II. Use 2 to 3 L of item 14 to rinse the part I container, pump, and hoses. Add the rinsings to the batch. Allow any foam to dissipate.
7. QS to 45 L with item 14 and mix thoroughly for at least 15 minutes.

Sterile Filtration

1. Sterilize for 1 hour (range 45–60 minutes) at 121°C (–0, +5°C) in autoclave at 15 psi, the Sartorius mini cartridge, filter, and 100-L stainless steel pressure vessel. Transfer to solution preparation area.
2. Attach the cartridge mini prefilter/final filter and hosing sterilization chart.
3. Mix the product for at least 10 minutes before filtration.
4. Connect the sterilized Sartorius mini cartridge filter and sterile filter with the aid of N_2 pressure (15–30 lb). Discard initial 10 L of filtrate, attach sterilized hose to sterilized filter holder, and connect to sterilized 100-L stainless steel pressure vessel, aseptically. *Note*: Before sterile filtration to the 100-L pressure vessel, perform the bubble point test at NLT 46 psi.
5. After completing product filtration, disconnect the Sartorius mini cartridge filter from the pressure vessel, flush the sterilizing filter with at least 20 L of water purified (distilled) for the bubble point test (after filtration).
6. After filtration, decontaminate the outer surface of bulk holding pressure vessel and then transfer to filling cubicle. Sample (ca. 60 mL) for bulk assay.

Sterilization

Sterilize at 121°C (–0°, +2°C) and 5-psi pressure for 1 hour the filling unit, 20-L surge bottle, or manifold of filling unit and uniforms.

Sterile Filling

1. Transfer the presterilized bottles, plugs, and caps to the filling cubicle after swabbing their outer polyethylene

packing with filtered methylated spirit and keep under the laminar flow hood.
2. Transfer the sterilized assembly line to filling room and surgical gloves and uniforms to change room sterile side. Aseptically connect the sterilized filling tubing and N_2 line from the 100-L pressure vessel to surge bottle.
3. Aseptically fill 15.40 mL of sterile solution into sterilized container by the automatic filling, plugging, and sealing machine and apply sterile closure components (plugs and caps). *Note*: Discard 50 to 100 bottles initially during volume adjustment. While filtering, do not exceed to N_2 pressure 5 to 10 lb.
4. Perform the bubble point test on a 0.22-μm inline gas filter before and after filtration at 18 psi.

Antithymocyte Globulin (Rabbit) for Injection

Bill of Materials (Batch Size 5 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Antithymocyte globulin (rabbit)	25.00	g
50.00	mg	2	Glycine	50.00	g
50.00	mg	3	Mannitol	50.00	g
10.00	mg	4	Sodium chloride diluent vial	10.00	g
5.00	mL	5	Water for injection, USP	QS to 5.00	L

Note: Viral inactivation step (pasteurization, i.e., heat treatment of active ingredient at 60°C/10 h) is performed for each lot. After reconstitution pH is 6.6 to 7.4.

Aprotinin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10,000	KIU[a]	1	Aprotinin	1.40	g
9.00	mg	2	Sodium chloride	9.00	g
QS	mL	3	Hydrochloric acid for pH adjustment		
QS	mL	4	Sodium hydroxide for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

[a] Kallikrein inhibitor units; adjust pH to 4.5 to 6.5 with item 3 or 4.

Argatroban (Thrombin Inhibitor) Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Argatroban	100.00	g
100.00	mg	2	D-Sorbitol	100.00	g
100.00	mg	3	Dehydrated alcohol	100.00	g

Note: Fill 2.5 mL into each single-use vial.

Arsenic Trioxide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Arsenic trioxide	1.00	g
QS	mL	2	Hydrochloric acid for pH adjustment	QS	
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 7.0 to 9.0 with item 2 or 3. Fill 10 mL into glass ampoules.

Ascorbic Acid and B Complex Vitamins (Two Vials)

Bill of Materials Vial 1 (Batch Size 561 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Ascorbic acid, USP, 50% excess	16.83	kg
660	IU	2	Vitamin A, use retinol in polysorbate 80, 50% excess, labeled 555.39 million U, factored for potency (e.g., 1.5 million U/g)	—	—
40	IU	3	Vitamin D, 25% excess, labeled for 40 million U, factored for potency such as 28 million U/g	—	—
0.67	mg	4	Thiamine hydrochloride, USP, 25% excess	469.84	g
0.97	mg	5	Pyridoxine hydrochloride, USP, 25% excess	680.21	g
7.94	mg	6	Niacinamide, USP, 10% excess	4899.77	g
2.81	mg	7	Dexpanthenol[a]	1970.51	g
2.00	mg	8	DL-alpha tocopheryl acetate, NF, 25% excess	1402.50	g
48.00	mg	9	Polysorbate-20[b]	26.928	kg
20.00	mg	10	Gentisic acid ethanolamide	11.22	kg
0.30	mL	11	Propylene glycol	169.30	L
QS	mL	12	Sodium hydroxide, 10% solution, for pH adjustment	12807.63	g
QS	—	13	Carbon dioxide	QS	—
QS	mL	14	Water for injection, USP	QS to 561.00	L
0.984	mg	15	Riboflavin, 25% excess	690.03	g

[a] Includes 2% excess.
[b] Adjust for contribution from vitamins A and D.

Manufacturing Directions

1. Place 153.10 L of item 11 and 117.95 L of item 14 into appropriate vessels, bubble item 13 through the solution for 15 minutes, and then blanket with item 13.
2. Dissolve item 7 in 13.3 L of hot item 14 (50–60°C). Allow to cool. Add to the vessel above.
3. Add, with constant stirring, items 1, 4, 5, 6, 10, and 15. Allow each ingredient to dissolve before proceeding.
4. Place item 9 in a suitable container on a hot plate with stirrer and heat to 40°C to 50°C (do not exceed 60°C) and cover with a blanket of item 13. Do not pass gas through solution.
5. With constant stirring, add items 2, 3, and 8 to item 9 and allow for 5 to 6 minutes to mix. Carefully watch temperature—the solution should become crystal clear. Turn off the heat.
6. Using 10 mL at a time, add 15.2 L of item 11 to the polysorbate fat-soluble vitamin mixture. Allow the liquids to mix completely after dilution.
7. With constant stirring, pour the polysorbate mixture as a thin stream into the aqueous vitamins. Work slowly. Transfer final drops with a rubber policeman.
8. Dissolve item 12 in 145.81 L of item 14 and cool it to room temperature.
9. Add 10% item 12 to a pH of 4.9±0.1. Allow mixture to cool.
10. Add 10% item 12 to a final pH of 5.1 to 5.15.
11. QS to final volume with item 14. Cover with aluminum foil. Flush with item 13.
12. Sample after 3 days. After approval, fill by filtering through a 0.22-μm filter into a reservoir covered with CO_2 for filling; pre- and postflush vials (amber) with CO_2 during filling.

Ascorbic Acid and B Complex Vitamins

Bill of Materials Vial 2 (Batch Size 561 L)					
Scale/mL		Item	Material	Qty	UOM
80.00	mg	1	Folic acid, USP, 25% excess	56.10[a]	g
1.00	mg	2	Cyanocobalamin, USP, 25% excess	701.25[b]	mg
12.00	mg	3	Biotin FCC, 25% excess	8.42	g
30%	mL	4	Propylene glycol	168.30	L
QS	mL	5	0.2 M Citric acid for buffer	QS	mL
QS	mL	6	0.2 M Sodium citrate for buffer	QS	mL
QS	mL	7	0.2 M Sodium hydroxide	QS	mL
QS	mL	8	Water for injection, USP	QS to 561.00	L

[a] Calculate on anhydrous basis.
[b] Calculate the raw material on the assay value.

Manufacturing Directions

1. Prepare a solution of item 6 by dissolving 20.58 kg in 350 L of item 8.
2. Weigh 5 times the amount of item 2 required for the batch and dissolve in 1 L of item 8.
3. Weigh item 1 and completely dissolve in approximately 280.50 L of item 6 solution prepared in step 1.
4. Add item 3 and dissolve completely.
5. Take 200 mL of item 2 solution prepared in step 2 and add to the compounding tank. Mix thoroughly. *Note*: Item 2 is hygroscopic and weighing small amounts may result in excessive variation. This step precludes this variation.
6. Add item 4 and mix until dissolved.
7. Adjust volume to ca. 540 L with item 8.
8. Check pH and adjust to 7.9 to 8.0, if necessary, with item 5 solution.
9. Check pH check and filter through a 0.22-μm filter and fill under N_2 in amber vials.

Stopper Sterilization

Dissolve 6.375 kg of disodium edetate in 255 kg of purified water. Rinse stoppers with water that has undergone reverse osmosis (RO). Cover the stoppers with disodium edetate solution and autoclave at 121°C for 1 hour. Rinse stoppers at least 3 times with RO water.

Ascorbic Acid and B Complex Vitamins Lyophilized in Covial

Bill of Materials Lower Chamber (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	μg	1	Folic acid, 25% excess	250.00	mg
2.50	μg	2	Cyanocobalamin, 25% excess	3.125	mg
30.00	μg	3	Biotin, 25% excess	37.50	mg
7.02	mg	4	Dexpanthenol, 20% excess	8.43	g
19.84	mg	5	Niacinamide, 20% excess	23.81	g
5.00	mg	6	Mannitol	5.00	g
2.43	mg	7	Pyridoxine hydrochloride, 20% excess	2.92	g
QS	mL	8	0.2 M Sodium hydroxide to buffer	QS	mL
QS	mL	9	0.2 M Potassium phosphate monobasic to buffer	QS	mL
QS	mL	10	Water for injection	QS to 1.00	L
QS	–	11	Nitrogen gas	QS	–

Note: The lower chamber is lyophilized and filled first, followed by the upper chamber (see manufacturing directions).

Manufacturing Directions

1. Heat 50 mL of item 10 to 60°C and completely dissolve item 4. Keep aside.
2. Prepare a 0.2 M item 8 solution by dissolving 4 g of item 8 in 500 mL of item 10.
3. Prepare a 0.2 M item 9 solution by dissolving 13.61 g of item 9 in 500 mL of item 10.
4. Weigh accurately 312.5 mg of item 2 and dissolve in 1 L of item 10. Keep aside.
5. Weight item 1 and dissolve in 234 mL of item 8 solution prepared in step 2. Check pH.
6. Immediately add 246 mL of item 9 solution prepared in step 3.
7. Mix and note pH.
8. Add item 3 and dissolve completely.
9. Add 10 mL of item 2 solution prepared in step 4.
10. Add all other ingredients one by one (including item 4 solution prepared in step 1) with the exception of item 7. Check pH.
11. Add item 7 to solution, stir to dissolve, and check pH again.
12. Adjust the pH between 8.0 and 10.0 with item 8 or 9 solution. QS to volume with item 10.
13. Flush item 11 for 10 minutes.
14. Filter through a sterile 0.22-μm filter into the sterile area and fill the vials.
15. Lyophilize as follows:
    a. Prepare shelves to –40°C or less.
    b. Transfer the filled vials in covered trays onto the shelves of the lyophilizer (or if the system is autoloading, following directions accordingly).
    c. Place thermocouples in appropriate vials.
    d. The product thermocouples should register –35°C for at least 3 hours.
    e. Start condenser. Let the condenser cool to –55°C or less.
    f. Start vacuum and let the chamber achieve a level of 100 μm or less.
    g. Set the temperature controller at –30°C and let the lyophilizer run for 24 hours.
    h. Raise the shelf temperature to 0°C and let run for additional 6 hours.
    i. Raise the shelf temperature to +20°C and run for additional 12 hours.
    j. Raise shelf temperature to +35°C and run additional 6 hours.
    k. Bleed chamber to atmospheric pressure with item 11.
    l. Open the lyophilizer chamber door, withdraw nine sample vials (three from each of the top, middle, and lower shelves representing the left, center, and right positions, respectively) for determination of moisture.
    m. Submit samples to QC for moisture test while keeping the chamber door shut and vacuum pulled.
    n. If samples pass the test, remove them. If the samples fail the test, prolong lyophilization cycle.
    o. For finished samples, place center seal, fill the upper chamber, and seal with top seal.
    p. Place aluminum ferrule around the top seal.
    q. Deice and clean lyophilizer.

Ascorbic Acid and B Complex Vitamins

Bill of Materials Upper Chamber (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Ascorbic acid, USP, 50% excess	75.00	g
2.46	mg	2	Riboflavin-5′-phosphate USP, 20% excess	2.95	g
1.68	mg	3	Thiamine hydrochloride, USP, 50% excess	2.52	g
0.20	mg	4	Gentisic acid ethanolamide	200.00	mg
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	10% Sodium hydroxide (w/v) for pH adjustment	QS	mL
QS	–	7	Carbon dioxide	QS	–

Manufacturing Directions

1. Prepare 150 mL of 10% item 6 solution in item 5 and let it cool to room temperature.
2. Place approximately 500 mL of item 5 into a clean compounding tank and bubble item 7 for 10 minutes. Keep a CO_2 blanket over the solution during the remainder of the compounding steps.
3. Add items 2, 1, 3, and 4, in order, to the tank and stir to a complete solution.
4. Bring to approximately 800 mL with item 5 and check pH.
5. Adjust the pH between 4.0 and 4.5 with 10% item 6 solution prepared in step 1.
6. QS to final volume with water for injection.
7. Filter through a sterile 0.22-μm filter into the sterile room. Keep the receiving jug under CO_2 blanket and protected from light.
8. Fill the upper chamber.

Ascorbic Acid and B Complex Vitamins Lyophilized with Diluent

Bill of Materials B-Complex Lyophilized (Batch Size 3.9 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Thiamine hydrochloride, USP, ampoule grade, 10% excess	195.00	g
5.00	mg	2	Riboflavin, USP, 14% excess	14.40	g
	–	3	Riboflavin-5′-phosphate (combined with above for scale)	8.00	g
10.00	mg	4	Pyridoxine HCl, USP, 10% excess	39.00	g
100.00	mg	5	Niacinamide, USP, 10% excess	390.00	g
0.22	mg	6	Propyl paraben USP	0.78	g
0.89	mg	7	Methyl paraben, USP	3.16	g
QS	mL	8	Water for injection,	QS to 3.90	L
QS	mL	9	Sodium bicarbonate, USP, for pH adjustment (4.3–4.5)	QS	mL

Note: All ingredient quantities are based on 100% assay amounts; adjust accordingly; entire preparation protection under N_2 and light.

Manufacturing Directions

1. Measure 3 L of item 8 into a 4-L beaker, heat to 95°C, and hold it at that temperature and agitate vigorously.
2. Add items 6 and 7. Then add item 5.
3. Add item 2. Once the ingredients are in solution, cool the solution to 50°C with agitation in a water bath; let it stand to room temperature.
4. Add items 4, 1, and 3, in order. Measure pH and adjust with item 9 to 4.3 to 4.5.
5. QS to 3.9 L with item 8.
6. Filter aseptically into a previously sterilized vessel by passing through filter.
7. Aseptically fill into 10-mL vials. Place stoppers.
8. Lyophilize as follows:
   a. Freeze to -40°C for not less than 3 hours.
   b. Turn vacuum on to less than 300 μm for a 20-hour cycle time.
   c. Raise the temperature to +15°C for at least 8 hours. Break vacuum with N_2 and open under aseptic conditions.
   d. Stopper and seal with aluminum three-piece caps.

Ascorbic Acid and B Complex Vitamins

Bill of Materials (Batch Size 45 L)					
Scale/10 mL		Item	Material	Qty	UOM
2000.00	mg	1	Ascorbic acid, USP, ampoule grade, 10% excess	9.90	kg
1.00	mg	2	Sequestrene disodium purified	4.50	g
QS	mL	3	Sodium bicarbonate, USP, for pH adjustment (5.8–6.0)	4.695 (ca.)	kg
10.00	mg	4	Sodium bisulfite, USP	45.00	g
QS	mL	5	Water for injection	QS to 45.00	L

Manufacturing Directions

1. Add 20 L item 5 to a glass-lined steam jacketed kettle and heat to 95°C with stirring.
2. Add item 2, begin continuous N_2 gas flush, and cool to 50°C with cold water in jacket.
3. Add items 1 and 3 slowly to avoid foaming and agitate well until pH is between 5.8 and 6.0. Fumes of CO_2 need to be vented out.
4. Add item 4. Filter aseptically into a previously sterilized bottle.
5. Store in cold room until filling. Fill aseptically into 10-mL vials with N_2 flush.
6. Autoclave sealed vials at 105°C and 5 psi for 10 minutes.
7. Remove from autoclave and cool rapidly by squelching into 21°C water.

Ascorbic Acid, B Complex Vitamin, with Beta-Carotene Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Beta-carotene	5.00	g
5.00	mg	2	Tocopherol acetate	5.00	g
10.00	mg	3	Sodium ascorbate	10.00	g
3.50	mg	4	Ascorbyl palmitate	3.50	g
1.00	mg	5	Riboflavin-5′-phosphate sodium	1.00	g
1.00	mg	6	Thiamine hydrochloride	1.00	g
3.00	mg	7	Nicotinamide	3.00	g
1.00	mg	8	Pyridoxine hydrochloride	1.00	g
14.00	mg	9	Glycerol	14.00	g
35.00	mg	10	Lutrol F-68®	35.00	g
QS	mL	11	Sodium hydroxide for pH adjustment	QS	
QS	mL	12	Water for injection, USP	QS to 1.00	L
66.50	mg	13	Coconut oil fractionated (Miglyol 812)	66.50	g

Manufacturing Directions

1. To item 9, add item 10 and items 4 to 8.
2. Add 0.6 L of item 12, mix, and heat to 60°C; mix again.
3. Adjust pH to 7.4 with 1 M item 11.
4. Heat the mixture of items 13 and 3 to 180°C.
5. Add item 1 to step 4 with N_2 protection.
6. Emulsify the oily solution into the aqueous solution of the vitamins by using an Ultra-Tur-rax® at 3000 rpm. Further emulsification to a fine-particle emulsion takes place by two passages through a homogenizer under 1000 bars.
7. Subsequently, cool the emulsion to room temperature and dispense into vials. The particle size is 200 nm. The beta-carotene concentration is 5% of the weight of the oil phase.

Ascorbic Acid Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
250.00	mg	1	Ascorbic acid, USP, 20% excess	3000.00	g
1.00	mg	2	Parachlorometa cresol	1.00	g
145.80	mg	3	Sodium bicarbonate, NF	145.80	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS		7	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Boil approximately 110% of item 4 in a separate vessel and allow to cool to room temperature.
2. In another vessel, take approximately 0.60 L of item 4 and dissolve in it item 1 slowly with continuous mixing in an open vessel. Item 1 will not completely dissolve at this stage.
3. Provide continuous mixing of item 7 throughout manufacturing.
4. Add item 3 with vigorous mixing gradually and allowing effervescence to subside as more item 3 is added. Keep mixing until both items 1 and 3 are completely dissolved.
5. Add item 2 and dissolve completely.
6. Make up the volume with item 4.
7. Sample. Take pH (5.5, range 5.5–6.4). Adjust pH with item 5 or 6.
8. Filter through a presterilized filtration assembly using a 0.22-μm filter and a 0.45-μm prefilter.
9. Fill ca. 2.15 mL into amber type I glass ampoules.
10. Autoclave at 121°C for 30 minutes.
11. Sample for clarity and final check.

Ascorbic Acid, USP, Injection With Disodium Edetate

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
250.00	mg	1	Ascorbic acid as sodium ascorbate 300 mg	250.00	g
0.025	%	2	Disodium edetate	0.025	%
QS	mL	3	Water for injection	QS to 1.00	L
QS	mL	4	Hydrochloric acid for pH adjustment	QS	mL
QS	mL	5	Sodium hydroxide for pH adjustment	QS	mL

Ascorbic Acid, USP (250 mg/mL Injection)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
250.00	mg	1	Ascorbic acid as sodium ascorbate	300.00	g
1.00	mg	2	Sodium bisulfite, USP	1.00	g
1.50	%	3	Benzyl alcohol, NF	1.50	%
QS	mL	4	Water for injection, USP	QS to 1.00	L

Asparaginase for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
10,000	IU	1	Asparaginase	10MM	IU
80.00	mg	2	Mannitol	80.00	g
QS		3	Water for injection	1.00	L

Note: Lyophilized powder.

Manufacturing Directions

Dissolve items 1 and 2 in item 3 and lyophilize.

Atropine, Chlorpheniramine Maleate, and Phenylpropanolamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.20	mg	1	Atropine sulfate, USP	0.20	g
12.50	mg	2	Phenylpropanolamine HCl, NF	12.50	g
5.00	mg	3	Chlorpheniramine maleate, USP	5.00	g
5.00	mg	4	Chlorobutanol anhydrous, USP	5.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Atropine Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.50	mg	1	Atropine sulfate, USP, 5% excess	0.525	g
0.0003	mL	2	Acetic acid	0.30	mL
1.20	mg	3	Sodium acetate	1.20	g
6.50	mg	4	Sodium chloride, NF	6.50	g
1.00	mg	5	Sodium metabisulfite, NF	1.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	Cy	7	Nitrogen gas, NF	QS	cy

Manufacturing Directions

Note: This solution must be prepared in a clean Pyrex bottle. This product needs N_2 protection during all steps of production. Avoid contact; wear gloves, glasses, and mask. Definitely avoid eye and skin contact; if exposed wash promptly with water.

1. Bring to boil item 6 in a suitable vessel; allow to cool to room temperature.
2. Add items 1 through 5, one by one, and by applying vigorous mixing.
3. Measure pH 4.0 to 6.0; do not adjust pH.
4. Filter solution through a 0.22-μm filter assembly.
5. Fill 1.1 mL into a flint type I glass ampoule.
6. Terminally sterilize at 116°C for 30 minutes.
7. Sample for final testing, clarity, and sterility.

Atropine Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Atropine sulfate, USP	1.00	g
8.50	mg	2	Sodium chloride, USP	8.50	g
QS	mL	3	Sulfuric acid, reagent grade	QS	mL
QS	cy	4	Nitrogen gas, NF	QS	cy
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

See precautions above.

1. Collect ca. 0.9 L of item 5 in a suitable Pyrex bottle and 0.1 L of item 5 in another bottle.
2. Check pH range 5.5 to 6.5.
3. Bubble N_2 through step 1 preparation and continue bubbling throughout.
4. While bubbling N_2 gas, add and dissolve items 1 and 2. Mix well.
5. Check and record pH; adjust downward to 5.0 (range 4.8–5.2) by 0.1 N sulfuric acid. (Prepare a fresh solution by taking 0.3 mL of concentrated sulfuric acid and adding to it 99.7 mL freshly distilled water.)
6. QS to 1 L by item 5 previously saturated with N_2 gas.
7. Prepare a 0.2-μm filter and sterilize in autoclave at 121°C for 30 to 35 minutes.
8. Sterilize all Pyrex bottle fittings and filling parts in autoclave at 121°C for 30 to 35 minutes.
9. Sterilize sufficient number of Pyrex bottles with dry heat (270–280°C) for 2 hours and 50 minutes (range 2 hours and 45 minutes to 3 hours). Use bottles within 72 hours.
10. Perform the pressure test on the filter unit.
11. Filter the solution through the sterile filter unit into sterile Pyrex bottles. The process should not go beyond 24 hours.
12. Perform the bubble point test at the end of filtration.
13. Wash 1-mL ampoules and sterilize at 270°C to 280°C for 2 hours and 50 minutes to 3 hours. Use them within 24 hours.
14. Aseptically fill 1.15 mL (1.10–1.18 mL). Flush each ampoule with sterile-filtered N_2 gas. Seal.
15. Autoclave at 122°C (121–124°C) for 12 minutes (10–14 minutes).
16. Sample for complete testing.

Aztreonam for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
1.00	g	1	Aztreonam	1.00	kg
0.78	g	2	Arginine	0.78	kg

Note: After reconstitution, pH is 4.5 to 7.5.

Basiliximab for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
20.00	mg	1	Basiliximab	20.00	g
7.21	mg	2	Potassium phosphate monobasic	7.21	g
0.99	mg	3	Disodium hydrogen phosphate anhydrous	0.99	g
1.61	mg	4	Sodium chloride	1.61	g
20.00	mg	5	Sucrose	20.00	g
80.00	mg	6	Mannitol	80.00	g
40.00	mg	7	Glycine	40.00	g
5.00	mL	8	Water for injection for reconstitution		

Benzylpenicillin + Dihydrostreptomycin Injectable Suspension (200,000 U + 200 mg/mL)

Formulation

I. Procaine benzylpenicillin, 20.0 g; dihydrostreptomycin sulfate, 20.0 g.

II. Kollidon 12 PF [1], 0.5 g; carboxymethyl cellulose sodium, 0.5 g; sodium citrate, 0.6 g; paraben, QS; water for injectables, add 100 mL.

Manufacturing Directions

Prepare solution II, add the components I to the well-stirred solution II, and pass through a colloid mill.

B Complex Injection: Niacinamide, Pyridoxine, Riboflavin, and Thiamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Thiamine hydrochloride, 25% excess	12.50	g
0.50	mg	2	Riboflavin, use sodium phosphate, 12.5% excess	0.80	g
1.00	mg	3	Pyridoxine, use HCl, 15% excess	1.20	g
20.00	mg	4	Niacinamide, 12.5% excess	22.50	g
0.50	%	5	Liquefied phenol, NF	5.00	mL
0.012	mL	6	Benzyl alcohol, NF	12.00	mL
1.00	mg	7	Disodium edetate, NF	1.00	g
1.00	mg	8	Thiourea	1.00	g
0.02	mL	9	Polysorbate 80 (Tween)	20.00	mL
0.10	mL	10	Propylene glycol	100.00	mL
QS	mL	11	Sodium hydroxide for pH adjustment	QS	
QS	mL	12	Hydrochloric acid for pH adjustment	QS	
QS	mL	13	Water for injection, USP	QS to 1.00	L
QS		14	Nitrogen gas, NF	QS	
0.0175	mL	15	Concentrated hydrochloric acid (10%)	17.50	mL

Manufacturing Directions

1. Use freshly distilled item 13; autoclave at 121°C for 30 minutes, cooled and bubbled with item 14 for 20 minutes.
2. Dissolve items 4 and 2 in sufficient item 13 in a suitable container.
3. Dissolve items 1, 3, and 7.
4. Add item 15 to step 3 and then one by one add items 10, 6, and 5. Mix well.
5. Add item 9 slowly with vigorous mixing.
6. Check pH to 3.8 to 4.2 and adjust with items 11 or 12, as necessary.
7. Let the solution age in a covered vessel flushed with item 14 for 7 days.
8. Filter through a presterilized assembly using a 0.45-μm prefilter and a 0.22-μm membrane filter into a sterilized staging vessel.
9. Fill aseptically into type I 10-mL amber vials (sterilized at 200°C for 4 hours) and using butyl coated with Teflon® rubber stoppers sterilized at 115°C for 30 minutes after washing. Provide pre- and postflush with item 14.
10. Sample for complete testing.

B Complex Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Thiamine hydrochloride, 10% excess	110.00	g
2.00	mg	2	Riboflavin-5′-phosphate, 10% excess	2.20	g
2.00	mg	3	Pyridoxine hydrochloride, 10% excess	2.20	g
100.00	mg	4	Niacinamide, 10% excess	110.00	g
20.00	mg	5	Benzyl alcohol	20.00	g
QS	mL	6	0.1 N sodium hydroxide for pH adjustment	QS	
QS	mL	7	3 N hydrochloric acid for pH adjustment	QS	
QS	mL	8	Water for injection	QS to 1.00	L

Manufacturing Directions

1. Measure ca. 0.5 L of water for injection in appropriate clean vessel. Heat to between 50°C and 60°C. Cool to room temperature.
2. Add thiamine, riboflavin, pyridoxine, niacinamide, and benzyl alcohol with constant stirring.
3. Bring to final volume of 30 L with water for injection. Check pH and adjust to between 4.5 and 7.0 if necessary.
4. Sample for pH.
5. Filter through a sterile 0.45- and 0.22-μm membrane filter. Check for integrity.
6. Autoclave vials at 121°C for 20 minutes.
7. Sample for assay, sterility, pyrogen/LAL, and stability.

B Complex Injection: Niacinamide, Pantothenate, Pyridoxine, Riboflavin, Thiamine Injection

This product is made up of two solutions prepared separately and mixed at the time of administration.

Solution 1

Bill of Materials for Solution 1 (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
160.00	mg	1	Thiamine hydrochloride, USP, 5% excess	168.00	g
8.00	mg	2	Pyridoxine hydrochloride, USP, 0.5% excess	8.04	g
0.90	%	3	Benzyl alcohol, NF (0.9%)	9.075	g
0.38	mg	4	Sodium formaldehyde sulfoxylate	379.82	g
QS	—	5	Carbon dioxide gas, technical	QS	—
QS	mL	6	Water for injection, USP	QS to 1.00	L

Solution 2

Bill of Materials for Solution 2 (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Niacinamide, USP, powder 3% excess	206.00	mg
0.10	mg	2	Sodium sulfide (nonahydrate) crystals[a]	103.00	mg
1.00	%	3	Charcoal activated, USP[b]	2.06	mg
5.30	mg	4	Riboflavin, use riboflavin-5′-phosphate sodium, USP[c]	7.26	g
0.90	%	5	Benzyl alcohol, NF (0.9%)	9.00	g
13.25	mg	6	Sodium pantothenate dextro, 10% excess	14.57	g
QS	—	7	Carbon dioxide gas, technical	QS	—
QS	mL	8	Acid hydrochloric, reagent-grade bottles[d]	QS	mL
QS	mL	9	Water for injection, USP	QS to 1.00	L

Note: The 3% excess of niacinamide is allowed for possible loss in charcoal-sodium sulfide treatment.
[a] Sodium sulfide calculated at 0.05% w/w niacinamide.
[b] Charcoal activated is calculated at 1% w/w niacinamide.
[c] Riboflavin-5′-phosphate sodium is calculated at 73% of riboflavin.
[d] Used for pH adjustment only.

Manufacturing Directions

Note: Protect solution from light and oxidation. Use CO_2 gas at all times to protect solution. Sodium formaldehyde sulfoxylate precipitates out metallic impurities and also acts as an antioxidant. Use glass equipment wherever possible. Avoid inhaling hydrogen sulfide fumes given off during the sodium sulfate purification treatment of niacinamide.

Solution 1

1. Preparation.
   a. Dissolve items 1, 2, and 3 in 370 mL of item 6. Saturate with CO_2 gas.
   b. Dissolve item 4 in 14 mL of item 6 and add to the solution in step 1a.
   c. Age for 2 days under CO_2 protection.
   d. QS with item 6 to 1 L and age another 2 days under CO_2 gas protection.
   e. Check pH (range 2.5–3.5). Sample.
   f. Transfer solution to a portable glass-lined tank for filling. Seal tank under CO_2 gas protection.
   g. Prepare for sterilization a 0.22-μm membrane and approved prefilter.
2. Preparation of containers. Wash, dry, stack, and then sterilize ampoules in an electric oven for 2 hours at 200°C. Deliver to sterile filling area.
3. Filtration. *Precaution*: Sterile solution; handle aseptically. Protect from light and oxidation.
   a. Protect surge bottle headspace with sterile CO_2 gas.
   b. Connect tank, the sterile filtration setup, which has been previously prepared, and a sterile surge bottle with aseptic technique.
   c. Apply 5 to 10 lb (do not use more than 10-lb pressure) of CO_2 pressure to the tank and filter enough solution to half-fill surge bottle. Use aseptic technique.
   d. Transfer filter delivery tube to filling siphon in an empty, sterile surge bottle. Siphon should be attached to filling machine.
   e. Filter enough solution to fill surge bottle and start filling.
   f. Sterile-fill the appropriate amount of solution into each clean, dry sterile container. Displace remaining air with sterile-filtered CO_2 gas and seal the ampoules. Sample.

Solution 2

1. Preparation.
   a. Boil 550 mL of item 9 and dissolve items 1, 2, and 3.
   b. Filter solution through a carbon precoated filter by using approved pads and papers. Recirculate until solution is clear.
   c. Reheat solution from step 1b to 75°C to 85°C, then add and dissolve item 4. When solution is complete, cool to 25°C under CO_2 protection.
   d. Add and dissolve items 5 and 6. Circulate solution through bottom tank valve to ensure complete solution.
   e. QS with item 9 to 1 L. Keep solution protected with CO_2 gas.
   f. Check pH. Adjust to 5.6 to 5.9 with concentrated hydrochloric acid. Sample.
   g. Transfer solution to a portable glass-lined tank for filling. Seal tank under CO_2 gas protection.
   h. Prepare for sterilization a 0.22-μm membrane and approved prefilter.
   i. Sterilize ampoules in an electric oven for 2 hours at 200°C.
   j. Transfer filter delivery tube to filling siphon in an empty, sterile surge bottle. Siphon should be attached to filling machine.
   k. Filter enough solution to fill surge bottle and start filling. Adjust flow through the filter to equal that of filling so that there is no surge on the filter.
   l. Sterile-fill the appropriate amount of solution into each clean, dry sterile container. Displace remaining air with sterile-filtered CO_2 gas and seal the ampoules. Sample.

B Complex Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Thiamine hydrochloride, 50% excess	15.00	g
2.00	mg	2	Riboflavin, use sodium phosphate, 20% excess	3.30	g
2.00	mg	3	Pyridoxine, use HCl, 20% excess	2.40	g
100.00	mg	4	Niacinamide, injectable grade, 15% excess	115.00	g
0.50	%	5	Liquefied phenol, NF	5.00	mL
0.012	mL	6	Benzyl alcohol, NF	12.00	mL
1.00	mg	7	Disodium edetate, NF	1.00	g
1.00	mg	8	Thiourea	1.00	g
0.020	mL	9	Polysorbate 80 (Tween)	20.00	mL
0.10	mL	10	Propylene glycol	100.00	mL
QS	mL	11	Sodium hydroxide for pH adjustment	QS	
QS	mL	12	Hydrochloric acid for pH adjustment	QS	
QS	mL	13	Water for injection, USP	QS to 1.00	L
QS		14	Nitrogen gas, NF	QS	
0.0175	mL	15	Concentrated hydrochloric acid (10%)	17.50	mL
5.00	mg	16	D-Panthenol, 20% excess	6.00	g

Manufacturing Directions

1. Use freshly distilled item 13. Autoclave at 121°C for 30 minutes, cooled and bubbled with item 14 for 20 minutes.
2. Dissolve items 4 and 2 in sufficient item 13 in a suitable container.
3. Dissolve items 1, 3, and 7.
4. Add item 16 to solution in step 3 and dissolve.
5. Add item 15 to solution in step 3 and then one by one add items 10, 6, and 5. Mix well.
6. Add item 9 slowly with vigorous mixing.
7. Check pH to 3.8 to 4.2 and adjust using items 11 or 12, as necessary.
8. Let the solution age in a covered vessel flushed with item 14 for 7 days.
9. Filter through a presterilized assembly using a 0.45-μm prefilter and a 0.22-μm membrane filter into a sterilized staging vessel.
10. Fill aseptically into 10-mL amber type I vials (sterilized at 200°C for 4 hours) and using butyl coated with Teflon or latex rubber stoppers sterilized at 115°C for 30 minutes after washing. Provide pre- and postflush with item 14.
11. Sample for complete testing.

B Complex Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Thiamine hydrochloride, 50% excess	15.00	g
3.00	mg	2	Riboflavin-5′-phosphate, 20% excess	3.30	g
5.00	mg	3	Pyridoxine, use HCl, 20% excess	2.40	g
60.00	mg	4	Niacinamide, injectable grade, 15% excess	115.00	g
0.50	%	5	Chlorbutol	5.00	mL
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Hydrochloric acid for pH adjustment	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L
QS		9	Nitrogen gas, NF	QS	
5.00	mg	10	D-Panthenol, 20% excess	6.00	g

Manufacturing Directions

1. Use freshly distilled item 8. Autoclave at 121°C for 30 minutes, cooled and bubbled with item 14 for 20 minutes.
2. Dissolve items 2 and 4 in 0.4 L of item 8 in a suitable container.
3. Dissolve items 1 and 3 in 0.4 L of item 8 in another vessel.
4. Dissolve item 10 in 0.15 L of item 8 and add this solution to step 3.
5. Add this solution to the solution in step 2.
6. Make up volume with item 8 and add item 5. Stir to dissolve completely.
7. Check and adjust pH with item 6 or 7 to 5.0 to 5.5 (do not adjust if within this range).
8. Keep the preparation at 10°C for 7 days and then at room temperature for another 7 days.
9. Filter through a presterilized assembly using a 0.45-μm prefilter and a 0.22-μm membrane filter into a sterilized staging vessel.
10. Fill aseptically into 10-mL amber type I vials (sterilized at 200°C for 4 h) and using butyl coated with Teflon or latex rubber stoppers sterilized at 115°C for 30 minutes after washing. Provide pre- and postflush with item 9 (purified by passing through 1% phenol solution).
11. Sample for complete testing.

B Complex, Vitamin D, Vitamin E Lyophilized Injection

This product comprises two solutions, which are mixed together before injecting.

Solution 1

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.02	mg	1	Sodium formaldehyde sufoxylate, NF	0.02	g
10.20	mg	2	Thiamine HCl ampoule powder 200 mesh, 10% excess	11.22	g
2.55	mg	3	Pyridoxine HCl, USP	2.55	g
38.25	mg	4	Niacinamide, USP, powder for ampoules	38.25	g
0.02	mg	5	Sodium sulfide (nonahydrate) crystals	0.02	g
		6	Charcoal activated, USP	1.00	g
2.55	mg	7	Riboflavin-5′-phosphate sodium USP, 10% excess	3.842	g
51.00	mg	8	Ascorbic acid, USP, 15% excess	58.65	g
39.02	mg	9	Polysorbate 80 NF	39.02	g
510	U	10	Vitamin D, use Vitamin D_3 in arachis oil with 20% excess	0.612	g
4080	U	11	Vitamin A, use vitamin A palmitate 1.7 million IU/g with 31.25% excess; use only potency 1375–1500/g	3.15	g
1.02	IU	12	Vitamin E USP, use D-alpha-tocopheryl acid succinate USP	0.843	g
QS	mL	13	Carbon dioxide gas, technical	QS	
QS	mL	14	Water for injection, USP	QS	

Note: Solution 1 contains a 2% manufacturing excess of all vitamins to satisfy label claim when between 10.0 and 10.3 mL of lyophilized solution is reconstituted to 10.2 mL. The scale column includes this 2% manufacturing excess. Figures in the Standard Qty column include both the manufacturing excesses and any stability excesses indicated in bill of materials.

Manufacturing Directions

Note: Protect solution from light. Use CO_2 gas at all times during manufacturing process to protect solution. Sodium formaldehyde sulfoxylate precipitates out metallic impurities and also acts as an antioxidant. Use glass equipment wherever possible.

1. Preparation.
   Part I
   a. Heat 16% of final volume of water for injection to boiling.
   b. Cool to room temperature while bubbling through CO_2 gas.
   c. Add sodium formaldehyde sulfoxylate, thiamine HCl, and pyridoxine HCl.
   d. Seal under CO_2 gas protection and age 2 or more days.
   e. If a precipitate forms, remove by filtering through paper.
   Part II
   a. Heat 300 mL water for injection to boiling.
   b. Add and dissolve niacinamide and sodium sulfide.
   c. Add charcoal and stir for 1 hour under a hood. Cut off heat supply to allow cooling.
   d. Filter off the charcoal.
   e. Add and dissolve riboflavin-5′-phosphate sodium and cool to 25°C under CO_2 gas protection.
   f. After aging part I combine with part II.
   g. Add and dissolve ascorbic acid. Add ascorbic acid slowly while constantly stirring and bubbling CO_2 gas through solution.
   h. Saturate polysorbate 80 with CO_2 gas and add vitamin D_3 in arachis oil, vitamin A palmitate, and vitamin E. Mix well.
   i. Add polysorbate–vitamin mixture (step h) to main batch and mix thoroughly while bubbling CO_2 gas through solution.
   j. Add water for injection to a QS of 1000 mL. Check pH (range 3.0–4.0).
   k. Sample for testing.
   l. Transfer solution to a portable glass-lined tank for filling. Seal tank under CO_2 gas protection.
   Caution: Do not hold solution more than 4 days without reassay of vitamins before filling. Seal under CO_2 gas protection.
   m. Prepare a sterile 0.22-μm membrane filter, using an approved prefilter.
   Note: Protect solution from light and oxidation. Handle aseptically.
2. Filtration.
   a. Connect tank, sterile filter, and sterile surge bottle with aseptic technique.
   b. Apply 5 to 10 lb CO_2 pressure to tank (do not use more than 10 lb) and filter to fill surge bottle. When full, remove filling tube and replace with sterile venting filter by using aseptic technique.
   c. Transfer full surge bottles to filling area.
3. Preparation of vials.
   a. Wash and dry vials and load in appropriate containers for sterilization.

   b. Sterilize using dry heat at 200°C (–0, +50°C) glass temperature for 225 minutes (–0, +360 minutes).
      Note: This cycle or an equivalent cycle that ensures sterile, pyrogen-free vials may be used.
   c. Deliver vials to the sterile filling area.
4. Preparation of stoppers.
   a. Leach stoppers by boiling for 10 minutes in deionized water.
   b. Wash stoppers using rubber cycle (slow tumbling) with Triton X-100.
   c. Dry in a fast dryer at 55°C.
   d. Store in suitable containers until ready for use.
   e. Tray, inspect, and rinse thoroughly. Wrap tray and identify.
   f. Sterilize in a steam autoclave at 121°C for 60 minutes.
5. Filling. Sterile 25-mL vial or sterile 2-mL vial.
   a. Under aseptic conditions, fill the appropriate amount of solution 1 into each sterile vial.
      1. Fill 10.1 mL (range 10.0–10.3 mL) for the 10-mL final reconstituted product.
      2. Alternatively, fill 1.13 mL (range 1.05–1.18 mL) for the 1-mL final reconstituted product.
   b. Sample for testing.
   c. Place each filled vial into a sterile tray. Immediately cover the vial with a rubber stopper. Label trays.
   d. Place each tray in a freezer at -40°C and freeze overnight.
   e. Transfer to lyophilizer (at -40°C) and lyophilize to less than 2% moisture. Do not allow temperature to go more than 45°C.
   f. At end of lyophilization cycle, bring chamber to 5-in vacuum with sterile CO_2 gas. Ram stoppers home into vials and then bring chamber to atmospheric pressure with sterile CO_2 gas.
   g. Apply aluminum caps.
   h. Sample for testing.

Solution 2
B Complex Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.73	mg	1	Sodium pantothenate dextro, 20% stability excess	6.12	g
10.31	mg	2	Benzyl alcohol, NF	9.176	g
2.29	μg	3	Cyanocobalamin (B_{12}), USP, 25% stability excess	2.548	mg
114.60	mg	4	Polyethylene glycol 400, NF low color	101.98	g
QS	mL	5	Hydrochloric acid, reagent grade, for pH adjustment[a]		
QS	mL	6	Nitrogen gas, NF[b]	QS	
QS	mL	7	Water for injection, USP	QS to 890.00	mL

Note: Solution 2 contains a 14.6% manufacturing excess of vitamins and benzyl alcohol to insure label claim when 8.9 mL of solution is reconstituted to 10.2 mL. Figures in the Scale column include this 14.6% manufacturing excess. Figures in the Standard Qty column include both the manufacturing excess and any stability excesses indicated in the bill of materials. Alternatively, solution 2 contains a 14.6% manufacturing excess of vitamins and benzyl alcohol to ensure label claim when 1.0 mL of solution is reconstituted to 1.15 mL. Figures in the Scale column include this 14.6% manufacturing excess. Figures in the Standard Qty column include both the manufacturing excess and any stability excess indicated in the bill of materials.

[a] Used only for pH adjustment if necessary.

[b] Bulk container should be flushed with N_2 and resealed after weighing.

Manufacturing Directions

1. Preparation.
   a. Dissolve sodium pantothenate and benzyl alcohol in 560 mL of water for injection.
   b. Add vitamin B_{12} and polyethylene glycol 400.
   c. Add water for injection and QS to 890 mL. Check pH. If pH is more than 8, adjust down to 6 to 8 with 0.1 N hydrochloric acid.
   d. Allow solution to stand overnight. Check pH (range 6–8).
   e. Sample for testing.
   f. Prepare a sterile 0.22-μm membrane filter by using an approved prefilter.
2. Filtration
   C*aution*: Handle solution aseptically to preserve sterility.
   a. Connect tank, sterile filter, and sterile surge bottle with aseptic technique.
   b. Apply 5 to 10 lb of N_2 gas pressure to tank (do not use more than 10 lb) and filter enough solution to half-fill surge bottle. If pH does not have pressure head, connect pump between tank and filter.
   c. Transfer filter delivery tube to filling siphon in an empty, sterile surge bottle. Siphon should be aseptically attached to filling equipment.
   d. Filter sufficient solution to fill surge bottle. Check quality of filtrate and start filling. Adjust flow through the filter to equal that of filling.
3. Preparation of ampoules.
   a. Wash and dry ampoules and load in appropriate containers for sterilization.
   b. Sterilize by using dry heat at 200°C (–0, +50°C) glass temperature for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (+10°C) for the duration of the cycle.
      Note: This cycle or an equivalent cycle that ensures sterile, pyrogen-free ampoules may be used.
   c. Deliver to the sterile filling area.
4. Filling. Sterile 10- or 1-mL ampoule.
   a. Aseptically fill the appropriate amount of solution 2 into each sterile ampoule and seal.
      1. Fill 9.2 mL (range 9.1–9.3 mL) for the 10-mL final reconstituted product.
      2. Alternatively, fill 1.1 mL (range 1.05–1.15 mL) for the 1-mL final reconstituted product.
   b. Sample for testing.

1. Finishing.
   a. Label each vial of freeze-dried solution 1 and each ampoule of solution 2. Pack one of each into product carton.
   b. Sample for testing.

B Complex Vitamin Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Pyridoxine HCl, USP, as riboflavin-5′-phosphate sodium	10.00	g
15.00	mg	2	D-Panthenol	15.00	g
150.00	μg	3	Cyanocobalamin USP	150.00	mg
10.00	mg	4	Choline chloride	10.00	g
0.70	mg	5	Cobalt gluconate	0.70	g
0.20	mg	6	Copper gluconate	0.20	g
15.00	mg	7	Ferric ammonium citrate	15.00	g
2.00	%	8	Benzyl alcohol, NF	2.00	%
100.00	mg	9	Niacinamide, USP	100.00	g
5.00	mg	10	Chlorobutanol anhydrous, USP	5.00	g
10.00	mg	11	Inositol	10.00	g
10.00	μg	12	Biotin	10.00	mg
20.00	mg	13	Methionine, NF	20.00	g
20.00	mg	14	*dl*-Lysine	20.00	g
20.00	mg	15	Glycine	20.00	g
QS	mL	16	Water for injection, USP	QS to 1.00	L

B Complex Vitamin Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
150.00	mg	1	Thiamine HCl, USP	150.00	g
150.00	mg	2	Niacinamide, USP	150.00	g
2.00	mg	3	Riboflavin as riboflavin-5′-phosphate sodium	2.00	g
10.00	mg	4	D-Panthenol	10.00	g
10.00	mg	5	Pyridoxine HCl, USP	10.00	g
20.00	mg	6	Choline chloride	20.00	g
20.00	mg	7	Inositol	20.00	g
100.00	μg	8	Cyanocobalamin, USP	100.00	mg
2.00	%	9	Benzyl alcohol, NF	2.00	%
QS	mL	10	Water for injection, USP	QS to 1.00	L

B Complex Vitamin Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
125.000	mg	1	Niacinamide, USP	125.000	g
100.000	mg	2	Ascorbic acid as sodium ascorbate, USP	100.000	g
5.000	mg	3	Riboflavin-5′-phosphate sodium	5.000	g
5.000	mg	4	Pyridoxine HCl, USP	5.000	g
50.000	mg	5	D-Panthenol	50.000	g
1.169	mg	6	Methyl paraben, USP	1.169	g
0.134	mg	7	Propyl paraben, USP	0.134	g
QS	mL	8	Water for injection	QS to 1.00	L
QS	mL	9	Hydrochloric acid for pH adjustment	QS	mL

B Complex Vitamin Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Choline chloride	100.00	g
50.00	mg	2	Inositol	50.00	g
50.00	mg	3	Methionine, NF	50.00	g
2.00	%	4	Benzyl alcohol, NF	2.00	%
QS	mL	5	Water for injection	QS to 1.00	L
QS	mL	6	Hydrochloric acid for pH adjustment	QS	mL

B Complex with Minerals Injection (Veterinary)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Thiamine HCl, USP	10.00	g
1.00	mg	2	Pyridoxine HCl, USP	1.00	g
1.50	mg	3	Riboflavin-5′-phosphate sodium	1.50	g
7.00	mg	4	D-Panthenol	7.00	g
50.00	μg	5	Cyanocobalamin, USP	50.00	mg
8.00	μg	6	Sodium chloride, USP	8.00	mg
0.10	mg	7	Copper gluconate	0.10	g
1.00	mg	8	Cobalt gluconate	1.00	g
8.00	mg	9	Ferric ammonium citrate (16–18% elemental iron)	8.00	g
100.00	mg	10	Niacinamide, USP	100.00	g
1.50	%	11	Benzyl alcohol, NF	1.50	%
QS	mL	12	Water for injection, USP	QS to 1.00	L

B Complex Vitamins with Hormones

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Testosterone, NF	10.00	g
0.50	mg	2	Estrone, NF	0.50	g
100.00	μg	3	Cyanocobalamin, USP	100.00	mg
50.00	mg	4	Thiamine HCl, USP	50.00	g
1.00	mg	5	Pyridoxine HCl, USP	1.00	g
5.00	mg	6	D-Panthenol	5.00	g
100.00	mg	7	Niacinamide, USP	100.00	g
20.00	mg	8	Lidocaine HCl, USP	20.00	g
0.20	%	9	Carboxymethylcellulose sodium, USP	0.20	%
0.20	%	10	Sodium phosphate, USP	0.20	%
4.00	%	11	Benzyl alcohol, NF	4.00	%
QS	mL	12	Water for injection, USP	QS to 1.00	L

B Complex Vitamins with Liver Extract Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Thiamine HCl, USP	10.00	g
5.00	mg	2	Riboflavin-5′-phosphate sodium	5.00	g
50.00	mg	3	Niacinamide, USP	50.00	g
3.00	mg	4	D-Panthenol	3.00	g
5.00	mg	5	Pyridoxine HCl, USP	5.00	g
30.00	μg	6	Cyanocobalamin, USP	30.00	mg
0.25	mL	7	Liver injection (20 μg/mL concentrate, supplies 5 μg B132 activity)	0.25	L
0.01	%	8	Edetate sodium	0.01	%
2.00	%	9	Benzyl alcohol, NF	2.00	%
QS	mL	10	Water for injection, USP	QS to 1.00	L

Benzodiazepine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
15.00	mg	1	Benzodiazepine[a]	15.00	g
0.18	mL	2	Polyethylene glycol (MW 300)	180.00	mL
0.75	mL	3	Propylene glycol (~QS volume)	750.00	mL
0.020	mL	4	Benzyl alcohol	20.00	mL

[a] 7-Chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepine-2-one.

Manufacturing Directions

1. To item 2 in a suitable container, mix items 3 and 4.
2. Add item 1 and dissolve.
3. Make up solution with item 3.
4. Filter and sterilize.

Benztropine Mesylate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Benztropine mesylate	1.00	g
9.00	mg	2	Sodium chloride	9.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Beta-Carotene Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
32.00	mg	1	Beta-carotene (30% dispersed in coconut oil; Miglyol 810)	32.00	g
40.00	mg	2	Poloxamer 188 (Pluronic F-68®)	40.00	g
10.00	mg	3	Glycerol	10.00	g
1.00	mg	4	Thimerosal	1.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take 418 mL of item 5 and mix in it item 2 in a suitable jacketed vessel.
2. Add 10 g of item 3 and heat to 45°C.
3. Add item 1 in a separate container and heat to 180°C to dissolve. Cool to 45°C.
4. Add to aqueous solution above with stirring to yield an emulsion.
5. The emulsification takes place at 45°C. Use an emulsifier such as an Ultraturrax® (7000–8000 rpm) for 8 minutes. Homogenize the emulsion at 1000 bar. The finished emulsion has an item 1 content of 1.6% and an average particle size of 210 nm.
6. Add item 4 and mix.
7. Fill 10 mL into vials aseptically.

Betamethasone Suspension Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3.00	mg	1	Betamethasone as betamethasone sodium phosphate	3.00	g
3.00	mg	2	Betamethasone acetate	3.00	g
7.10	mg	3	Sodium phosphate dibasic	7.10	g
3.40	mg	4	Sodium phosphate monobasic	3.40	g
0.10	mg	5	Disodium edetate	0.10	g
0.20	mg	6	Benzalkonium chloride	0.20	g
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Fill 5 mL into multidose vials; pH 6.8 to 7.2.

Bethanechol Chloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Bethanechol chloride	5.15	g
QS	mL	2	Water for injection, USP	QS to 1.00	L

Note: May be autoclaved at 120°C for 20 minutes without loss of potency.

Biotin Injection

Bill of Materials (Batch Size 1.5 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	μg	1	Biotin FCC	150.00	mg
QS	mL	2	Water for injection	1.50	L
QS	mL	3	Sodium hydroxide, NF, 1% for pH adjustment	QS	mL
QS	—	4	Nitrogen gas, NF	QS	—

Manufacturing Directions

1. Put approximately 1.2 L of item 2 into a suitable mixing tank and dissolve item 1.
2. Add 1 N item 3 in drops until item 1 is dissolved and pH is around 7.0.
3. Carefully adjust the pH between 7 and 7.5 with 1 N item 3.
4. QS to volume with item 2. Check pH.
5. Filter using a 0.22-μm filter and fill under item 4 into sterilized vials (220°C for at least 240 minutes). Autoclave stoppers at 121°C for 60 minutes in 2% disodium edetate solution (final rinse stopper with RO water 3 times).

Biperiden Lactate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Biperiden lactate	5.00	g
14.00	mg	2	Sodium lactate	14.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Bisantrene Emulsion Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.52	mg	1	Bisantrene base (96.15%)	0.52	g
100.00	mg	2	Sorbitan triisostearate	100.00	g
20.00	mg	3	Benzyl alcohol	20.00	g
30.00	mg	4	Sesame oil refined	30.00	g
7.50	mg	5	Pluronic C-68®	7.50	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Mix and stir item 1 at room temperature with items 2 to 5 until complete solution is obtained.
2. Make up the volume with item 6. Shake and sonicate for 20 seconds using a Branson Sonifier driver at a DC setting of 6 to 7 A to yield an emulsion wherein 95% of the particles are from 2 to 5 μm in size.

Bisantrene Emulsion Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.52	mg	1	Bisantrene base (96.15%)	0.52	g
100.00	mg	2	Triglycerol pentaoleate	100.00	g
20.00	mg	3	Benzyl alcohol	20.00	g
8.00	mg	4	Soy lecithin, 95% PC	8.00	g
22.50	mg	5	Glycerin, USP	22.50	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Borax Sodium Lubricating Ophthalmic Drops

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.70	mg	1	Borax sodium borate, NF, powder/borax EP	5.70	g
2.50	mg	2	Sorbic acid, NF/BP	2.50	g
1.00	mg	3	Disodium edetate, USP/BP	1.00	g
5.15	mg	4	Boric acid, NF, granular/EP	5.15	g
5.00	mg	5	Glycerin, USP (96%)/Glycerol, BP	5.00	g
1.00	mg	6	Sodium chloride, USP	1.00	g
4.50	mg	7	Hydroxypropyl methylcellulose 2906, USP, 4000 cps	4.50	g
QS	mg	8	Sodium hydroxide, reagent-grade pellets	QS	mL
QS	mL	9	Hydrochloric acid, reagent-grade bottles	QS	mL
QS	mL	10	Water purified	QS to 1.00	L

Manufacturing Directions

Note: Use thoroughly clean glass-lined or 304 or better-grade stainless steel steam-jacketed tank equipped with a speed-control agitator and cover. Keep cover closed.

1. Preparation of bulk solution.
   a. Charge 750 mL of item 10 into the mixing tank and begin mixing. Begin heating item 10 to 72°C to 82°C.
   b. While heating, slowly add items 1 to 6 with mixing, allowing each to disperse prior to addition of next in-
   e. Discontinue heating and continue mixing for at least 20 minutes after last addition of item 7.
   f. With mixing, continue to cool batch to less than 40°C and make up to 1 L with water, taking care to avoid foaming. Make the final adjustment with the stirrer turned off. Continue mixing for at least 20 minutes while batch is cooling to less than 40°C. Check pH (range 6.7–6.9). Adjust, if necessary, with 1 N item 8 or 1 N item 9. Mix for 15 minutes. Sample.
2. Sterilization and filling. Initiate sterilization within 48 hours of completion of bulk solution.

gredient. Rinse the inside tank walls and agitator shaft with 15 mL of item 10.

   c. Continue mixing the solution for at least 20 minutes. Stop agitation and visually verify dissolution. With continued agitation, verify that the solution temperature is in the range of 72°C to 82°C.
   d. With mixing, slowly add and disperse item 7 by slowly sprinkling on the surface of solution. Allow each addition to be dispersed before adding more powder. Adjust agitation rate so as to avoid excessive foaming.
   a. Sterilize bulk solution at 121°C to 123°C for 30 to 35 minutes. As the tank temperature reaches 121°C to 123°C, carefully bleed air from tank.
   b. After sterilization, as the batch is cooling, pressurize tank to approx 10 psig with sterile-filtered compressed air. With mixing, cool batch to less than 30°C. Stop mixing and store in tank at ambient temperature until ready to fill. Maintain a positive pressure in the tank until filling is complete.
   c. Set up a previously sterilized product filter and transfer line. Aseptically fill sterile solution into sterilized containers and apply sterile closure components. Sample.

Botulinum Toxin: Type A Purified Neurotoxin Complex

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
100.00	U	1	Clostridium botulinum type A neurotoxin complex	100,000	U
0.50	mg	2	Albumin (human)	0.50	g
0.90	mg	3	Sodium chloride	0.90	g

Note: Vacuum-dried.

Botulinum Toxin (Type B Injectable Solution)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1428	U	1	Clostridium botulinum type B neurotoxin complex	1428,000	U
0.50	mg	2	Human serum albumin	0.50	g
0.01	M	3	Sodium succinate	0.01	M
0.10	M	4	Sodium chloride	0.10	M
QS	mL	5	Hydrochloric acid for pH adjustment		
QS	mL	6	Sodium hydroxide for pH adjustment		
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Fill 3.5 mL for 5000 IU; adjust pH to 5.6 with item 5 or 6.

Bretylium Tosylate in Dextrose Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Dextrose anhydrous, USP	50.00	g
4.00	mg	2	Bretylium tosylate	4.00	g
QS	mL	3	Sodium hydroxide for pH adjustment		
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Water for injection, USP		

Note: This is the formula for 4.0 mg/mL; for other strengths, 2.0 or 8.0 mg/mL, use appropriate amounts of bretylium tosylate.

Manufacturing Directions

1. Add item 6 to ca. 95% of the final volume into tank.
2. Add and dissolve item 1 with mixing.
3. Add and dissolve item 2 with mixing.
4. Check pH, adjust if necessary to between 5.5 and 6.5 with item 4 or 5.
5. QS to final volume with item 6; mix to a uniform solution.
6. Check pH and adjust again as in step 4.
7. Filter solution through an appropriate filtration setup using an approved 0.45-μm or finer filter membrane with approved prefilter.
8. Autoclave using appropriate cycle with F_0 ranging from 8.0 to 18.0.
9. When filled in flexible plastic container, perform sterilization by circulated hot water spray and steam sterilization.

Buflomedil Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Buflomedil hydrochloride, injectable grade	10.00	g
42.00	mg	2	Dextrose hydrous, USP (use 38.18 g if anhydrous)	42.00	g
8.00	mg	3	Sodium chloride, USP	8.00	g
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Carbon dioxide, technical grade	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: Prepare the solution in a glass-lined or a 316 or higher temper-grade stainless steel tank cleaned according to approved plant SOPs. In place of item 6, N_2 gas, NF, can be used.

1. Preparation.
   a. Add water for injection to tank to ca. 90% of the final volume and bubble in CO_2 gas. Continue CO_2 protection throughout processing.
   b. With agitation, add and dissolve the buflomedil hydrochloride and dextrose. Mix until completely dissolved and solution is formed.
   c. QS to final volume with water for injection and mix well.
   d. Check and record pH (range 3.9–4.5). Adjust if necessary to pH 4.2 with 10% sodium hydroxide solution or dilute hydrochloric acid solution.
   e. Filter solution through a previously rinsed filtration setup by using an approved 0.45-μm or finer membrane and an approved prefilter. Filter into clean glass-lined or 316 stainless steel tank and protect with CO_2 gas.
   f. Sample for testing.
   g. Prepare an in-line 0.22-μm membrane filter for the filling line.
2. Filling. Use type I 5-mL glass ampoules.
   a. Using the inline filter, fill 5.3 mL into each clean, dry ampoule.
   b. Flush headspace with filtered CO_2 gas and seal.
   c. Sterilize in a steam autoclave at 120°C for 20 minutes.
   d. Sample for testing.

Bupivacaine Hydrochloride Injection 1: 0.75% in Dextrose 8.25% Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
7.50	mg	1	Bupivacaine hydrochloride (anhydrous), use bupivacaine HCl, USP, monohydrate	7.50	g
82.50	mg	2	Dextrose, powder, anhydrous, USP[a]	82.50	g
QS	mL	3	Hydrochloric acid[b]	QS	mL
QS	mL	4	Sodium hydroxide[b]	QS	mL
QS	mL	5	Water for injection, USP	QS to 1.00	L

[a] For tonicity adjustment.
[b] For pH adjustment.

Manufacturing Directions

1. Prepare the solution in a glass-lined or 316 stainless steel tank.
2. Mix and dissolve items 1 and 2.
3. Check pH (range 5.8–6.2). If necessary, adjust pH with item 3 or 4 solution.

Bupivacaine Hydrochloride Injection (0.25%)

1. QS with item 5 to final volume and mix.
2. Check the pH (range 5.8–6.2). If necessary, adjust pH with item 3 or 4 solution. Sample.
3. Prior to filling, filter the solution through a 0.22-μm membrane with an approved prefilter, if needed.
4. Fill appropriate volume into ampoules. Sample.

Bupivacaine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.50	mg	1	Bupivacaine hydrochloride, use bupivacaine HCl, USP, monohydrate	2.64	g
1.00	mg	2	Methyl paraben NF (Aseptoform M) powder	1.00	g
8.55	mg	3	Sodium chloride, USP	8.55	g
QS	mg	4	Sodium hydroxide, reagent-grade pellets[a]	QS	mg
QS	mL	5	Acid hydrochloric, reagent-grade bottles[a]	QS	mL
QS	mL	6	Water for injection	QS to 1.00	L

[a] Used for pH adjustment only.

Manufacturing Directions

Note: The solution must be prepared in a glass-lined or a 316 or more resistant-grade stainless steel tank cleaned according to approved plant basic operating procedure.

1. Preparation.
   a. Add item 6 to ca. 90% of the final volume into the tank and heat to NLT 90°C.
   b. Add item 2 and mix until dissolved.
   c. Cool to 25°C (range 25–30°C). Add and dissolve item 1. *Note*: Item 1 goes into solution slowly. Do not proceed until all drug is completely in solution.
   d. Add and dissolve item 3 with mixing. Mix solution for at least 10 minutes.
   e. Check pH. Adjust to 5.6 (range 5.6–5.8) with diluted item 4 (1%) or 5 (1%). Allow solution to mix for 10 minutes and recheck adjusted pH. *Note*: Make dilute item 4, 1.0% w/v, by dissolving 1.0 g of item 4 in sufficient water for injection to make 100 mL. Make diluted item 5 solution, 1.0% v/v, by dissolving 1.0 g of item 5 in sufficient water for injection to make 100 mL.
   f. QS solution to final volume with item 6. Mix for 10 minutes.
   g. Check pH (range 5.4–5.8). Readjust, if necessary, to pH 5.6 with dilute item 4 or 5.
   h. Filter solution through a previously rinsed filtration setup, using an approved 0.45-μm or finer membrane with an approved prefilter into a glass-lined or a 316 stainless steel tank.
2. Filling. Bottle: Type II glass.
   a. Fill specified amount into each clean, dry bottle. Apply stopper and overseal.
   b. Sterilize in a steam autoclave at 115°C for an F_0 of 8 to 18. Use terminal air overpressure and water spray cooling. Sample.

Bupivacaine Hydrochloride Injection: Bupivacaine with Epinephrine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.50	mg	1	Bupivacaine hydrochloride, use bupivacaine HCl, USP, monohydrate	2.64	g
0.005	mg	2	Epinephrine as epinephrine bitartrate	0.005	g
0.50	mg	3	Sodium metabisulfite	0.20	g
0.20	mg	4	Citric acid anhydrous	0.20	g
1.00	mg	5	Methyl paraben, NF (Aseptoform M) powder[a]	1.00	g
QS	ft^3	6	Nitrogen gas	QS	
8.00	mg	7	Sodium chloride	8.00	g
QS	mg	8	Sodium hydroxide, reagent-grade pellets[a]	QS	mg
QS	mL	9	Hydrochloric acid, reagent-grade bottles[a]	QS	mL
QS	mL	10	Water for injection	QS to 1.00	L

[a] Add only in multiple-dose vials. Adjust pH to 3.3 to 5.5 with item 4 or 5. Fill under N_2.

Buprenorphine Hydrochloride Injectable

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.30	mg	1	Buprenorphine as buprenorphine hydrochloride	0.324	g
50.00	mg	2	Dextrose anhydrous, USP	50.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Hydrochloric acid for pH adjustment		

Note: Adjust pH using item 4.

Caffeine Citrate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Caffeine anhydrous	10.00	g
5.00	mg	2	Citric acid monohydrate	5.00	g
8.30	mg	3	Sodium citrate dihydrate	8.30	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Hydrochloric acid for pH adjustment		
QS	mL	6	Sodium hydroxide for pH adjustment		

Note: Caffeine citrate (20 mg) is formed by addition of caffeine as above; adjust pH to 4.7.

Calcitonin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	IU	1	Calcitonin, Eel	5000.00	IU
2.00	mg	2	Albumin, human	2.00	g
0.414	mg	3	Sodium phosphate monobasic monohydrate	0.414	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: For 100 IU dose per vial, increase the label quantity to 10.00 mg/mL.

Calcitonin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200	IU	1	Calcitonin-salmon synthetic[a]	200,000	IU
2.25	mg	2	Acetic acid	2.25	g
5.00	mg	3	Phenol	5.00	g
2.00	mg	4	Sodium acetate trihydrate	2.00	g
7.50	mg	5	Sodium chloride	7.50	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a] Calcitonin–salmon synthetic is a synthetic polypeptide of 32 amino acids in the same linear sequence found in calcitonin of salmon origin.

Manufacturing Directions

1. Dissolve item 3 in a suitable quantity of item 4.
2. Add and dissolve, with slow agitation, item 2 to prevent frothing.
3. Add item 1 and dissolve.
4. Filter and fill 10 mL into each vial; stopper loosely.
5. Lyophilize [each vial contains 50 IU of calcitonin (SerGln GluLeuHisLysLeuGlnThr-TyrProArgThrAspValGlyAla GlyThrProNH_2)].

Calcitriol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00[a]	mg	1	Calcitriol in polysorbate 20 concentrate, 575 mg/g	2.00	g
2.00	mg	2	Polysorbate 20 (Tween 20), NF	2.00	g
1.50	mg	3	Sodium chloride, USP	1.50	g
10.00	mg	4	Sodium ascorbate microcrystalline, USP	10.00	g
7.60	mg	5	Sodium phosphate dibasic, USP, anhydrous	7.60	g
1.84	mg	6	Sodium phosphate, monobasic, USP, monohydrate	1.84	g
1.11	mg	7	Disodium edetate (dihydrate), USP	1.11	g
QS	mL	8	Water for injection, USP	QS to 1.00	L

[a] Consists of 1.0 mg of calcitriol and 2.00 mg polysorbate 20.

Manufacturing Directions

1. Prepare solution in a pressurizable glass-lined tank.
2. Add item 8 to ca. 110% of final volume into a suitable tank and commence bubbling of N_2 gas.
3. Heat item 8 to a temperature of NLT 85°C and hold at that temperature for 10 minutes. Vapor generated must be vented from the tank.
4. Continue to bubble N_2 gas into the water and begin to cool. Before the water reaches 30°C (range 30–45°C) transfer all but 90% of the final volume to a separate covered tank that has been pregassed with N_2 and maintain this water under an N_2 sparge as it continues to cool. This water is to be used for QS. Continue bubbling N_2 gas into the mixing tank.
5. When the water in the mixing tank has cooled to 20°C to 30°C, begin drug addition. *Note*: For all drug additions, minimize excessive agitation of solution with mixer (to avoid introducing oxygen into solution).
6. Add and dissolve items 3 to 7 with mixing.
7. Mix until all ingredients are dissolved and solution is uniform. Switch to an N_2 gas blanket.
8. Check pH (range 7.0–7.6). If the pH falls outside of the specific pH range, discard the solution and prepare another aqueous solution.
9. Add item 2 with mixing. Maintain an N_2 gas blanket, exercising caution to avoid excessive foaming.
10. Add an accurately weighed factored amount of item 1 to the aqueous solution with gentle mixing.
11. QS to final volume with item 8 that has been previously boiled and cooled under N_2 gas protection. Mix gently until solution is uniform. Sample.
12. Filter the solution through an approved 0.45-μm or finer membrane connected in series to a prefilter, if needed, into a glass-lined holding tank.
13. Prior to filling, aseptically filter solution through a filtration setup by using an approved 0.22-μm or finer membrane.
14. Aseptically fill appropriate quantity into sterile ampoules. Maintain N_2 gas protection.

Calcitriol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
4.00[a]	mg	1	Calcitriol in polysorbate 20 concentrate, 575 mg/g	2.00	g
1.50	mg	2	Sodium chloride, USP	1.50	g
10.00	mg	3	Sodium ascorbate microcrystalline, USP	10.00	g
7.60	mg	4	Sodium phosphate dibasic, USP, anhydrous	7.60	g
1.84	mg	5	Sodium phosphate monobasic, USP, monohydrate	1.84	g
1.11	mg	6	Disodium edetate (dihydrate), USP	1.11	g
QS	mL	7	Water for injection, USP	QS to 1.00	L

[a] Consists of 2.0 mg of calcitriol and 4.00 mg polysorbate 20.

Manufacturing Directions

1. Prepare solution in a pressurizable glass-lined tank.
2. Add item 7 to ca. 110% of final volume into a suitable tank and commence bubbling of N_2 gas.
3. Heat item 7 to a temperature of NLT 85°C and hold at that temperature for 10 minutes. Vapor generated must be vented from the tank.
4. Continue to bubble N_2 gas into the water and begin to cool. Before the water reaches 30°C (range 30–45°C) transfer all but 90% of the final volume to a separate covered tank that has been pregassed with N_2 and maintain this water under an N_2 sparge as it continues to cool. This water is to be used for QS. Continue bubbling N_2 gas into the mixing tank.
5. When the water in the mixing tank has cooled to 20°C to 30°C, begin drug addition. *Note*: For all drug additions, minimize excessive agitation of solution with mixer (to avoid introducing oxygen into solution).
6. Add and dissolve items 2 to 6 with mixing.
7. Mix until all ingredients are dissolved and solution is uniform. Switch to an N_2 gas blanket.
8. Check pH (range 7.0–7.6). If the pH falls outside the specific pH range, discard the solution and prepare another aqueous solution.
9. Add an accurately weighed factored amount of item 1 to the aqueous solution with gentle mixing.
10. QS to final volume with item 7 that has been previously boiled and cooled under N_2 gas protection. Mix gently until solution is uniform. Sample.
11. Filter the solution through an approved 0.45-μm or finer membrane connected in series to a prefilter, if needed, into a glass-lined holding tank.
12. Prior to filling, aseptically filter solution through a filtration setup by using an approved 0.22-μm or finer membrane.
13. Aseptically fill appropriate quantity into sterile ampoules. Maintain N_2 gas protection.

Calcium Glycerophosphate Injection with Lactate

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Calcium glycerophosphate	5.00	g
5.00	mg	2	Calcium lactate pentahydrate	5.00	g
0.25	%	3	Liquefied phenol, USP	2.50	g
5.00	mg	4	Sodium chloride, USP	5.00	g
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Hydrochloric acid for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	mL	8	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Preboil the total volume of item 7, maintain N_2 flush, and blanket throughout production.
2. In three separate suitable containers, dissolve item 1 in 40% of item 7, item 2 in 30% of item 7, and item 4 in 20% of item 7.
3. Let the calcium glycerophosphate and calcium lactate stand for at least 60 minutes and then combine in a suitable container. Add the liquefied phenol (item 3) and mix.
4. Add item 4 solution and mix to homogeneity.
5. Record pH and adjust to 7.0 to 7.5 with items 5 and 6.
6. Bring to volume with N_2-saturated item 7 and mix.
7. Sample for testing. Test for tonicity.

Calcium Glycerophosphate Injection: Calcium Glycerophosphate Injection (Human and Veterinary)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Calcium glycerophosphate	10.00	g
15.00	mg	2	Calcium levulinate	15.00	g
5.00	mg	3	Chlorobutanol anhydrous, USP	5.00	g
9.00	mg	4	Sodium chloride, USP	9.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Calcium Gluconate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
94.00	mg	1	Calcium gluconate, USP	94.00	g
5.00	mg	2	Calcium-*d*-saccharate. $4H_2O$	5.00	g
QS		3	1 N sodium hydroxide for pH adjustment	QS	
QS		4	Nitrogen gas, NF	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: Complete step 3 at least 90 hours prior to start of filling.

1. Boil 0.8 L of water for injection, bubble filtered N_2 for 10 to 15 minutes, and maintain an N_2 blanket throughout the following operation.
2. Add calcium gluconate to the water for injection and stir until the solution is clear.
3. Add calcium-*d*-saccharate and mix to a clear solution.
4. Transfer to another tank. After 24 hours, take into account the solution temperature and check pH and adjust to between 7.0 and 7.5, using 1 N sodium hydroxide solution.
5. Allow the above solution to come to room temperature and bring to final volume with water for injection. Do not reheat even if a few crystals come out of solution.
6. After cooling and pH adjustment, filter the solution once every 24 hours through a 0.45-μm prefilter and a sterilized 0.22-μm filter into a clean stainless steel tank. Repeat this for 3 days (see note).
7. After third filtration, sample and submit to QC; after QC approval pass again through a 0.45-μm prefilter and a 0.22-μm sterilized filter and fill under N_2 (postflush).
8. Heat the filled vials in autoclave at 105°C±5°C for 10 minutes. Carefully monitor for slow exhaust and temperature. Autoclave stoppers in 2% disodium edetate solution after rinsing with RO water and final rinsing again with RO water.
9. Finish. Sample.

Calcium Glycerophosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Calcium glycerophosphate	10.00	g
15.00	mg	2	Calcium levulinate	15.00	g
5.00	mg	3	Chlorobutanol anhydrous, USP	5.00	g
9.00	mg	4	Sodium chloride, USP	9.00	g
12.00	mg	5	Lactic acid, USP	12.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	mL	7	Sodium hydroxide for pH adjustment	QS	

Camphor Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Camphor	200.00	g
20.00	mg	2	Benzyl alcohol	20.00	g
QS	mg	3	Sesame oil	QS to 1.00	L

Camptothecin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.40	%	1	Camptothecin[a]	0.40	%
30.00	%	2	Alcohol absolute, USP	QS to 30.00	%
4.60	%	3	Benzyl alcohol	4.60	%
10.00	%	4	Citric acid	10.00	%
50.00	%	5	Polyethylene glycol 400	55.00	%
5.00	%	6	Polysorbate 80 (Tween®)	5.00	%

[a] Highly lipophilic derivative or 7-ethyl-10-hydroxy or 10,11-methylenedioxy or 10-bromo compounds of camptothecin-labeled quantity to be adjusted according to the derivative used.

Manufacturing Directions

1. Add item 1 to item 2 and mix well.
2. Add item 5 and mix well.
3. Add and dissolve item 6.
4. Add item 4 and mix well.
5. Add item 1 and mix thoroughly in a homogenizer.

Carboplatin for Infusion

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
50.00	mg	1	Carboplatin	50.00	g
50.00	mg	2	Mannitol	50.00	g

Note: Lyophilized powder 50, 150, or 450 mg per vial with equal parts by weight of mannitol.

Carboplatin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Carboplatin	10.00	g
QS	ft^3	2	Nitrogen gas, NF	QS	cy
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Add ca. 75% of item 3 to a clean mixing vessel. Manufacturing should be done at temperature of 30°C or less.
2. Bubble N_2 through step 1 for at least 15 minutes prior to adding item 1.
3. Add item 1 by first making a slurry in small amount of item 3 and then adding this slurry to step 1 with mixing to achieve complete solution.
4. Check pH (4.0–7.0); do not adjust pH.
5. Make up volume.
6. Check pH again (4.0–7.0); do not adjust.
7. Filter through 0.2-μm sterile filter and transfer via silicon tubing into a sterile receiving vessel vented by a sterile bacteria-retaining filter. Fill volume 15.4 to 15.6 mL. Filter integrity checked before and after filling. Use West Type 1888 S63 stoppers, type I 20-mL glass vial with flip-off aluminum metal cap, and medical-grade silicone tubing.
8. Sterilized closures are aseptically inserted into vials.

Carprofen Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
88.50	mg	1	Glycocholic acid	88.50	g
0.019	mL	2	Sodium hydroxide, NF, 40%	19.00	mL
169.00	mg	3	Lecithin, fine	169.00	g
30.00	mg	4	L-Arginine	30.00	g
50.00	mg	5	Carprofen	50.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	mL	7	Hydrochloric acid 2 N		
QS	ft^3	8	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Put 0.5 L of item 6 into a suitable vessel and pass item 8 into it for 20 minutes.
2. Add item 2 to it and mix.
3. Add item 1, mix, and dissolve.
4. Add item 3 and dissolve with strong stirring.
5. Heat the solution to between 50°C and 60°C. This is a micelle solution.
6. Add item 4 to 150 mL of item 6 (purged with item 8) at 40°C in a separate vessel.
7. Add item 5 in the mixed micelle solution heated to 50°C to 60°C.
8. Add the preparation in step 6 to it slowly with mixing maintaining the temperature of 50°C to 60°C.
9. Check and adjust pH to 5.8 to 6.2 with item 7.
10. Filter solution through a 0.45-μm membrane filter and fill into type I glass ampoule under aseptic conditions with pre- and postflush of item 8.
11. Sterilize by autoclaving 121°C for 20 minutes.

Cefamandole Nafate for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
1.00	g	1	Cefamandole as cefamandole nafate equivalent	1.00	kg
63.00	mg	2	Sodium carbonate	63.00	g

Note: On reconstitution, the pH is 6.0 to 8.5; cefamandole nafate rapidly hydrolyzes to cefamandole, which is also active.

Cefazolin Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/50 mL		Item	Material	Qty	UOM
1.00	g	1	Cefazolin	20.00	g
2.00	g	2	Dextrose hydrous, USP	40.00	g
QS	mL	3	Water for injection,	QS to 1.00	L

Note: For a 500-mg dose, the amount of item 2 is 2.40 g/vial; fill 50 mL per container and keep it frozen. Also available as 0.5 or 1.0 g lyophilized powder. The pH of reconstituted solution is between 4.5 and 6.0.

Cefepime Hydrochloride for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	g	1	Cefepime hydrochloride	1.00	kg
725.00	mg	2	L-Arginine to control pH	725.00	g

Note: Dry mixture for reconstitution; pH of reconstituted solution is 4 to 6.

Cefotaxime Injection

Bill of Materials (Batch Size 1 L)					
Scale/50 mL		Item	Material	Qty	UOM
1.00	g	1	Cefotaxime	20.00	g
1.70	g	2	Dextrose hydrous, USP	34.00	g
QS	mg	3	Sodium citrate hydrous for buffering	QS	
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: The 2.0-g dose uses 0.7 g of item 2 (for tonicity).

Cefotetan Injection

Bill of Materials (Batch Size 1 L)					
Scale/50 mL		Item	Material	Qty	UOM
1.00	g	1	Cefotetan	20.00	g
1.90	g	2	Dextrose hydrous, USP	38.00	g
QS	mg	3	Sodium bicarbonate for pH adjustment	QS	
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Sodium bicarbonate also added to convert cefotetan free acid to the sodium salt. The pH is adjusted to 4.0 to 6.5 with item 3 or 4. Frozen until used. Cefotetan disodium powder is supplied as 80 mg/vial for reconstitution.

Cefoxitin Injection Premixed IV Solution

Bill of Materials (Batch Size 1 L)					
Scale/50 mL		Item	Material	Qty	UOM
1.00	g	1	Cefoxitin	20.00	g
2.00	g	2	Dextrose hydrous, USP	44.00	g
QS	mg	3	Sodium bicarbonate for pH adjustment	QS	
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: For a 2.0-g dose, the quantity of item 2 is 1.1 g. The pH is ca. 6.5. After thawing, the solution is intended for IV use only.

Ceftazidime for Injection: L-Arginine Formulation

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
1.00	g	1	Ceftazidime pentahydrate eq.	1.00	kg
349.00	mg	2	L-Arginine[a]	349.00	g

[a] Quantity calculated on the basis of ceftazidime activity 1:0.349 ratio. The pH of freshly constituted solution ranges from 5 to 7.5. Other strengths include 2 and 10 g/vial.

Ceftazidime Injection Dry Powder

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
1.00	g	1	Ceftazidime pentahydrate eq.	1.00	kg
118.00	mg	2	Sodium bicarbonate	118.00	g

Note: Other strengths include 2 and 6 g; pH of reconstituted solution is 5 to 8.

Ceftazidime Injection Premix

Bill of Materials (Batch Size 1 L)					
Scale/50 mL		Item	Material	Qty	UOM
1.00	g	1	Ceftazidime pentahydrate eq.	20.00	g
2.20	g	2	Dextrose hydrous, USP	44.00	g
QS	mL	3	Sodium hydroxide for pH adjustment		
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 5 to 7.5 with item 3 or 4; item 3 also used to convert acid to salt.

Ceftriaxone Injection: 500-mg Injection (IM and IV)

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
596.60	mg	1	Ceftriaxone, use ceftriaxone disodium (3.5 H_2O), 8% excess	645.00	g
QS	mL	2	Water for injection, USP	QS to 1.75	L

Manufacturing Directions

1. Solution. Suspend item 1 under N_2 gas flushing, using freshly distilled water, and stir to dissolve.
2. Filter through a 0.22-μm filter.
3. Fill aseptically into vials, freeze, and lyophilize.
4. After drying, close the vials under N_2 protection, apply rubber stopper and an aluminum cap with a rim, and check them visually. Avoid microbial contamination during processing.

Water for reconstitution is filtered, germ-free distilled water sterilized in an autoclave after filling aseptically in ampoules.

Ceftriaxone Injection (250-mg Injection, IM and IV)

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
298.30	mg	1	Ceftriaxone, use ceftriaxone disodium (3.5 H_2O), 8% excess	322.50	g
QS	mL	2	Water for injection, USP	QS to 1.75	L

Manufacturing Directions

1. Solution. Suspend item 1 under N_2 gas flushing, using freshly distilled water, and stir to dissolve.
2. Filter through a 0.22-μm filter.
3. Fill aseptically into vials, freeze, and lyophilize.
4. After drying, close the vials under N_2 protection, apply rubber stopper and an aluminum cap with a rim, and check them visually. Avoid microbial contamination during processing.

Water for reconstitution is filtered, germ-free distilled water sterilized in an autoclave after filling aseptically in ampoules.

Ceftriaxone Injection Premix

Bill of Materials (Batch Size 1 L)					
Scale/50 mL		Item	Material	Qty	UOM
1.00	g	1	Ceftriaxone sodium	20.00	g
2.00	g	2	Dextrose hydrous, USP	40.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: For a 2-g strength, use 1.2 g of item 2.

Cefuroxime for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.75	g	1	Cefuroxime sodium	15.00	g
1.40	g	2	Dextrose hydrous, USP	28.00	g
300.00	mg	3	Sodium citrate hydrous	300.00	g
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 5 to 7.50. For a 1.5-g strength, the quantity of item 3 is 600 mg.

Cetrorelix Acetate for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
0.25	mg	1	Cetrorelix as cetrorelix acetate	0.27	g
54.80	mg	2	Mannitol	54.80	g

Note: For a 3.0-mg dose, use 164.40 mg of item 2. The pH of reconstituted solution is 5 to 8.

Chloramphenicol and Phenylmercuric Nitrate Ophthalmic Drops

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Qty	UOM
Part I					
0.1327	mL	1	Polyethylene glycol 300	5.972	L
70.00	mg	2	Polyoxyl 40 stearate, NF	3.15	kg
6.20	mg	3	Chloramphenicol, USP (24% overage)	279.00	g
Part II					
		4	Water Purified (distilled), USP	25.00	L
0.127	mg	5	Disodium edetate, USP	5.72	g
0.04	mg	6	Phenylmercuric nitrate	1.80	g
QS	mL	7	5 N Hydrochloric acid, NF[a]	QS	mL
QS	mL	8	1 N Sodium hydroxide, NF[a]	QS	mL
QS	mL	9	Water purified (distilled), USP	QS to 45.00	L

[a] Use only for pH adjustment.

Manufacturing Directions

Note: Weigh out the chloramphenicol in the antibiotic weigh room. Be careful to prevent any cross contamination of the antibiotic during weighing and handling. The temperature of part I is critical and must be precisely controlled or precipitation may result. Mixing must be continuous while adding part II to part I or precipitation may result.

Part I

1. Add items 1 and 2 to a suitable water-jacketed heating kettle of at least 45-L capacity. Begin mixing with a suitable mixer.
2. Heat to 85°C to 90°C while mixing. Do not allow the temperature to rise more than 90°C. Mix until all of item 2 has melted.
3. When all of the item 2 has melted, turn off the heat source and allow the mixture to cool to 53°C to 55°C by circulating cold water through the kettle jacket.
4. When the temperature of part I reaches 53°C to 55°C, add item 3. Mix thoroughly for at least 15 minutes.
5. Maintain the temperature of part I at 53°C to 55°C and immediately add part II at 50°C to 52°C according to the instructions that follow.

Part II

1. Measure out ca. 25 L of item 4 into a suitable water-jacketed heating kettle. Begin mixing.
2. Add items 5 and blended item 6, in order, allowing the first to dissolve completely before adding the next. Rinse out the blender cup with item 9 and add the rinsings to the kettle.
3. Heat part II to 50°C to 52°C.
4. With part I at 53°C to 55°C and part II at 50°C to 52°C, add part II to part I, while mixing parts I and II.
5. Use 4 to 5 L of item 9 to rinse the part II kettle, pump, and hoses.
6. Add the rinsings to combined parts I and II. Continue mixing and allow the batch to cool to 30°C or less.
7. When the temperature is at 30°C or less, transfer the batch into a suitable mixing tank for a final QS of 45 L.
8. Use 2 to 3 L of item 9 to rinse out the kettle, pump, and hoses. Add the rinsings to the calibrated mixing tank. Mix well for at least 15 minutes.
9. Check pH (range 5.4–5.8). If necessary, adjust the pH to 5.4 to 5.8 with item 7 or 8.
10. Allow any foam to dissipate and QS the batch to 45 L with item 9. Mix thoroughly for at least 15 minutes.

Sterile Filtration

1. Sterilize for 1 hour (range 45–60 minutes) at 121°C (–0, +5°C) in an autoclave at 15 psi and then filter to a 100-L stainless steel pressure vessel. Transfer to solution preparation area.
2. Mix the product for at least 10 minutes before filtration.
3. Connect the sterilized filter and sterile-filter with the aid of N_2 pressure (15–30 lb). Discard initial 10 L of filtrate, attach sterilized hose to sterilized filter holder, and connect to the sterilized 100-L stainless steel pressure vessel aseptically. *Note*: Before sterile filtration to 100-L pressure vessel, perform the bubble point test at NLT 40 psi and on 0.22-μm inline gas filter at 18 psi.
4. After completion of product filtration, disconnect filter from pressure vessel and flush the sterilizing filter with at least 10 L of water purified (distilled) for the bubble point test (after filtration).
5. After filtration, decontaminate the outer surface of bulk holding pressure vessel and then transfer to filling cubicle. Sample.

Sterilization

1. Filling unit, 20-L surge bottle, manifold of filling unit, and uniforms.
2. Sterilize at 121°C (–0°, +2°C) pressure 15 psi for 1 hour.

Sterile Filling

1. Aseptically connect the sterilized filling tubing and N_2 line from 100-L pressure vessel to surge bottle.
2. Aseptically fill sterile solution into sterilized container.
3. Perform the bubble point test on a 0.22-μm in-line gas filter before and after filtration at 18 psi. Sample.

Chloramphenicol Ophthalmic Solution (3%)

Formulation

Chloramphenicol, 3 g; Kollidon 25 [1], 15 g; preservative, QS; water, add 100 g.

Manufacturing Directions

Dissolve the preservative in hot water, cool, dissolve Kollidon 25, add chloramphenicol, and stir until a clear solution is obtained.

Chloramphenicol for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
1.44	g	1	Chloramphenicol hemisuccinate	1.92	kg
136.55	mg	2	Sodium hydroxide	136.55	g
QS	mL	3	Sodium hydroxide for pH adjustment		
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Measure ca. 0.3 L of water for injection in a clean, identified Pyrex bottle and dissolve sodium hydroxide. Cool the solution to between 10°C and 15°C.
2. Measure ca. 0.4 L of water for injection in a clean, identified mixing tank.
3. Add chloramphenicol hemisuccinate into the mixing tank with constant agitation to suspend the material.
4. Add sodium hydroxide solution slowly to the chloramphenicol hemisuccinate suspension in a steady stream to pH 6.6 to 6.8.
5. Bring to final volume and check pH.
6. Prefilter through a 1-mm prefilter cartridge and through a Millipore® prefilter #CW03 012 02 Milligard cartridge.
7. QC sample for pH, UV scan, and specific gravity.
8. Sterile-filter through a 0.22-mm filter and fill as required and lyophilize.
9. Cool the shelves in the lyophilizer to approximately −40°C. Load the product and place thermocouples.
10. The product thermocouples should register −30°C or less for at least 4 hours before starting the cycle.
11. Cool condenser until it attains −45°C or less. Start vacuum pump to achieve a vacuum level of 300 μm or less in the chamber.
12. Set to low heat and set temperature control to +30°C. Let the product temperature rise by itself. When it reaches +30°C, hold at this temperature ±3°C for at least 4 hours.
13. Set temperature controller to +45°C, hold at this temperature for at least 12 hours, stop the vacuum, bleed the chamber with sterile dry air, and take out one vial from each shelf. Send these samples (stoppered) for moisture check. Immediately close the lyophilizer chamber and start vacuum to as low as it will go. Continue to dry for at least 12 hours.
14. Bleed chamber slowly to approximately 5 in Hg vacuum with sterile dry air.
15. Stopper vials by using the internal stoppering mechanism and bleed chamber to atmosphere pressure.
16. Withdraw the product from the lyophilizer. Seal the stoppered vials.

Chloramphenicol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
123.00	mg	1	Chloramphenicol, USP	125.00	g
5.14	mg	2	Lidocaine HCl, USP	5.14	g
4.05	mg	3	Lidocaine base, USP	4.05	g
10.00	mg	4	Chlorocresol	10.00	g
0.12	mL	5	Water for injection, USP	0.12	L
QS	mL	6	Propylene glycol, NF	QS to 1.00	L
QS		7	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Take approximately 0.75 L of item 6 and heat in a steam-jacketed kettle for 30 minutes.
2. Add item 1 to above kettle at 80°C, stir, and dissolve. Allow to cool.
3. In a separate vessel, take freshly boiled item 5 and dissolve in it items 4 and 2 to complete solution.
4. Cool the solution in step 3 and make up volume with step 2.
5. Flush with item 7 and keep covered.
6. Check pH (6.5–6.8); do not adjust.
7. Filter through a 0.22-μm presterilized assembly with a 0.45-μm prefilter.
8. Flush amber type I glass vials presterilized with item 7 and fill 10.5 mL. Stopper and seal.
9. This is the aseptic filling process; no terminal heating allowed.
10. Sample for sterility, particles.

Chloramphenicol Sodium Succinate for Injection

Bill of Materials (Batch Size 118 L)					
Scale/Vial		Item	Material	Qty	UOM
1.44	mg	1	Chloramphenicol hemisuccinate	22.656	kg
136.55	mg	2	Sodium hydroxide, USP	2.1483	kg
QS	mg	3	10% Sodium hydroxide, USP, for pH adjustment	QS	mL
QS	mL	4	Water for injection, USP	QS to 118.00	L

Manufacturing Directions

1. Measure ca. 40 L of item 4 in a clean, identified Pyrex bottle and dissolve item 2. Cool the solution to between 10°C and 15°C.
2. Measure ca. 50 L of item 4 in a clean, identified mixing tank.
3. Add item 1 into the mixing tank with constant agitation to suspend the material.
4. Add item 2 solution from step 1 slowly to item 1suspension in a steady stream to pH 6.6 to 6.8.
5. Bring to final volume and check pH.
6. Prefilter through a 1-μm prefilter cartridge and through a Millipore® prefilter #CW03 01202 Milligard cartridge. Sample.
7. Sterile filter through a 0.22-μm filter and fill as required and lyophilize.
8. Cool the shelves in the lyophilizer to approximately −40°C, load the product, place thermocouples.
9. The product thermocouples should register −30°C or less for at least 4 hours before starting the cycle.
10. Cool condenser until it attains −45°C or less. Start vacuum pump to achieve a vacuum level of 300 μm or less in the chamber.
11. Set to low heat and set temperature control to +30°C. Let the product temperature rise by itself. When it reaches +30°C, hold at this temperature ±3°C for at least 4 hours.
12. Set temperature controller to +45°C, hold at this temperature for at least 12 hours, stop the vacuum, and bleed the chamber with sterile dry air. Sample. Immediately close the lyophilizer chamber and start vacuum to as low as it will go. Continue to dry for at least 12 hours.
13. Bleed chamber slowly to approximately 5 in Hg vacuum with sterile dry air.
14. Stopper vials by using the internal stoppering mechanism and bleed chamber to atmosphere pressure. Withdraw the product from the lyophilizer. Seal the stoppered vials.

Chlordiazepoxide Hydrochloride Injection

Bill of Materials (Batch Size 2 L for Diluent)					
Scale/mL		Item	Material	Qty	UOM
Powder Vial					
100.00	mg	1	Chlordiazepoxide hydrochloride	100.00	g
Diluent Vial					
15.00	mg	1	Benzyl alcohol	15.00	g
40.00	mg	2	Polysorbate 80	40.00	g
200.00	mg	3	Propylene glycol	200.00	g
16.00	mg	4	Maleic acid	16.00	g
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 2.00	L

Note: Adjust pH to ca. 3.0.

Chloroprocaine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Chloroprocaine hydrochloride	10.00	g
6.70	mg	2	Sodium chloride	6.70	g
0.111	mg	3	Disodium edetate dihydrate	0.111	g
1.00	mg	4	Methyl paraben	1.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: For infiltration and nerve block. Also available without items 3 and 4 at 20- and 30-mg concentrations; the quantity of item 2 is 4.7 mg/mL for 20-mg and 3.3 mg/mL for 30-mg concentration.

Chloroquine Phosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Chloroquine base, use chloroquine phosphate	64.50	g
5.00	mg	2	Chlorbutol	5.00	g
0.01	mL	3	benzyl alcohol, NF	10.00	mL
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take ca. 0.75 L of item 4 freshly boiled and cooled to room temperature and dissolve item 1 into it.
2. Dissolve item 2 in item 3 and add this solution to step 1 gradually to ensure good dispersion and dissolution.
3. When the solution is clear, make up the volume with item 4.
4. Sample and check final product to pH 3.5 to 4.5; do not adjust.
5. Filter through 0.45-μm and 0.22-μm filters.
6. Fill 30.5 to 31.0 mL into presterilized vials under aseptic conditions.
7. Sample for clarity, sterility.

Chlorothiazide Sodium for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.50	g	1	Chlorothiazide sodium equivalent to chlorothiazide	0.50	kg
0.25	g	2	Mannitol	0.25	kg
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Lyophilize for reconstitution.

Chlorpheniramine Maleate Injection (25 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Chlorpheniramine maleate, USP	25.00	g
2.50	mg	2	Liquefied phenol, NF	2.50	g
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Hydrochloric acid for pH adjustment	QS	

Manufacturing Directions

1. Dissolve item 1 in 0.6 L of item 3.
2. In a separate vessel, dissolve item 2 in 0.2 L of item 3 and add to step 1.
3. Bring to volume with item 3.
4. Mix well and sample for pH to 4.3 (range 4.3–4.5). Adjust with item 4 or 5, if necessary.
5. Filter through a 0.22-μm presterilized filter to a sterilized vessel.
6. Fill 2.1 mL into presterilized ampoules.
7. Sterilize in an autoclave at 121°C for 30 minutes.
8. Sample for clarity, sterility.

Chlorpheniramine Maleate Injection (10 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Chlorpheniramine maleate	10.00	g
5.00	mg	2	Chlorobutanol anhydrous	5.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Chlorpromazine Hydrochloride Injection (10 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Chlorpromazine HCl, USP	10.00	g
2.00	mg	2	Ascorbic acid, USP	2.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS		6	Nitrogen gas, NF	QS	

Manufacturing Directions

Caution: Avoid exposure to product. Solutions should be colorless to faint yellow; discard if turns pink.

1. Dissolve item 1 in 0.90 L of item 3, which has been freshly boiled and allowed to cool.
2. Dissolve item 2 and make up volume with item 3.
3. Begin and maintain cover of item 6 throughout.
4. Measure pH to 5.5 (5.0–6.0). Adjust with 10% item 4 or 4% item 5 if necessary.
5. Filter through 0.22- and 0.45-μm prefilters.
6. Flush presterilized ampoules with item 6 and fill under cover of item 6.
7. Fill 5.2 mL into flint type I glass ampoules.
8. Autoclave at 116°C for 30 minutes.

Chlorpromazine Hydrochloride Injection (25 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Chlorpromazine hydrochloride, USP	25.00	g
2.00	mg	2	Ascorbic acid (as sodium ascorbate), USP	2.00	g
1.00	mg	3	Sodium metabisulfite, NF	1.00	g
1.00	mg	4	Sodium chloride, USP	1.00	g
20.00	mg	5	Benzyl alcohol, NF	20.00	g
QS	mL	6	Water for injection	QS to 1.00	L
QS	mL	7	Hydrochloric acid for pH adjustment	QS	mL

Choriogonadotropin-Alpha (Recombinant) for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
285.00	mg	1	Recombinant human chorionic gonadotropin	285.00	g
30.00	mg	2	Sucrose	30.00	g
0.98	mg	3	Phosphoric acid	0.98	g
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 6.5 to 7.5; lyophilize. Can be given to newborns.

Chorionic Gonadotropin for Injection (20,000 U/10 mL Covial)

Bill of Materials (Batch Size 24- and 75-L Diluent)					
Scale/m		Item	Material	Qty	UOM
5000	U	1	Chorionic gonadotropin, USP (potency U/mg)	120,000,000	U
50.00	mg	2	Mannitol USP, 10% overage	1.32	kg
1.50	mg	3	Sodium phosphate monobasic (85–95%)	40.00	g
6.50	mg	4	Sodium phosphate Dibasic	156.00	g
QS	mL	5	Water for injection, USP	QS to 24.00	L
0.90	%	6	Benzyl alcohol, 20% excess	810.00	mL
QS	mL	7	Water for injection, USP	QS to 75.00	L
QS	mL	8	Hydrochloric acid for pH adjustment	QS	mL

Manufacturing Directions

1. Measure 69 L of item 7 into a tank. Add item 6 to the tank with agitation until a clear solution results. Bring to ca. 73 L (item 7) and check pH and adjust to 5 to 7 and recheck with item 8.
2. Bring the final volume with item 7 and then pass through a 0.22-μm filter into a sterile reservoir for filling. Check first vials for reconstitution pressure, which should be less than 5 kg.
3. Dry mix item 1 with ca. 2 times its weight, using item 2 in an appropriate container.
4. Measure 15 L of item 5 in a container. Add the dry-mixed items 1 and 2 from step 5 to the mixing tank with slow agitation to avoid vortex and foaming.
5. Dry rinse all utensils needed for items 1 and 2 with the balance of item 2 and add to the mixing tank. Dissolve items 3 and 4 in ca. 1 L of item 5 which has been heated to ca. 35°C.
6. Add items 3 and 4 solution from step 5 to the mixing tank with slow agitation. Bring to final volume and check pH; do not adjust pH. Expect pH to be around 7.2 to 7.4. Sample.
7. Pass the solution through a 0.22-μm filter into a sterile reservoir for filling. Lyophilize.
8. Load the product into the lyophilizer keeping the covials covered during the transfer.
9. Set temperature for −40°C; product thermocouple should register –30°C or less for at least 2 hours before starting the cycle.
10. Start condenser and start vacuum only when condenser is less than –40°C; start vacuum to chamber to at least 300 μm.

11. Bring up temperature controller to +25°C. Set to low heat and switch on heat. Hold at +25°C for at least 36 hours.
12. Bring up temperature controller to 45°C. Hold at 45°C for 8 hours.
13. Shut off the lyophilizer and bleed chamber slowly with dry sterile air to atmosphere pressure. Remove product sample. Repeat if not dried to specifications.

Chorionic Gonadotropin for Injection (10000 U//10 mL)

Bill of Materials (Batch Size 1 L)					
Scale/Vial		Item	Material	Qty	UOM
10,000	U	1	Chorionic gonadotropin	10 MM	U
5.00	mg	2	Sodium phosphate monobasic	5.00	g
4.40	mg	3	Sodium phosphate dibasic	4.40	g
5.60	mg	4	Sodium chloride	5.60	g
9.00	mg	5	Benzyl alcohol	9.00	g
QS	mL	6	Sodium hydroxide for pH adjustment		
QS	mL	7	Phosphoric acid for pH adjustment		
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: This composition is after reconstitution with 10 mL of water for injection.
Not for use in newborns.

Chromium Chloride Additive Injection (5-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
102.50	mg	1	Chromium chloride hexahydrate	102.50	mg
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Sulfuric acid for pH adjustment	QS	

Chromium Chloride Additive Injection (10-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.50	mg	1	Chromium chloride hexahydrate	20.50	mg
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Sulfuric acid for pH adjustment	QS	

Chromium Chloride Additive Injection (30-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.50	mg	1	Chromium chloride hexahydrate	20.50	mg
0.90	%	2	Benzyl alcohol, NF	0.90	%
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Sulfuric acid for pH adjustment	QS	

pH 3.0 to 6.0
Assay by colorimeter 85% to 115%
Packaging commodity: type I glass vial, West Co.1888 gray stopper, West Co.
flip-off aluminum seals.

Cidofovir Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
75.00	mg	1	Cidofovir	75.00	g
QS	mL	2	Sodium hydroxide for pH adjustment	QS	
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: Fill 5 mL per vial; adjust pH to 7.4 with item 2.

Cimetidine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Cimetidine	100.00	g
QS	mL	2	Hydrochloric acid, reagent-grade bottles[a]	QS	mL
QS	mL	3	Water for injection, BP	QS to 1.00	L

[a] Sufficient to protonate 95 to 97.5% of cimetidine. Fill 2 mL.

Manufacturing Directions

1. Item 1 is only slightly soluble in item 3 but yields a highly soluble protonated ion.
2. Adjust pH to 5.1 to 6.2. The solution should be clear, colorless, and particle free, with no noticeable odor but a mercaptan-like color.
3. Sterilize the ampoule at 121°C for 30 minutes.
4. Determine item 1 content by HPLC method.
5. Determine cimetidine impurities TLC: corresponds to raw material plus moderate spot Compound II and traces spot Compound I and spot at *Rf* 0.09. TLC loaded at 1000 mg to trace small impurities. Trace spots.

Cimetidine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
150.00	mg	1	Cimetidine hydrochloride equivalent to cimetidine	150.00	g
10.00	mg	2	Phenol	10.00	g
QS	mL	3	Sodium hydroxide for pH adjustment		
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.8 to 6.0 with item 3. Fill 50 mL for premixed in plastic container.

Ciprofloxacin Hydrochloride Ophthalmic Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3.00	mg	1	Ciprofloxacin base as ciprofloxacin hydrochloride	3.50	g
0.06	mg	2	Benzalkonium chloride	0.06	g
QS	mg	3	Sodium acetate	QS	
QS	mg	4	Acetic acid	QS	
46.00	mg	5	Mannitol	46.00	g
0.50	mg	6	Disodium edetate	0.50	g
QS	mL	7	Sodium hydroxide for pH adjustment	QS	
QS	mL	8	Hydrochloric acid for pH adjustment	QS	
QS	mL	9	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 4.5; ointment contains 3.3 mg of ciprofloxacin hydrochloride in mineral oil/white petrolatum.

Ciprofloxacin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Ciprofloxacin	10.00	g
1.00	M	2	Lactic acid	1.00	M
50.00	mg	3	Dextrose anhydrous, USP	50.00	g
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.3 to 3.9 with item 4 in vials and 3.5 to 4.6 in infusion solutions.

Cisplatin Diaminedichloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.33	mg	1	Cisplatin (II) diaminedichloride	1.33	g
6.00	mg	2	Sodium chloride, USP	6.00	g
QS	mL	3	Hydrochloric acid (1 N) for pH adjustment	QS	
0.00214	mL	4	Isopropyl alcohol	214.00	mL
1.40	mg	5	Mannitol, USP	1.40	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: For higher label amount of active, substitute appropriate amounts (25 or 50 mg).

Manufacturing Directions

1. In 90% of item 6, deaerated by bubbling in of N_2, dissolve item 2 under agitation.
2. Heat the resulting solution to 40°C to 45°C and dissolve item 1 under bubbling N_2 gas and vigorous agitation. Perform this operation protected from light. In the subsequent processing, also keep the solution protected from light.
3. Slowly cool the solution to 28°C to 30°C and dissolve item 5.
4. Check and adjust the pH of the solution to 3.5 with item 3.
5. Under agitation, add item 4 and make up to the final volume.
6. Aseptically filter the solution through a membrane filter of pore size 0.22 mm.
7. Aseptically dispense the solution into colorless, sterile glass filters, type I, capacity 20 mL, to a volume of 7.5 mL/vial.
8. Freeze the vials at -45°C.
9. Proceed to freeze-drying, heating the shelves of the freeze-dryer system to 4°C. Limit the time employed for the final drying of the product at 25°C to 30°C (preferably 30°C) to 3 to 6 hours, and preferably 4 hours.
10. Stopper the freeze-dried vials with sterile stoppers made of elastomeric material, preferably halobutylic rubbery material (a mixture in chlorobutyl rubber type PH 21/50, manufactured by Pharmagummi), and seal with sterile aluminum caps. The freeze-drying time (excluding freezing time) should be 18 hours.

Cisplatin with 2,2′-Dithio-*bis*-Ethane Sulfonate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.90	mg	1	Cisplatin	0.90	g
14.30	mg	2	2,2′-Dithio-*bis*-ethane sulfonate	14.30	g
0.90	%	3	Sodium chloride, USP	0.90	%
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable container, dissolve item 3 in item 5 to yield a 0.9% solution.
2. Check and adjust pH to 2.0 to 6.0 with item 4.
3. Add and dissolve item 3 with fast agitation (1500–2500 rpm) at room temperature for 60 to 90 minutes.
4. Add portion by portion of item 2, agitating to dissolve completely.
5. Check and adjust pH as in step 2.
6. Filter through a 0.22-μm membrane filter aseptically into type I glass vials.

Cladribine Injection Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Cladribine	1.00	g
9.00	mg	2	Sodium chloride	9.00	g
QS	mg	3	Phosphoric acid for pH adjustment	QS	
QS	mg	4	Sodium phosphate dibasic for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill 10 mL into flint single-use vials; adjust pH to 5.5 to 8.0 with item 3 or 4.

Clarithromycin Injection

Bill of Materials (Batch Size 10.4 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Clarithromycin (approved excess range 0–3%)	520.00	g
QS	mL	2	Water for injection	QS to 10.40	L
QS	—	3	Nitrogen gas, NF	QS	—
QS	mL	4	Lactobionic acid 12% w/v solution[a]	QS	L
QS	mL	5	Sodium hydroxide 1 N solution	QS	mL

[a] Preparation shown in the next table.

Lactobionic Acid (12% w/v Solution)

Bill of Materials (Batch Size 430 L)					
Scale/mL		Item	Material	Qty	UOM
120.00	mg	6	Lactobionic acid	51.660	kg
QS	mL	7	Water for injection	QS to 430.00	L

Manufacturing Directions

1. Sterilization of vials and stoppers. Sterilize the empty vials by dry heat by using a standard nominal cycle of 225°C for 270 minutes. Sterilize the lyophilization stoppers in an autoclave at 121°C for 60 minutes, followed by vacuum drying for 90 minutes.
2. Preparation of lactobionic acid solution.
   a. Transfer an appropriate volume of item 7 into a clean stainless steel tank.
   b. Add item 6 and mix to give a clear solution. Bring to volume with item 7.
   c. Filter through a 0.22-μm filter into sterilized vessels. Sample.
   d. Store solution between 2°C and 8°C. Use within 90 days.
3. Preparation of process solution.
   a. Transfer appropriate volume of item 2 into a clean stainless steel tank. Cool to 0°C to 10°C.
   b. Mix item 1, stirring slowly for 15 minutes.
   c. Add item 4 solution cautiously so the pH does not fall to less than 4.8 at any time during the addition. Stir until the solution is clear.
   d. Check pH and adjust to 5.3 (range 5.0–5.6) with either item 4 or 5. Add item 2 to volume.
   e. Filter the clarithromycin solution through a 0.22-μm or smaller pore-size filter into a clean storage container. Sample.
   f. Maintain solution at (2–15°C) until ready for filling.
4. Sterile filtration and filling.
   a. Connect storage container to sterilized 0.22-μm or smaller pore-size filter. Test filter integrity.
   b. Fill surge bottle with sterile-filtered solution and start filling. If the assay of the solution is outside action limits, calculate the fill volume to be delivered into each vial.
   c. Perform final filter integrity test.
   d. Apply lyophilization stoppers to filled vials and place on lyophilizer trays.
5. Lyophilization.
   a. Transfer trays to lyophilizer.
   b. Freeze product to -25°C or lower.
   c. Cool condenser to -40°C or lower.
   d. Reduce chamber pressure to 200 to 600 mm Hg.
   e. Raise shelf to 15°C to 25°C.
   f. After sublimation of ice, raise shelf to 40°C to 50°C and reduce chamber pressure to minimum.
   g. When lyophilization cycle is complete, release vacuum with filtered N_2.
   h. Collapse the shelves to stopper the vials.
   i. Apply over seals. Sample.

Clindamycin Injection in 5% Dextrose

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
300.00	mg	1	Clindamycin phosphate equivalent	300.00	g
50.00	mg	2	Dextrose anhydrous, USP	50.00	g
0.04	mg	3	Disodium edetate	0.04	g
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Use 600 or 900 mg of item 1 for other concentrations.

Clindamycin Phosphate Injection 150 mg/mL (4 mL in 5-mL Vial, 600 mg; 6-mL in 10-mL vial, 900 mg)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
150.00	mg	1	Clindamycin base, use clindamycin phosphate, USP, 5% excess	157.50[a]	g
0.50	mg	2	Disodium edetate anhydrous, use disodium edetate, USP (dihydrate)	0.554	g
9.45	mg	3	Benzyl alcohol, NF	9.45	g
QS	mg	4	Sodium hydroxide, reagent-grade pellets[b]	QS	mL
QS	mL	5	Hydrochloric acid, reagent-grade bottles[b]	QS	mL
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a] This value is multiplied by an appropriate lot-specific factor, which accounts for the phosphate moiety and bulk drug potency.
[b] Used for pH adjustment.

Manufacturing Directions

Note: The solution must be prepared in glass-lined or a 316 or higher temper-grade stainless steel tank.

Allow adequate time for ingredient's dissolution between each drug or excipient step.

1. Preparation.
   a. Collect ca. 45% of the batch size of item 6 in a stainless steel tank.
   b. With mixing, add item 3 and mix until solution is uniform.
   c. Add and dissolve item 2. Mix until ingredient is dissolved and solution is uniform.
   d. Slowly add ca. 20% of the total item 1 to the solution with continued mixing. Mix for not less than 15 minutes. Maintain a minimal vortex.
   e. Slowly add one-half of the sodium hydroxide slurry to the solution. *Note*: Prepare sodium hydroxide slurry by dissolving 11 g of item 4 per liter of total batch size in a volume of item 6 equal to 5% of the total batch size.
   f. Add slowly ca. 25% of the remaining total item 1 to the solution with mixing. Mix for not less than 10 minutes before proceeding.
   g. Slowly add the remaining volume of the sodium hydroxide slurry from step 1e to the solution.
   h. Slowly add the remaining item 1 to the solution with mixing. Mix for not less than 30 minutes and until all ingredients are dissolved and solution is uniform. Make sure any ingredients that have accumulated on the sides of the tank and mixing shaft are dissolved into the solution.
   i. Check pH. Adjust pH to 6.4 (range 6.2–6.6) with a 10% sodium hydroxide solution or 1:10 hydrochloric acid (see note). Mix thoroughly between pH samplings. *Note*: A 10% sodium hydroxide solution is made mixing 100 g of item 4 with sufficient item 6 to make 1 L. A 1:10 hydrochloric acid solution is prepared by mixing 100 mL of item 5 with sufficient item 6 to make 1 L.
   j. QS to final volume with item 6.
   k. Check pH. If necessary, readjust to 6.4 (range 6.2–6.6) with 10% sodium hydroxide solution or 1:10 hydrochloric acid solution, both from step 1.
   l. Filter the solution through a previously rinsed filtration setup, using an approved 0.45-μm or finer membrane filter with an approved prefilter into a stainless steel tank. Sample.
   m. Prepare for sterilization, a 0.22-μm or finer membrane filtration setup with a prefilter if needed.
2. Preparation of vials and stoppers. Use type I glass, treated, 13-mm 5-mL vials.
   a. Wash and dry vials and load in appropriate containers for sterilization.
   b. Sterilize by using dry heat to 200°C (–0°C, +50°C) glass temperature for 225 minutes (–0, +360 minutes).
   c. Leach stoppers by boiling for 10 minutes in deionized water. Wash stoppers by using rubber cycle. Dry in a fast dryer at 55°C. Sterilize in a steam autoclave at 121°C for 60 minutes.
   d. Fill. Sample.

Clonidine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.10	mg	1	Clonidine hydrochloride	0.10	g
9.00	mg	2	Sodium chloride	9.00	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP,	QS to 1.00	L

Note: Adjust pH to 5 to 7 with item 3 or 4. Fill 10 mL; other concentrations include 1.0 mg or 5.0 mg of item 1.

Closantel Veterinary Injectable Solution (12–20 g/100 mL)

Formulation

I. Closantel, 12.0–20.0 g.
II. Kollidon 12 PF or Kollidon 17 PF [1], 9.0–12.0 g; sodium hydroxide, 50% in water, 2.5–3.0 g; propylene glycol [1], ca. 60 g.
III. Sodium bisulfite, 0.01–0.04 g; water for injectables, ca. 20 g.

Manufacturing Directions

Dissolve Closantel in solution II and add solution III. The sterilization can be done by heating (120°C, 20 minutes)

The function of Kollidon 12 PF or Kollidon 17 PF is to reduce strongly the local side effects (e.g., formation of edemas) and to increase the retention time in the tissue.

Coagulation Factor VIIa (Recombinant) for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
1.20[a]	mg	1	rFVIIa	1.20	g
5.84	mg	2	Sodium chloride	5.84	g
2.94	mg	3	Calcium chloride dihydrate	2.94	g
2.64	mg	4	Glycine	2.64	g
0.14	mg	5	Polysorbate 80	0.14	g
60.00	mg	6	Mannitol	60.00	g

[a] 60 KIU; reconstitute with water for injection.

Coagulation Factor IX (Recombinant) for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
500	IU	1	Coagulation factor IX	500,000	IU
10.00	mM	2	L-Histidine	10.00	mM
1.00	%	3	Sucrose	1.00	%
260.00	mM	4	Glycine	260.00	mM
0.005	%	5	Polysorbate 80	0.005	%
QS	mL		Water for injection, USP,	QS to 1.00	L

Note: Lyophilized product. After reconstitution gives above concentration.

Colistin Sulfate, Neomycin Sulfate, Thonzonium Bromide, and Hydrocortisone Acetate Otic Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3.00	mg	1	Colistin base, use colistin sulfate equivalent	3.00	g
3.30	mg	2	Neomycin activity as sulfate	3.30	g
0.50	mg	3	Thonzonium bromide	0.50	g
10.00	mg	4	Hydrocortisone acetate	10.00	g
0.50	mg	5	Polysorbate 80	0.50	g
QS	mg	6	Sodium acetate for buffering	QS	
QS	mg	7	Acetic acid for buffering	QS	
0.02	mg	8	Thimerosal	0.02	g
QS	mL	9	Water for injection, USP	QS to 1.00	L

Note: Fill 10 mL into dropper bottle.

Conjugated Estrogens for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
Lyophilized Vial					
25.00	mg	1	Conjugated estrogens	25.00	g
200.00	mg	2	Lactose	200.00	g
0.20	mg	3	Simethicone	0.20	g
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
Reconstitution Solution (5 mL)					
20.00	mg	1	Benzyl alcohol	20.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L

Copper Sulfate Additive Injection (5-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
7.85	mg	1	Copper sulfate pentahydrate	7.85	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Sulfuric acid for pH adjustment	QS	

Copper Sulfate Additive Injection (10-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.57	mg	1	Copper sulfate pentahydrate	1.57	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Sulfuric acid for pH adjustment	QS	

Copper Sulfate Additive Injection (30-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.57	mg	1	Copper sulfate pentahydrate	1.57	g
0.90	%	2	Benzyl alcohol, NF	0.90	%
QS	mL	3	Water for injection, USP	QS to1.00	L
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Sulfuric acid for pH adjustment	QS	

pH: 1.5 to 2.5
Assay by atomic absorption (85–115%) Packaging Commodity: type I glass vials, West Co. 1888 gray stoppers, West Co. flip-off aluminum seals.

Corticorelin Ovine Triflutate for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
0.10	mg	1	Corticorelin ovine (as the trifluoroacetate)	0.10	g
10.00	mg	2	Lactose	10.00	g
26.00	mg	3	Cysteine hydrochloride monohydrate	26.00	g

Cortisone Acetate Injectable Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Cortisone acetate	50.00	g
9.00	mg	2	Sodium chloride	9.00	g
4.00	mg	3	Polysorbate 80	4.00	g
5.00	mg	4	Carboxymethylcellulose 2910	5.00	g
9.00	mg	5	Benzyl alcohol	9.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Fill into 10-mL vials.

Cosyntropin for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
Lyophilized Vial					
0.25	mg	1	Cosyntropin	0.25	g
Reconstitution Solution					
9.00	mg	1	Sodium chloride	9.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L

Cromolyn Sodium Ophthalmic Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Cromolyn sodium	4.00	g
1.00	mg	2	Disodium edetate	1.00	g
0.10	mg	3	Benzalkonium chloride	0.10	g
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 4.0 to 7.0 with item 4 or 5. Fill into 10-mL dropper bottles.

Crude Liver Extract Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Crude liver extract (concentrate 20 mg/mL) to give B12 activity of 2 mg (limit 1.8–4.0 mg/mL)	2.00	mg
5.00	mg	2	Phenol, USP, as preservative	5.00	g
QS	mL	3	Water for injection	QS to 1.00	L

Cyanocobalamin and Thiamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Thiamine HCl, USP	100.00	g
1.00	mg	2	Cyanocobalamin, USP	1.00	g
15.00	mg	3	Benzyl alcohol, NF	15.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Sodium hydroxide for pH adjustment	QS	

Cyanocobalamin, Choline, and Niacinamide Injection

Bill of Materials (Batch Size L)					
Scale/mL		Item	Material	Qty	UOM
300.00	mg	1	Cyanocobalamin, USP	300.00	mg
100.00	mg	2	Choline chloride	100.00	mg
50.00	mg	3	Niacinamide, USP	50.00	g
15.00	mg	4	Benzyl alcohol, NF	15.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Glacial acetic acid for buffering	QS	
QS	mL	7	Sodium acetate for buffering; see item 6	QS	

Cyanocobalamin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Cyanocobalamin, USP, 20% excess	1.00	g
0.010	mL	2	Benzyl alcohol, NF	10.00	mL
7.50	mg	3	Sodium chloride, NF	7.50	g
3.00	mg	4	Sodium dihydrogen phosphate	3.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS		6	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Use freshly boiled and cooled item 5, bubble item 6, and provide cover all the time.
2. Take 0.9 L of item 5 and dissolve items 1 to 4 in it, one at a time, and allowing complete dissolution.
3. Check pH 4.0 to 5.5; do not adjust pH.
4. Filter through a 0.45-μm prefilter and a 0.22-μm filter into a sterilized staging assembly.
5. Fill 10.0 mL into 10-mL amber type I vials presterilized (200°C for 4 h); use butyl or latex rubber stoppers previously disinfected and sterilized. Sterile-fill; do not autoclave.
6. Sample for complete testing.

Cyanocobalamin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.6294	mg	1	Glacial acetic acid, USP	629.40	g
QS	–	2	Nitrogen gas, NF	QS	–
2.25	mg	3	Sodium acetate trihydrate, USP	2.25	g
8.00	mg	4	Sodium chloride, USP	8.00	g
QS	mg	5	Sodium hydroxide, reagent-grade pellets	QS	mg
0.115	mg	6	Vitamin B_{12} cyanocobalamin, USP, 15% excess	115.00	mg
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: The product requires N_2 gas and light protection during solution preparation.

1. Preparation.
   a. Add item 7 to ca. 75% of the final volume into glass-lined light-protected tank. Bubble-filter N_2 into item 7 for 10 minutes.
   b. Add and dissolve items 4, 3, and 1 with mixing. Dissolve item 6 in approximately 25 mL of item 7 and add to other ingredients.
   c. Check and adjust pH to 5 (range 4.5–5) with 0.1 N acetic acid solution or 0.1 N sodium hydroxide solution.
   d. QS with item 7 to final volume. Sample.
   e. Sterilize a 0.2- or 0.22-μm membrane filter with an approved prefilter.
   f. Filter the solution through the sterilized filter unit into a sterile glass-lined holding container.
2. Preparation of ampoules. Wash and dry type 1, 1-mL sulfur-treated ampoules and sterilize by using dry heat at 245°C for at least 3 hours and 25 minutes to assure sterile, pyrogen-free bottles.
3. Filling.
   a. Connect bulk solution container with an aseptic technique to the filling machine.
   b. Aseptically fill solution into each clean, sterile ampoule.
   c. Flush headspace of each ampoule with sterile-filtered N_2 and immediately seal.

Cyanocobalamin Injection for Veterinary Use

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00[a]	μg	1	Cyanocobalamin, USP	100.00[a]	mg
9.00	mg	2	Sodium chloride, USP	9.00	g
1.50	%	3	Benzyl alcohol, NF	1.50	%
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Acetic acid for buffering	QS	mL
QS	mL	6	Sodium acetate for buffering	QS	mL

[a] Adjust according to required strength; 1000, 3000, and 5000 μg for veterinary use.

Cyanocobalamin Repository Injection (1000 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1000.00	μg	1	Cyanocobalamin, USP	1000.00	mg
9.00	mg	2	Sodium chloride, USP	9.00	g
1.50	%	3	Benzyl alcohol, NF	1.50	%
4.00	%	4	Gelatin, USP	4.00	%
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Acetic acid for buffering	QS	mL
QS	mL	7	Sodium acetate for buffering; see item 6	QS	mL

Cyanocobalamin, Pyridoxine, and Thiamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
33.33	mg	1	Thiamine HCl, 20% excess[a]	40.00	g
33.33	mg	2	Pyridoxine HCl, 20% excess[b]	40.00	g
0.33	mg	3	Cyanocobalamin crystalline,[c] 40% excess	0.47	g
10.00	mg	4	Benzyl alcohol	10.00	g
QS	mg	5	Sodium hydroxide[d]	QS	mg
QS	mL	6	Hydrochloric acid, 1 N	QS	mL
QS	mL	7	Water for injection,	QS to 1.00	L
QS	–	8	Nitrogen gas	QS	–

[a] Quantity of thiamine HCl $= 40 \times \frac{(100)}{100-\%\ \text{moisture}} \times \frac{(100)}{\%\ \text{Assay on dry basis}}\text{g}$

[b] Quantity of pyridoxine HCl $= 40 \times \frac{(100)}{100-\%\ \text{moisture}} \times \frac{(100)}{\%\ \text{Assay on dry basis}}\text{g}$

[c] Quantity of cyanocobalamin $= 0.47 \times \frac{(100)}{100-\%\ \text{moisture}} \times \frac{(100)}{\%\ \text{Assay on dry basis}}\text{g}$

[d] For pH adjustment, make 10% sodium hydroxide solution.

Manufacturing Directions

1. Check item 7 to be used for solution preparation and verify that it meets conductivity (NMT 1.0 mS/cm) and pH (5.0–7.0).
2. Put 900 mL of item 7 into the preparation vessel and bubble N_2 gas to expel dissolved oxygen (O_2% Limit = NMT 1).
3. Add and dissolve item 4 into step 2 preparation vessel. Mix well with stirring to make clear solution. Then dissolve items 1 and 2 and make clear solution.
4. Put 9 mL of item 7 into flask, slowly add item 3, and make slurry of item 3.
5. Transfer item 3 slurry from step 4 to the solution, rinse the flask 2 or 3 times with item 7, and transfer to the above solution. Mix well till it becomes clear solution.
6. Check pH (range 3.5–4.0). Adjust pH if necessary with 10% NaOH solution or 1 N HCl solution.
7. After adjustment of the pH, make up volume to 1 L by adding item 7 and mix while bubbling N_2 gas until O_2% is less than 1. Check final pH (range 3.5–4.0). Sample.
8. Clean and sterilize filtration assembly before starting the primary filtration. Check the integrity of filter cartridge by the bubble point test.
9. Transfer the solution from the preparation vessel to mobile vessel through filtration assembly containing 0.45-μm filter cartridge.
10. Sterilize the ampoules by dry heat.
11. Before starting the final filtration, check the integrity of filter cartridge by the bubble point test.
12. Aseptically connect the N_2 line through sterile N_2 filter to the inlet of mobile vessel. Check the validity of N_2 filter.
13. Aseptically connect one end of previously sterilized filtration assembly with 0.22-μm pore-size filtration cartridge to the outlet of mobile vessel and other end to buffer holding tank on the ampoules filling machine parts. Filter the solution.
14. Fill solution from the bulk into each sterile dry clean ampoule and seal it. Perform the leak test.

Cyanocobalamin, Pyridoxine, and Thiamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Thiamine HCl, USP	100.00	g
100.00	mg	2	Pyridoxine HCl, USP	100.00	g
1000.00	mg	3	Cyanocobalamin, USP	1000.00	mg
15.00	mg	4	Benzyl alcohol, NF	15.00	mg
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Sodium hydroxide for pH adjustment	QS	

Cyanocobalamin, Pyridoxine, and Thiamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
33.00	mg	1	Thiamine hydrochloride, USP (B_1), 15% excess	38.00	g
33.00	mg	2	Pyridoxine (B_6), 12% excess	36.97	g
0.333	mg	3	Cyanocobalamin (B_{12}), 45% excess	0.45	g
1.80	mg	4	Methyl paraben sodium	1.80	g
0.20	mg	5	Propyl paraben sodium	0.20	g
4.80	mg	6	Disodium hydrogen phosphate	4.80	g
1.00	mg	7	Disodium edetate	1.00	g
0.015	mL	8	Thioglycerol	1.50	mL
0.10	mg	9	Ferric chloride	0.10	g
QS	mL	10	Water for injection, USP	QS to 1.00	L
QS		11	Nitrogen gas, NF	QS	
QS	mL	12	Hydrochloric acid for pH adjustment	QS	
QS	mL	13	Sodium hydroxide for pH adjustment	QS	

Manufacturing Directions

1. Vitamin formulations are highly prone to degradation and are affected by exposure to light and air. As a general rule, these must be manufactured protecting them from light and providing continuous N_2 (or in some cases CO_2) cover.
2. Use freshly distilled and freshly autoclaved (121°C for 30 minutes) item 10; bubble item 11 for 20 minutes.
3. Add and dissolve items 4 and 5 in item 10 at 70°C; allow to cool.
4. Add items 6, 7, and 8 and stir to dissolve.
5. Add 1, 2, 3 to step 4, one at a time, and with complete solution stirring.
6. Check pH to 3.8 to 4.0; adjust pH with item 12 or 13.
7. Filter aseptically through a 0.45-μm prefilter and a 0.22-μm membrane filter into a staging sterilized vessel.
8. Fill into sterilized (200°C for 4 hours) amber type I glass ampoule using pre- and post-item 11 flushing.
9. Sample for complete testing.

Cyanocobalamin, Pyridoxine, and Thiamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
33.30	mg	1	Thiamine HCl, USP, ampoule grade, 20% excess	40.00	g
33.30	mg	2	Pyridoxine HCl, 20% excess	40.00	g
0.16	mg	3	Sodium formaldehyde sulfoxylate, NF	0.16	g
0.333	mg	4	Vitamin B_{12} (cyanocobalamin, USP), 40% excess	0.467	g
QS		5	Nitrogen gas, NF	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: The solution must be prepared in glass-lined or 316 stainless steel tank cleaned according to approved plant BOPs. Use N_2 protection throughout.

1. Preparation of solution.
   a. Heat 800 mL water for injection to boiling.
   b. Add and dissolve thiamine HCl, pyridoxine HCl, and sodium formaldehyde sulfoxylate.
   c. Boil solution slowly for 15 minutes.
   d. Dissolve vitamin B_{12} in a small quantity of N_2-saturated water for injection and add to the thiamine–pyridoxine solution from step d.
   e. Make up to 1 L with N_2-saturated water for injection.
   f. Adjust pH to 3.8 to 4.2 with freshly prepared 10 N sodium hydroxide solution.
   g. Filter solution through a previously rinsed filter using an approved 0.45-μm membrane and an approved prefilter.
   h. Sample for testing.
   i. Prepare a sterile 0.22-μm membrane filtration setup for the filling line.
2. Preparation of ampoules. Use type I 3-mL glass ampoules.
   a. Wash and dry ampoules and load into appropriate containers for sterilization.
   b. Sterilize using dry heat at 200°C glass temperature for 225 minutes or equivalent cycle.
3. Filling. *Caution*: Careful protection with N_2 is essential for stability.
   a. Aseptically connect tank and sterile-filter setup. Fill specified amount into each clean, dry sterile ampoule.
   b. Flush with sterile-filtered N_2 and seal.
   c. Inspect. Sample for testing.

Cyclosporine Ampoules for Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Cyclosporine, USP	10.00	g
130.00	mg	2	Polyoxyethylated castor oil (Cremophor® EL)	130.00	g
32.90	%	3	Alcohol, USP (by volume)	32.90	%
QS		4	Nitrogen gas, NF	QS	

***Note*: This solution can be further diluted with 0.9% sodium chloride, USP, or 5% dextrose injection, USP.**

Manufacturing Directions

1. Dissolve item 1 in item 2 in a suitable vessel. Provide item 4 cover throughout the process.
2. Add item 2 gradually and mix thoroughly.
3. Bring to volume with item 3; note that this is by volume preparation.
4. Filter through a prefilter of 0.45- and a 0.22-μm filter.
5. Fill 5 mL into each ampoule and sterilize.

Cytarabine Liposome Injection for Intrathecal Use (50 mg/5 mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Cytarabine	10.00	g
4.10	mg	2	Cholesterol	4.10	g
1.20	mg	3	Triolein	1.20	g
5.70	mg	4	Dioleoyphosphatidylcholine (DOPC)	5.70	g
1.00	mg	5	Dipalmitophosphatidylglycerol (DPPG)	1.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
0.90	%	7	Sodium chloride, USP	90.00	g
QS	mL	8	Hydrochloric acid for pH adjustment	QS	
QS	mL	9	Sodium hydroxide for pH adjustment	QS	
QS	ft^3	10	Nitrogen gas, NF		

Manufacturing Directions

1. This is a liposomal preparation, a suspension of cytabarine in normal saline. Do all manufacturing under item 10 cover.
2. Add and mix items 2 to 5 in a suitable vessel under item 10 cover. Add sufficient item 6 to make a fine dispersion.
3. Add fine cytarabine to step 2 and homogenize into liposomal structure.
4. Add item 7 and mix well.
5. Check and adjust pH (5.5–8.5).
6. Aseptically fill into 5-mL vial (for intrathecal use only).

Cytomegalovirus Immune Globulin IV (Human)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Immunoglobulin (IgG, traces of IgA and IgM)	40–60	g
50.00	mg	2	Sucrose, NF	50.00	g
10.00	mg	3	Albumin, NF	10.00	g
0.02–0.30	mEq	4	Sodium chloride	20–30	mEq
QS		5	Nitrogen gas, NF	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Item 1 is treated by a solvent–detergent inactivation process to remove viral load.

Manufacturing Directions

1. Place adequate quantity of item 6 into a suitable vessel purged with item 5 for at least 20 minutes.
2. Add item 2 and mix well. Add item 4 and mix well (calculate equivalent amounts)
3. While stirring, add item 1 slowly to avoid foaming. Keep covered with item 5.
4. Filter through appropriate filter system and fill 10 or 50 mL into each vial aseptically.

Dacarbazine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Dacarbazine	100.00	g
6.00	mg	2	Citric acid anhydrous	6.00	g
5.00	mg	3	Mannitol	5.00	g
QS		4	Nitrogen gas, NF	QS	
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium hydroxide for pH adjustment		
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: This is a light-sensitive product. Protect from light and provide N_2 cover throughout. The lyophilized powder is administered intravenously after reconstitution.

1. Add and dissolve items 2 and 3 in item 7 with item 4 cover.
2. Check and adjust pH to 3 to 4.
3. Add item 1 and dissolve.
4. Filter and fill either 1 or 2 mL and lyophilize.

Daclizumab for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Daclizumab	5.00	g
3.60	mg	2	Sodium phosphate monobasic monohydrate	3.60	g
11.00	mg	3	Sodium phosphate dibasic heptahydrate	11.00	g
4.60	mg	4	Sodium chloride, USP	4.60	g
0.20	mg	5	Polysorbate 80 (Tween®)	0.20	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	mL	7	Sodium hydroxide for pH adjustment	QS	
QS	mL	8	Hydrochloric acid for pH adjustment	QS	
QS	ft^3	9	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Put approximately 0.8 L of item 6 into a suitable vessel; purge with item 9 for 20 minutes.
2. Add and dissolve items 2 and 3.
3. Add item 4 and dissolve to complete solution.
4. Add item 5 slowly to avoid frothing and mix well; do not overstir.
5. Add item 1 and stir to dissolve.
6. Check and adjust pH 6.9 (6.7–7.0)
7. Filter product and fill vials aseptically.

Dactinomycin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.50	mg	1	Dactinomycin	0.50	g
20.00	mg	2	Mannitol	20.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: To be used after reconstitution for IV or regional perfusion.

Manufacturing Directions

1. Place a suitable quantity of item 3 into a suitable vessel.
2. Add and dissolve item 2.
3. Add item 1 and dissolve.
4. Filter product and fill vials.
5. Lyophilize.

Dalteparin Sodium Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
64.00	mg	1	Dalteparin sodium (10000 antifactor Xa IU/mL)	64.00	g
0.90	%	2	Sodium chloride, NF	90.00[a]	mg
14.00	mL	3	Benzyl alcohol, NF[b]	14.00	g
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a] Adjust for content of sodium to isotonic. Dalteparin sodium is produced through controlled nitrous acid depolymerization of sodium heparin from porcine intestinal mucosa followed by a chromatographic purification process. It is composed of strongly acidic sulfated polysaccharide chains (oligosaccharide, containing 2,5-anhydro-D-mannitol residues as end groups) with an average molecular weight of 5000 and approximately 90% of the material within the range 2000 to 9000. It is a low-molecular-weight heparin. It is available in two presentations: prefilled syringe and multiple-dose vial.
[b] Added only in multiple-dose vials.

Manufacturing Directions

1. Take appropriate quantity of item 6 and dissolve item 2 (calculate amount) and item 1 in it. (Optionally, add item 3 for multiple-dose vials.)
2. Check and adjust pH to 5.0 to 7.5 with item 4 or 5.
3. Bring to volume.
4. Filter and fill 0.1 mL (2500 IU) or 0.2 mL (5000 IU) into syringes or 9.5 mL into vial (95000 IU) aseptically.

Danaparoid Sodium Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1,250	U	1	Danaparoid sodium (anti-Xa units)	1250,000	U
0.15	%	2	Sodium sulfite	0.15	%
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	ft^3	6	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Place appropriate amount of item 5 into a stainless steel vessel and purge with item 6.
2. Add and dissolve item 2 under cover of item 6.
3. Add item 1 and dissolve completely.
4. Check and adjust pH to 7.0 (range 6.9–7.1).
5. Filter and fill aseptically into syringes (0.6 mL) or ampoule (0.6 mL); each unit containing 750 anti-Xa units.

Dantrolene Sodium for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.281	mg	1	Dantrolene sodium	0.281	g
42.85	mg	2	Mannitol	42.85	g
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	ft^3	4	Nitrogen gas, NF	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Add sufficient quantity of item 5 to a stainless steel tank. Purge with item 4 for not less than 20 minutes.
2. Add and dissolve item 2.
3. Add item 1 and stir to dissolve.
4. Check and adjust pH with item 3 to 9.5 (range 9.4–9.6).
5. Filter and fill 70 mL (to give 20 mg of dantrolene sodium and 3000 g of mannitol) into each vial and lyophilize.

Dapiprazole Hydrochloride Ophthalmic Solution (0.5%)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Dapiprazole hydrochloride	5.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Add item 1 to item 2 and dissolve.
2. Fill 5 mL into 10-mL vials and lyophilize.
3. Dispense with 5-mL diluent (water for injection) and a dropper for dispensing.

Daunorubicin HCl Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Daunorubicin, use daunorubicin hydrochloride	5.35	g
25.00	mg	2	Mannitol, USP	25.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	ft^3	4	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Add and dissolve item 2 to appropriate quantity of item 3 under cover of item 4.
2. Add and dissolve item 1.
3. Filter and fill 4 mL into 5-mL vials (equivalent to 20 mg of daunorubicin and 100 mg of mannitol) and lyophilize.
4. Dispense with water for injection for reconstitution (4 mL) to give activity of 5 mg daunorubicin/mL.

Daunorubicin Citrate Liposome Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Daunorubicin base, use daunorubicin citrate	2.72	g
28.16	mg	2	Distearoylphosphatidylcholine	28.16	g
6.72	mg	3	Cholesterol	6.72	g
85.00	mg	4	Sucrose, NF	85.00	g
18.80	mg	5	Glycine	18.80	g
0.28	mg	6	Calcium chloride dihydrate	0.28	g
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	mL	8	Sodium hydroxide for pH adjustment	QS	
QS	mL	9	Hydrochloric acid for pH adjustment	QS	
QS	ft^3	10	Nitrogen gas, NF	QS	

Manufacturing Directions

1. To 0.9 L of item 7 in a suitable stainless steel vessel, purge item 10 for 20 minutes.
2. Add items 4, 5, and 6; stir to dissolve.
3. Check and adjust pH with item 8 or 9 to between 4.9 and 6.0.
4. In a separate container, add items 2 and 3 and mix rapidly.
5. Add item 1 and homogenize.
6. Add the lipid solution to the aqueous phase with rapid mixing.
7. Check and adjust pH again to 4.9 to 6.0.
8. Filter and fill 25 mL in each vial.

The lipid to drug weight ratio is 18.7:1 (total lipid:base), equivalent to a 10:5:1 molar ratio of distearoylphosphatidylcholine:cholesterol:daunorubicin. Each vial (25 mL) contains daunorubicin citrate equivalent to 50 mg of daunorubicin base, encapsulated in liposomes consisting of 704 mg distearoylphosphatidylcholine and 168 mg cholesterol. The liposomes encapsulating daunorubicin are dispersed in an aqueous medium containing 2125 mg sucrose, 94 mg glycine, and 7 mg calcium chloride dihydrate in a total volume of 25 mL.

Desmopressin Acetate Injection (Intranasal)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
4.00	μg	1	Desmopressin acetate	4.00	mg
9.00	mg	2	Sodium chloride	9.00	mg
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: For multidose vial (10-mL fill) or for intranasal drops, use, additionally, chlorobutanol 5.0 mg/mL. Adjust pH to 4.0 with item 3.

Dexamethasone Acetate Suspension Injection: Dexamethasone Acetate (8 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
8.00	mg	1	Dexamethasone acetate equivalent to dexamethasone	8.00	g
1.00	mg	2	Sodium bisulfite, USP	1.00	g
0.75	mg	3	Sodium chloride, USP	0.75	g
5.00	mg	4	Carboxymethylcellulose sodium, USP	5.00	g
5.00	mg	5	Creatinine	5.00	g
0.50	mg	6	Disodium edetate	0.50	g
0.90	%	7	Benzyl alcohol, NF	0.90	%
QS	mL	8	Water for injection	QS to 1.00	L

Dexamethasone Acetate/Sodium Phosphate Suspension (8/2 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
8.00	mg	1	Dexamethasone acetate	8.00	g
2.00	mg	2	Dexamethasone sodium phosphate, USP	2.00	g
0.75	mg	3	Polysorbate 80, USP	0.75	g
6.67	mg	4	Sodium chloride, USP	6.67	g
5.00	mg	5	Carboxymethylcellulose sodium, USP	5.00	g
0.50	mg	6	Disodium edetate	0.50	g
1.00	mg	7	Sodium bisulfite, USP	1.00	g
5.00	mg	8	Creatinine	5.00	g
0.90	%	9	Benzyl alcohol, NF	0.90	%
QS	mL	10	Water for injection, USP	QS to 1.00	L
QS	mL	11	Acetic acid for buffering	QS	mL
QS	mL	12	Sodium acetate for buffering	QS	mL

Dexamethasone Sodium Phosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
24.00	mg	1	Dexamethasone sodium phosphate, USP, equivalent to dexamethasone phosphate	24.00	g
10.00	mg	2	Sodium citrate, USP	10.00	g
1.00	mg	3	Sodium bisulfite, USP	1.00	
1.50	mg	4	Methyl paraben, USP	1.50	g
0.20	mg	5	Propyl paraben, USP	0.20	g
8.00	mg	6	Creatinine	8.00	g
0.50	mg	7	Disodium edetate	0.50	g
QS	mL	8	Water for injection, USP	QS to 1.00	L
QS	mL	9	Sodium hydroxide for pH adjustment	QS	mL

Dexamethasone Sodium Phosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
4.00	mg	1	Dexamethasone phosphate, use dexamethasone sodium phosphate, USP	4.40	g
8.00	mg	2	Creatinine	8.00	g
10.00	mg	3	Sodium citrate, USP, dihydrate powder	10.00	g
1.00	mg	4	Sodium metabisulfite, NF	1.00	g
1.50	mg	5	Methyl paraben, NF (Aseptoform M) powder	1.50	g
0.20	mg	6	Propyl paraben, NF (Aseptoform P) powder	0.20	g
QS	mg	7	Sodium hydroxide[a]	QS	mg
QS	mL	8	Water for injection, USP	QS to 1.00	L
QS		9	Nitrogen gas, NF	QS	—

[a] Use for pH adjustment only.

Manufacturing Directions

1. Preparation of solution. *Note*: Use N_2 protection throughout process.
   a. Heat 80% of final volume of item 8 to boiling.
   b. Dissolve items 5 and 6 in step a with N_2 flushing.
   c. Discontinue heating and allow solution to cool to room temperature slowly while bubbling N_2 through solution.
   d. Add and dissolve items 1 to 4 in step c with continuous N_2 flushing.
   e. Check pH (range 7.0–8.5). Adjust pH to 8.0 if necessary, using freshly prepared 10% sodium hydroxide solution. Sample.
   f. QS to final volume with N_2-saturated item 8.
   g. Filter solution through a previously rinsed filtration setup, using a 0.45-μm or finer membrane and a prefilter.
   h. Prepare for the filling line a sterile 0.22-μm membrane filtration setup.
2. Preparation of ampoules. Use type I 1-mL glass ampoules. Wash and dry ampoules and sterilize by using dry heat at 200°C (–0, +50°C) glass temperature, for 225 minutes (–0, +360 minutes). This cycle or another cycle providing equivalent heat input may be used.
3. Filling. *Note*: Careful protection with N_2 is essential for stability.
   a. Aseptically connect tank and sterile filter setup.
   b. Fill specified amount into each clean, dry sterile ampoule. Sample.
   c. Flush with sterile-filtered N_2 and seal. Sample.

Dexamethasone Injection, Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Dexamethasone, USP	2.00	g
1.80	mg	2	Methyl paraben, USP	1.80	g
0.20	mg	3	Propyl paraben, USP	0.20	g
0.18	mg	4	Benzyl alcohol, NF	0.18	g
0.05	mL	5	Ethyl alcohol, USP	0.05	g
50.00	%	6	Polyethylene glycol 400, USP	50.00	%
QS	mL	7	Water for injection	QS to 1.00	L

Dexamethasone Sodium Phosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
4.00	mg	1	Dexamethasone, as dexamethasone sodium phosphate	5.20	g
8.00	mg	2	Creatinine	8.00	g
10.00	mg	3	Sodium metabisulfite	10.00	g
1.00	mg	4	Disodium edetate	1.00	g
10.00	mg	5	Sodium citrate	10.00	g
0.18	%	6	Methyl paraben sodium	1.80	g
0.02	%	7	Propyl paraben sodium	0.20	g
0.02	mL	8	Propylene glycol	20.00	mL
QS	mL	9	Water for injection, USP	QS to 1.00	L
0.030	g	10	Sodium hydroxide, NF, for pH adjustment	3.00	g
QS		11	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Autoclave item 9 at 121°C for 30 minutes and use this throughout manufacture.
2. Heat 0.2 L of item 9 to 80°C and dissolve items 6 and 7 in it.
3. In a separate vessel, dissolve item 5 in 0.1 L of item 9.
4. In a separate vessel, dissolve items 3 and 4 in 0.1 L of item 9.
5. Add contents of steps 2 and 3 into step 1, mix thoroughly, and then add item 8 with mixing.
6. Add and dissolve item 10 in 0.4 L of item 9 and add to step 5.
7. Make up the volume to 0.99 L.
8. Filter the solution in step 6, using a presterilized assembly and a 0.45-μm prefilter and a 0.22-μm filter into a sterile vessel.
9. Autoclave solution in step 7 at 121°C for 20 minutes.
10. On cooling to room temperature, add items 1 and 2 to step 8 and mix.
11. Check pH and adjust to between 7.5 and 8.5 with 4 N presterilized sodium hydroxide solution.
12. Make up the volume to 1 L with item 9.
13. Filter through presterilized assembly, using a 0.45-μm prefilter and a 0.22-μm filter into a staging sterilized vessel.
14. Fill 2.1 mL into presterilized type I flint vials with pre- and postflush with item 11. Use neoprene rubber stoppers sterilized by autoclaving at 121°C for 20 minutes.
15. Fill under aseptic conditions.

Dexpanthenol, Niacinamide, Pyridoxine, Riboflavin, and Thiamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Thiamine hydrochloride, USP, ampoule powder 200 mesh, 45% excess	145.50	g
5.00	mg	2	Pyridoxine hydrochloride, USP, 5% excess	5.25	g
9.00	mg	3	Benzyl alcohol, NF, 5% manufacturing excess	9.45	g
0.875	mg	4	Sodium formaldehyde sulfoxylate, NF[a]	875.00	mg
75.00	mg	5	Niacinamide, USP, powder for ampoule, 20% excess	90.00	g
1.00	%	6	Charcoal activated, USP[b]	900.00	mg
2.00 2.740	mg mg	7	Riboflavin, use riboflavin-5'-phosphate sodium, USP, 15% excess[c]	3.15	g
5.00	mg	8	D-Pantothenyl alcohol (dexpanthenol, FCC), 10% excess	5.50	g
QS	—	9	Carbon dioxide gas, technical	QS	—
QS	mg	10	Hydrochloric acid, reagent-grade bottles[d]	QS	mL
QS	mL	11	Water for injection, USP	QS to 1.00	L

[a] Sodium formaldehyde sulfoxylate is calculated to be ca. 0.0092% concentration in volume during first aging.
[b] Charcoal is calculated at 1% w/w of niacinamide.
[c] Riboflavin-5′-phosphate sodium is calculated at 73% riboflavin.
[d] Used for pH adjustment only.

Manufacturing Directions

Note: Protect solution from light and oxidation. Sodium formaldehyde sulfoxylate precipitates out metallic impurities and also acts as an antioxidant.

1. Take a sample from the water for injection and verify that it has NMT 3.0 (iS conductivity) and pH 5.0 to 7.0.
2. Boil 1.5 L of item 11 for 5 minutes in a jacketed pressure vessel. Cool to ambient temperature with continuous bubbling of CO_2 gas, and continue purging the headspace with CO_2 until the water has been used in manufacture.
3. Transfer 250 mL of the CO_2-saturated water to a suitable glass or stainless steel vessel. Purge vessel with CO_2 for the remainder of the process.
4. To the water from step 3, add and dissolve items 1, 2, and 3.
5. Dissolve item 4 in 20 mL of CO_2-saturated item 11 and add to the solution in step 4.
6. Dissolve item 5 in 200 mL of CO_2-saturated water and add to step 5.
7. Dissolve item 7 in 125 mL of CO_2-saturated water and add to step 6. Rinse the container with two 10-mL portions of the CO_2-saturated water and add to the solution.
8. Dissolve item 8 in 25 mL of CO_2-saturated water, warmed to 30°C to 40°C, cool and add to step 7. Rinse the container with two 10-mL portions of the CO_2-saturated water and add to the solution.
9. Add item 6 and mix under CO_2 gas protection using a stirrer for 1 hour.
10. Filter solution through a previously rinsed prefilter assembly and recirculate for at least 30 minutes until solution is clear of charcoal. Filter into another glass-lined or 316 stainless steel tank.
11. Make up to a volume of 950 mL with CO_2-saturated water.
12. Check pH (range 3.3–3.7). Adjust the pH to 3.5, if necessary, with concentrated hydrochloric acid. Age for 2 days under CO_2 gas protection.
13. Check pH (range 3.3–3.7). Adjust the pH to 3.5, if necessary, with concentrated hydrochloric acid or 10 M sodium hydroxide solution.
14. Make up to 1 L with CO_2-saturated water. Sample.
15. Filter solution through a previously rinsed filtration setup using an approved 0.45-μm or finer membrane and an approved prefilter into a glass-lined or 316 stainless steel holding tank and seal under CO_2 protection. Perform the bubble point test on the membrane before and after filtration.
16. Prepare for sterilization an approved 0.22-μm membrane and prefilter.
17. Preparation of containers. Use type I 1-mL glass ampoules, washed and dried, if not sealed type, and sterilized using dry heat at 200°C (–0, +50°C). Maintain oven temperature for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for duration of the cycle.
18. Connect tank, sterile filtration setup, and a sterile surge bottle by using aseptic technique.
19. Aseptically fill solution into each clean, dry sterile ampoule. Displace headspace air with sterile-filtered CO_2 gas and seal the ampoules. Sample.

Dexrazoxane for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Dexrazoxane	10.00	g
0.167	M	2	Sodium lactate	0.167	M
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable quantity of item 4, add and mix item 2.
2. Add and dissolve item 1.
3. Bring volume up to 0.98 L.
4. Check and adjust pH to 3.5 to 5.5 with item 3.
5. Make up volume.
6. Filter through 0.22-μm membrane filter and fill into vials (25 mL for a 250-mg dose and 50 mL for a 500-mg dose) to lyophilize.

Dextrose 25% Injection (Flexible Container)

Bill of Materials (Batch Size 102 L)					
Scale/mL		Item	Material	Qty	UOM
245.00 269.31 269.31	mg mg mg	1	Dextrose anhydrous, USP, or dextrose, USP, powder hydrous or dextrose monohydrate, BP, for parenteral use	25.00 27.47 27.47	kg kg kg
QS	mg	2	Carbon activated (Darco Powder G-60) or charcoal activated, USP	QS	g
QS	mL	3	Water for injection, BP	QS to 102.00	L

Note: Water is added to 102 L to allow for losses during storage. Use of carbon is optional.

Manufacturing Directions

1. Check that item 3 meets conductivity (NMT 3 μS) and pH (5–7) requirements. Note temperature. Add item 3 to tank to ca. 70% of final volume, dissolve item 1 with mixing, and add item 3 to make up final volume. Check pH (4.0–6.5). Sample.
2. Filter through carbon precoated Sparkler or Niagara prefilter or equivalent until clear; filter through 0.45-μm or finer filter. Test filters by the bubble point test.
3. Fill into clean containers. Sample.
4. Sterilize. Sample.

Dextrose Injection (5% and 10% LVP)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Dextrose anhydrous, USP, 5% excess	52.50	g
0.15	mg	2	Activated charcoal, NF	0.15	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: For 10% strength, increase the quantity of item 1 accordingly; other items remain the same.

Manufacturing Directions

1. Use freshly prepared item 3 stored for NMT 24 hours at 80°C. Add item 1 to item 3 at 60°C and mix for 15 minutes.
2. Add item 2 and mix vigorously for 15 minutes.
3. Filter the mixture in step 2 through a presterilized filter assembled suitable for retaining charcoal and to yield a clean solution.
4. Filter by using at least a 0.45-μm filter before final filtration with 0.22-μm filter and fill into 540 mL type I glass bottles.
5. Fill 540 mL while maintaining solution at 45°C to 50°C and seal immediately by using butyl gray rubber stoppers prewashed and sterilized at 116°C for 30 minutes. Use triple aluminum seals and suitable plastic hangers.
6. Sterilize filled bottle by autoclaving at 121°C for 20 minutes. Do not exceed temperature by 3°C or time by 2 minutes either side of the limit. The autoclaving cycle should be fully validated to prevent excess 5-hydroxy methyl furfural test limits of USP.
7. Check pH of solution (4.0–4.3); before autoclaving, pH is 5.5 to 6.5.

Dextrose with Sodium Chloride Injection LVP

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Dextrose anhydrous, USP, 10% excess	55.00	g
9.00	mg	2	Sodium chloride, USP, 4% excess	9.33	g
0.50	mg	3	Activated charcoal, NF	500	mg
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Use freshly prepared item 3 stored NMT 24 hours at 80°C. Add item 1 to item 3 at 60°C and mix for 15 minutes.
2. Add items 2 and 3 and mix vigorously for 15 minutes.
3. Filter the mixture in step 2 through a presterilized filter assembled suitable for retaining charcoal and to yield a clean solution.
4. Filter using at least through a 0.45-μm filter before final filtration with 0.22-μm filter and fill into 540-mL type I glass bottles.
5. Fill 540 mL while maintaining solution at 45°C to 50°C and seal immediately by using butyl gray rubber stoppers prewashed and sterilized at 116°C for 30 minutes; use triple aluminum seals and suitable plastic hangers.
6. Sterilize filled bottle by autoclaving at 121°C for 20 minutes; do not exceed temperature by 3°C or time by 2 minutes either side of the limit. The autoclaving cycle should be fully validated to prevent excess 5-hydroxy methyl furfural test limits of USP.
7. Check pH of solution (4.0–4.3); before autoclaving, pH is 5.5 to 6.5.

Diazepam Injectable Solution (2.5 mg/mL)

Formulation

1. Diazepam, 0.25 g; Solutol HS 15 [1], 4.00 g; lecithin, 4.00 g.
2. Water for injectables, add 100 mL; Preservative, QS.

Manufacturing

Heat mixture I to 60°C to 70°C, stir well, and add very slowly the hot solution II.

Diazepam Emulsion Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Diazepam	5.00	g
100.00	mg	2	Ethyl ester, animal/vegetable fat	100.00	g
12.00	mg	3	Phospholipid from eggs	12.00	g
22.50	mg	4	Glycerol	22.50	g
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Dissolve item 1 in item 2.
2. Add item 3 to solution in step 1 and mix well.
3. In sufficient quantity of item 6, dissolve item 4.
4. Check and adjust pH of solution in step 3 to 7.0 to 10.5 with item 5.
5. Add solution of Step 4 into step 3 and mix rapidly. Pass through homogenizer to make emulsion.
6. Fill vials and sterilize by autoclaving at 120°C for 17 minutes.

Diazepam Emulsion Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Diazepam	5.00	g
120.00	mg	2	Egg lecithin	120.00	g
80.00	mg	3	Sodium glycolate	80.00	g
30.00	mL	4	Alcohol, USP (evaporated in processing)	30.00	L
QS	ft^3	5	Nitrogen gas, NF	QS	
QS	mL	6	Phosphate buffer solution (pH 7) 1/15	QS to 1.00	L
12.00	mg	7	Sodium ascorbate	12.00	g

Manufacturing Directions

1. Dissolve items 1, 2, and 3 in item 4 in a flask.
2. Evaporate item 4 in rotary evaporator under vacuum at 35°C. This yields a lipid film in the flask.
3. Make up the volume with item 6, which had been purged with item 5 for 20 minutes in a separate vessel. The micelles are formed spontaneously at room temperature.
4. Add item 7 and dissolve.
5. Filter the solution aseptically into ampoules.

Diazepam Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Diazepam, USP	5.00	g
1.00	mg	2	Benzoic acid	1.00	g
100.00	mg	3	Alcohol absolute, USP	100.00	g
400.00	mg	4	Propylene glycol	400.00	g
49.00	mg	5	Sodium benzoate	49.00	g
15.00	mg	6	Benzyl alcohol	15.00	g
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	cy	8	Nitrogen gas, NF	QS	cy
QS	mL	9	Sodium hydroxide for pH adjustment	QS	mL
QS	mL	10	Hydrochloric acid for pH adjustment	QS	mL

Manufacturing Directions

Note: The following operations must be carried out under aseptic conditions. All containers and filters must be sterilized. The equipment that cannot be sterilized must be washed with 3% solution of benzyl alcohol and rinsed with sterilized water. Protect the solution from light. If directions are not followed strictly, diazepam may crystallize out.

1. Add item 2 and item 1 to item 3 previously heated to 30°C to 35°C and stir to complete solution.
2. Separately dissolve item 4 in item 6.
3. Separately dissolve item 5 in the first portion of item 7. Let item 8 bubble through the solution for 30 minutes and then filter.
4. Pool together solutions of steps 1 and 2. Cautiously add solution in step 3 with stirring.
5. Bring to volume with item 7. Mix and let item 8 bubble through the solution for 30 minutes.
6. Check and adjust pH to 6.5 to 7.2 with item 9 or 10.
7. Filter the solution through a 0.15-μm Sartorius filter and collect filtrate in a glass container.
8. Fill into ampoules under N_2 atmosphere through a 0.22-μm filter.

Diazepam Rectal Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
4.00	mg	1	Diazepam, USP	4.00	g
1.00	mg	2	Benzoic acid	1.00	g
100.00	mg	3	Alcohol absolute, USP	100.00	g
400.00	mg	4	Propylene glycol	400.00	g
49.00	mg	5	Sodium benzoate	49.00	g
15.00	mg	6	Benzyl alcohol	15.00	g
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	cy	8	Nitrogen gas, NF	QS	cy
QS	mL	9	Sodium hydroxide for pH adjustment	QS	mL
QS	mL	10	Hydrochloric acid for pH adjustment	QS	mL

Manufacturing Directions

Note: The following operations must be carried out under aseptic conditions. All containers and filters must be sterilized. The equipment that cannot be sterilized must be washed with 3% solution of benzyl alcohol and rinsed with sterilized water. Protect the solution from light. If directions are not followed strictly, diazepam may crystallize out.

1. Add items 1 and 2 to item 3 previously heated to 30°C to 35°C and stir to complete solution.
2. Separately dissolve item 4 in item 6.
3. Separately dissolve item 5 in the first portion of item 7 and filter through 0.6-μm Millipore® filter.
4. Pool together solutions from steps 1 and 2 Cautiously add solution in step 3 with stirring.
5. Bring to volume with item 7.
6. Check and adjust pH to 6.5 to 7.2 with item 9 or 10.
7. Filter the solution through a 0.22-μm filter and collect filtrate in a glass container.
8. Fill into rectal tubes (2.9 mL fill volume; label 2.5 mL).

Dibenzazepine Carboxamide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.50	mg	1	5H-dibenz(b,f)azepine-5-carboxamide	2.50	
47.50	mg	2	Glucose anhydrous for injection	47.50	g
QS	ft^3	3	Nitrogen gas, NF	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Dissolve item 1 under a blanket of item 3 in a suitable quantity of item 4 with stirring at 60°C to 80°C.
2. After cooling to room temperature, add item 2 and dissolve by stirring under item 3 purging.
3. Make up the volume.
4. Filter with a 0.22-μm membrane filter.
5. Fill into type I flint glass vials.
6. Sterilize by autoclaving at 121°C for 15 minutes.

Diclofenac Injectable Solution (75 mg/3 mL)

Formulation

Diclofenac sodium, 7.5 g; propylene glycol [1], 50.0 g; Kollidon 17 PF [1], 5.0 g; benzyl alcohol, 12.0 g; water for injectables, to 300 mL.

Manufacturing Directions

Dissolve Kollidon 17 PF in the mixture of propylene glycol, benzyl alcohol and water and add diclofenac sodium and stir until a clear solution is obtained.

The sterilization could be made by aseptic filtration (0.2 μm).

Diclofenac Sodium Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
75.00	mg	1	Diclofenac sodium	25.00	g
120.00	mg	2	Benzyl alcohol, NF	40.00	g
630.00	mg	3	Propylene glycol, USP	210.00	g
3.00	mg	4	Sodium metabisulphite	1.00	g
1.15	mg	5	Sodium hydroxide	383.33	mg
QS	mg	6	Sodium hydroxide[a]	QS	mg
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	–	8	Nitrogen, NF	QS	–

[a] For pH adjustment, if necessary, to be used as 0.1 N sodium hydroxide solution, freshly prepared in water for injection.

Manufacturing Directions

Note: N_2 gas protection must be used throughout process. The solution must be prepared in a glass-lined or a 316 or higher temper-grade steel tank.

1. Preparation of water.
   a. Obtain a sample from the water for injection source to be used for rinsing and mixing and verify that it meets conductivity limit of NMT 3.0 mS and pH range of 5 to 7.
   b. Test the rinse draining from the tank for conductivity and oxidizable substances prior to batch preparation.
2. Preparation of solution.
   a. Boil ca. 1.5 L item 7 for 5 minutes in a jacketed pressure vessel.
   b. Transfer 500 mL of the boiling item 7 from step 2a to a suitable 316 stainless steel container.
   c. Allow the remaining item 7 from step 2a to cool to ambient temperature while bubbling through filtered N_2 gas.
   d. Dissolve by stirring item 4 and item 5 into the hot 500 mL item 7 from step 2b.
   e. Transfer item 3 to a separate glass container; add and dissolve item 1 and item 2. Stir until completely dissolved.
   f. Add the solution from step 2e to the solution of step 2d. Mix well with stirring while bubbling through filtered N_2 gas.
   g. Check pH (range 8.0–9.0). Adjust pH if necessary with freshly prepared 0.1 N sodium hydroxide solution.
   h. Make up to 1 L with item 7 saturated with N_2 gas cooled to ambient temperature from step 2c.
   i. QC sample.
   j. Transfer the solution from step 2h to a stainless steel pressure vessel and seal under filtered N_2 gas protection until filtration.
   k. Filter solution from the stainless steel pressure vessel through a sterilized filtration setup fitted with an approved prefilter and an approved 0.22-μm membrane filter into a sterilized glass container. Bubble sterile-filtered N_2 gas through the filtered solution and seal under sterile-filtered N_2 gas protection. *Note*: Perform the bubble point test on a 0.22-μm membrane filter before and after filtration.
   l. Prepare for sterilization an approved 0.22-μm membrane filter fitted to filtration unit, approved 0.2-μm gas filter, surge bottle, tubing, and filling unit.
3. Preparation of ampoules. Use type I 3-mL amber glass ampoules, USP.
   a. Wash and dry the ampoules and then load into appropriate covered stainless steel trays for sterilization.
   b. Sterilize the ampoules by using dry heat at 200°C (–0°C, +50°C) ampoule temperature for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for duration of cycle. *Note*: This cycle or a cycle providing equivalent heat input may be used.
   c. Transfer ampoules to the aseptic filling area.
   d. Filling. *Note*: Careful protection with sterile-filtered N_2 gas is essential for stability.
   e. Aseptically connect glass container containing the injection solution, sterile filtration setup, sterile surge bottle, N_2 gas filter, and filling unit.
   f. Filter the injection solution into the surge bottle and adjust flow rate through filter equal filling rate to prevent any surge on the filter.
   g. Flush ampoules with sterile-filtered N_2 gas before filling.
   h. Aseptically fill the solution into each clean, dry, sterile ampoule. Flush with sterile-filtered N_2 gas and heat seal. *Note*: Perform bubble point test on filters before and after filtration.
   i. Sample. Inspect ampoules.
   j. Sample.

Diclofenac–Lecithin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
7.50	mg	1	Diclofenac	7.50	g
1.00	mL	2	Methylene chloride	1.00	L
1.00	mg	3	Lecithin[a]	1.00	g

[a] The quantity may be varied 50% on each side of the listed amount.

Manufacturing Directions

1. Dissolve item 3 in item 2.
2. Filter through a 0.2-μm membrane filter.
3. Add item 1 (micronized to less than 20-μm size).
4. Homogenize or sonicate the suspension to deagglomerate the suspension.
5. Fill 10 mL into each vial (to contain 75 mg of item 1).
6. Remove item 2 under vacuum to leave in the vial a lecithin-coated powder of item 1.
7. Reconstitute with 2.0 mL of water for injection containing 0.9% sodium chloride and made isotonic with mannitol and sodium chloride.

Diclofenac with Acetylcysteine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Diclofenac sodium	25.00	g
333.33	mg	2	1,2-Propylene glycol	333.33	g
0.033	mg	3	Ethyl lactate	0.033	g
0.666	mg	4	Glutathione (or *N*-acetylcysteine)	0.666	g
QS	mL	5	Sodium hydroxide for pH adjustment (0.1 N)	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	ft^3	7	Nitrogen gas, NF	QS	

Manufacturing Directions

1. In ca. 0.8 L of item 6, under purging of item 7, dissolve item 4.
2. Add item 2 and dissolve after grinding it to an average particle size of ca. 100 μm or less.
3. Check and adjust pH to 8.3 (8.1–8.5) with item 5.
4. Add item 3 and dissolve.
5. Make up the volume with item 6.
6. Filter using a 0.20-im membrane filter (nylon, polypropylene, or acrylic copolymer).
7. Fill ampoules.
8. Sterilize by autoclaving at 121°C for 15 minutes.

Diclofenac Lyophilized Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
18.00	mg	1	Sodium chloride, USP	18.00	g
75.00	mg	2	Diclofenac sodium, micronized (less than 20 μm)	75.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable jacketed (cold) stainless steel vessel, add item 1 to item 3 and dissolve.
2. Filter through a 0.20-mm filter membrane.
3. Transfer the solution to a sterilization vessel and sterilize in autoclave at 120°C for 20 minutes.
4. Allow to cool to 5°C.
5. Add item 2 and suspension deagglomerated in a homogenizer or ultrasonic disintegrator.
6. Fill the crystalline suspension at 5°C into 1-mL sterilized vials.
7. Freeze the vials at –45°C, lyophilize, and seal.

Diclofenac Lyophilized Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
75.00	mg	1	Diclofenac sodium, micronized (less than 20 μm)	75.00	g
5.40	mg	2	Sodium chloride, USP	5.40	g
20.00	mg	3	Mannitol	20.00	g
0.07	mg	4	Pluronic® F-68	0.07	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable stainless jacketed vessel, dissolve items 2, 3, and 4 in 0.7 L of item 5.
2. Filter solution through a 0.20-mm membrane filter after transferring it to a sterilization vessel.
3. Autoclave the solution at 120°C for 15 minutes.
4. Transfer the solution to mixing vessel, cool to 5°C, and add item 1.
5. Mix in a homogenizer or sonicator to deagglomerate.
6. Fill 1 mL into type I vials, loosely stopper, freeze at -45°C, lyophilize, and seal.

Dicyclomine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Dicyclomine hydrochloride, USP	10.00	g
9.00	mg	2	Sodium chloride, USP	9.00	g
5.00	mg	3	Chlorobutanol anhydrous, USP	5.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Acetic acid for buffering	QS	mL
QS	mL	6	Sodium acetate for buffering	QS	mL

Digoxin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.10	mg	1	Digoxin	0.10	g
0.40	mL	2	Propylene glycol	0.40	
0.10	mL	3	Alcohol, USP	0.10	L
1.70	mg	4	Sodium phosphate	1.70	g
0.80	mg	5	Citric acid anhydrous	0.80	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	ft^3	7	Nitrogen gas	QS	

Note: For adult dosage the quantity of item 1 is 0.25 mg/mL.

Manufacturing Directions

1. Take 0.9 L of item 6 and purge with item 7.
2. Add and dissolve items 2 and 3; mix well.
3. Add and dissolve items 4 and 5 (for pH adjustment); mix well.
4. Check pH to 6.8 to 7.2; do not adjust.
5. Make up volume.
6. Filter through a 0.22-μm membrane filter.
7. Fill 1 mL for pediatric (0.1 mg) dosage into type I glass ampoules.
8. Sterilize.

Dihydroergotamine Mesylate Drops

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Dihydroergotamine mesylate, 10% excess	2.20	g
153.00	mg	2	Glycerin, USP	153.00	g
48.25	mg	3	Ethanol, USP, 190 proof	48.25	g
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	ft^3	7	Nitrogen gas NF	QS	

Manufacturing Directions

Caution: This product is highly susceptible to oxidation and should be continuously bubbled and blanketed with item 7 during all stages of manufacture. Use item 7 filtered through a 0.45-μm Millipore® or equivalent. Oxygen level should be less than 1 ppm at all times. Protect from light. All tubing must be stainless steel, Teflon (FEP), or silicone.

1. Preparation.
   a. Heat sufficient item 6 to 95°C. Hold at this temperature for 1 hour. Begin bubbling item 7 and continue to heat for a further 1 hour. Cool slowly to NMT 22°C while continuing to bubble item 7.
   b. Load item 2 into a suitable stainless steel or glass-lined tank.
   c. Load sufficient item 3 into a suitable stainless steel or glass-lined container. Bubble item 7 for at least 2 hours.
   d. Check oxygen concentration in the item 6 from step 1a. Continue item 7 bubbling until concentration is less than 1 ppm.
   e. Take sample for testing.
   f. Flush a suitable stainless steel or glass-lined tank with item 7 and then transfer ca. 700 mL of item 6 from step 1d and begin bubbling with item 7. From here on provide continuous item 7 blanket.
   g. Add ca. 40 mL of water from step 1d to item 2 in step 1b and bubble with item 7 at a minimum pressure of 1 kg for at least 1 hour. Continue bubbling until used.
   h. Weigh item 3 and container from step 1-c. Add 48.25 g of item 3 to the water in step 1f. Stir or mix by recirculation for at least 5 minutes.
   i. Dilute approximately 0.03 mL of acid item 4 with item 6 to make a 20% solution. Ensure that oxygen level is less than 1 ppm.
   j. Measure pH and adjust to 3.25 with solution in step 1i.
   k. Take sample. *Note*: Use protective clothing and mask; wear gloves while adding item 1.
   l. Add the item 1 to the batch and stir until completely dissolved
   m. Add the item 2/water mix from step 1g to the batch and adjust the volume to 995 mL with water from step 1d. Stir or recirculate for at least 15 minutes. Dissolve 4 g of sodium hydroxide in 100 mL water from step 1d.
   n. Measure and adjust pH to 3.75 with solution in step 1n. Stir for at least 30 seconds and recirculate for at least 5 minutes between each addition. Record final pH and amount used.
   o. Take testing samples.
   p. QS to 1 L with water.
   q. Just prior to filtration, take testing samples.
2. Filtration.
   a. Filter the solution through a Millipore filter unit or equivalent fitted with a 0.22-im pore-size filter previously sterilized by heating in an autoclave for 30 minutes at 121°C. Discard the first portion of filtrate. Record amount discarded.
   b. Carry out a bubble pressure leak test (21–28 psi) on the filter membrane to verify its integrity. Record bubble point pressure.
   c. Collect the filtrate in a suitable stainless steel or glass, clean sterile container under filtered item 7. The container should be sterilized at 121°C for 30 minutes. Continue bubbling with item 7.
   d. At the end of filtration, carry out the bubble pressure leak test. Record bubble point pressure.
3. Filling.
   a. Wash 100-mL amber glass bottles with distilled water only. Then sterilize bottles by using dry heat.
   b. Wash stoppers with distilled water only and sterilize by heating at 121°C in an autoclave for 30 minutes.
   c. Sterilize roll-on pilfer-proof caps by heating in an autoclave at 110°C for 1 hour.
   d. Set up a suitable liquid filling machine, ensuring that all fittings and tubing are clean and sterile.
   e. Fill into 100-mL sterilized, amber glass bottles from step 3-a. Prior to liquid addition, purge bottles with item 7. When each bottle is full, flush the headspace with item 7. Immediately seal by using sterilized stoppers from step 3-c.
   f. On start-up and after stoppages, take samples for testing.

Dihydroergotamine Mesylate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Dihydroergotamine mesylate	1.00	g
0.061	mL	2	Alcohol, USP	61.00	mL
QS	mL	3	Methanesulfonic acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
150.00	mg	5	Glycerin	150.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In sufficient quantity of item 6, add and dissolve item 5.
2. Add items 2 and 5; mix well.
3. Add and dissolve item 1.
4. Check and adjust pH to 3.2 to 4.0 with items 3 and 4.
5. Filter through a 0.22-μm membrane filter and sterilize.

Dihydroergotamine Mesylate Nasal Spray

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
4.00	mg	1	Dihydroergotamine mesylate	4.00	g
10.00	mg	2	Caffeine anhydrous	10.00	g
50.00	mg	3	Dextrose anhydrous, USP	50.00	g
QS	ft^3	4	Carbon dioxide	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Use amber type I glass ampoules.

Diisopropylphenol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.028	mM	1	2,6-Diisopropylphenol	28.00	mM
1.00	mL	2	2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol	1.00	L

Manufacturing Directions

1. Mix items 1 and 2 in a suitable vessel. Stir for 15 minutes in aseptic conditions.
2. Check pH to 5.3 (do not adjust).
3. Filter through a 0.22-μm membrane filter and fill into ampoule or vial.

Diltiazem Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Diltiazem hydrochloride	5.00	g
0.75	mg	2	Citric acid anhydrous	0.75	g
0.65	mg	3	Sodium citrate dihydrate	0.65	g
71.40	mg	4	Sorbitol solution, USP	714.00	g
QS	mL	5	Hydrochloric acid for pH adjustment		
QS	mL	6	Sodium hydroxide for pH adjustment		
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable stainless steel vessel, take approximately 0.9 L of item 7.
2. Add item 4 and mix.
3. Add items 2 and 3; mix well.
4. Check and adjust pH to 3.7 to 4.1 with item 5 or 6.
5. Filter through presterilized assembly by using a 0.22-μm membrane filter.
6. Fill appropriate volumes (5 or 10 mL) into type I glass vials.
7. Sterilize by autoclaving.

Lyo-Ject® syringe, 25-mg syringe, is available in a dual-chamber disposable syringe. Chamber 1 contains lyophilized powder composed of diltiazem hydrochloride, 25 mg, and mannitol, USP, 37.5 mg. Chamber 2 contains sterile diluent composed of 5 mL water for with 0.5% benzyl alcohol, NF, and 0.6% sodium chloride, USP. Monovial® for continuous IV infusion is available in a glass vial with transfer needle set. The vial contains lyophilized powder composed of diltiazem hydrochloride, 100 mg, and mannitol, USP, 75 mg.

Dimenhydrinate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Dimenhydrinate, USP	50.00	g
0.50	mL	2	Propylene glycol, USP	0.50	L
0.05	mL	3	Benzyl alcohol, NF	0.05	L
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Hydrochloric acid for pH adjustment	QS	mL

Dimethyl Sulfoxide Injection

Bill of Materials (Batch Size 120 kg)					
Scale/mL		Item	Material	Qty	UOM
0.455	mL	1	Dimethyl sulfoxide, 5% excess; sp. gr. 1.1	54.60	L
60.0	mL	2	Water for injection, USP	60.0	L

Manufacturing Directions

1. Mix items 1 and 2 in a suitable stainless steel tank and mix vigorously until a clear solution is obtained.
2. Filter mixture from step 1 by using only polyethylene tubing, a prefilter of 0.22-μm sterilizing membrane, and a presterilized Pyrex bottle, which serves as reservoir.
3. Aseptically fill into bottles—type I clear glass bottles (50 mL) size Kimble, caps low density PE (Union Carbide DMDA 0160-MP7) washed with filtered Freon (3-μm cartridge filter) and gas sterilized with ethylene oxide. Do not autoclave.
4. Sample for testing.

Dimethyl Sulfoxide Irrigation

This is dimethyl sulfoxide (DMSO) 50% w/w aqueous solution for intravesical instillation. Each milliliter contains 0.54 g dimethyl sulfoxide. Intravesical instillation for the treatment of interstitial cystitis. Not for IM or IV injection.

Dinoprostone Cervical Gel

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.20	mg	1	Dinoprostone[a]	0.20	g
96.00	mg	2	Colloidal silicon dioxide	96.00	g
1104.0	mg	3	Triacetin (ca. to QS to 1 L)	1104.00	g

[a] Naturally occurring form of prostaglandin E_2 (PGE_2); dispense 2.5 mL (3 g) into tube for endocervical application.

Diphenhydramine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Diphenhydramine hydrochloride, USP[a]	10.00	g
5.00	mg	2	Chlorobutanol anhydrous, USP	5.00	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

[a] Or 50 mg/mL; multidose vial contains benzethonium chloride, 0.1 mg/mL; pH adjusted 5.0 to 6.0 with item 3 or 4.

Diphenylmethyl Piperazine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
4.00	mg	1	1-Diphenylmethyl-4-[(2-(4-methyl-phenyl)-5-methyl-1H-imidazol-4-yl) methyl] piperazine	4.00	g
4.13	mg	2	Tartaric acid	4.13	g
5.78	mg	3	Citric acid	5.78	g
2.64	mg	4	Methanesulfonic acid	2.64	g
45.10	mg	5	Sorbitol	45.10	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In sufficient quantity of item 6, add and dissolve items 2 and 3 in a suitable stainless steel vessel.
2. Add item 1 and dissolve.
3. Add item 5 and dissolve.
4. Bring to volume with item 6.
5. Filter using a 0.22-μm filter and fill.

Dipyrone Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
500.00	mg	1	Dipyrone	500.00	g
4.00	mg	2	Chlorobutanol	4.00	g
2.00	%	3	Benzyl alcohol, NF	20.00	mL
QS	mL	4	Water for injection, USP	QS to 1	L
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Hydrochloric acid for pH adjustment	QS	
QS		7	Nitrogen gas, NF	QS	

Note: Also for veterinary use.

Manufacturing Directions

1. Dissolve item 1 in approximately 0.5 L of item 4 heated to 60°C to 70°C under constant stirring until dissolved completely.
2. Add items 2 and 3 with constant stirring to complete solution.
3. Bring the solution to room temperature and make up the volume with item 4.
4. Bubble item 7 thoroughly and let stand for 30 minutes.
5. Check pH (6.8–7.0), adjust with 10% item 6 or 4% item 5 as needed, sample.
6. Filter solution through a 0.22-μm filter assembly.
7. Fill flint ampoules 5.2 mL under item 7 cover.
8. Terminal sterilization at 121°C for 30 minutes.
9. Sample for leakage and final testing.

Dipyrone, Papaverine HCl, and Atropine Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
500.00	mg	1	Dipyrone	500.00	g
20.00	mg	2	Papaverine hydrochloride	20.00	g
0.50	mg	3	Atropine sulfate	0.50	g
1.00	mg	4	Sodium metabisulfite	1.00	g
5.00	mg	5	Chlorobutanol	5.00	g
0.0013	mL	6	Benzyl alcohol, NF	1.30	mL
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS		8	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Bring item 7 to boiling; cool to room temperature.
2. Add item 6 and dissolve rapidly, add item 5, mix again for not less than 5 minutes.
3. Add items 1 to 3 and bring volume.
4. Provide and keep item 8 cover throughout.
5. Measure pH (3.8–4.2); do not adjust pH.
6. Filter through a presterilized filtering assembly by using a 0.22-μm filter.
7. Sterilize empty ampoules at 200°C for 4 hours.
8. Fill 3.2 mL for 3.00-mL fill volume into amber type I glass ampoules with pre- and post-item 8 flush.
9. Terminally sterilize in an autoclave at 121°C for 30 minutes.
10. Sample for final testing, clarity, and particle test.

Disodium Edetate Injection (150 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
150.00	mg	1	Disodium edetate anhydrous, use disodium edetate dihydrate, USP	150.00	g
QS	mg	2	Sodium hydroxide	QS	mg
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Heat ca. 70% of final volume of item 3 in a glass-lined or stainless steel mixing tank. Add and dissolve item 1. Cool solution. Check pH (range 6.5–7.5). Readjust with dilute item 2 if necessary.
2. Prefilter solution through appropriate filtration setup.
3. Filter and fill into clean ampoule and seal. Steam sterilize. Sample.

Disulfonic Acids Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
121.30	mg	1	S-Adenosyl-D-methionine salts of disulfonic acids	121.30	g
66.66	mg	2	Lysine	66.66	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In sufficient quantity of item 3, dissolve item 1, filter, and lyophilize.
2. Prepare diluent by using item 2 and QS to 1 L.

Dobutamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.22	mg	1	Sodium metabisulfite, NF	0.22	g
12.50	mg	2	Dobutamine base, use dobutamine HCl, USP	12.50	g
QS	mL	3	Hydrochloric acid[a]	QS	mL
QS	mL	4	Sodium hydroxide[a]	QS	mL
QS	—	5	Nitrogen gas, NF	QS	—
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a] For pH adjustment if necessary.

Manufacturing Directions

1. Transfer an appropriate volume of item 6 into a glass-lined tank while sparging with N_2 gas.
2. Mix and dissolve items 1 and 2. Continue N_2 sparging.
3. Check pH (range 2.7–3.3). If necessary, adjust pH with item 3 or 4 solution.
4. QS with N_2-protected item 6 to final volume and mix.
5. Check pH (range 2.7–3.3). If necessary, adjust pH with item 3 or 4 solution.
6. Discontinue N_2 sparge and switch to N_2 gas protection.
7. Sample for in-process control, dobutamine assay, and pH determination.
8. Filter solution through a previously cleaned and rinsed approved 0.45-μm (or finer) membrane filter. If required, an approved prefilter may be used.
9. During filling, filter solution through an approved 0.45-μm (or finer) membrane filter. If required, an approved prefilter may be used.
10. Fill clean empty vials. Protect the headspaces of filled vials by using filtered N_2 gas. Apply stoppers and overseals.
11. Sterilize product by using an approved autoclave cycle. QC samples.

Dopamine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Dopamine hydrochloride, USP	40.00	g
9.12	mg	2	Sodium metabisulfite, NF	9.12	g
10.00	mg	3	Acid citric, USP, anhydrous powder	10.00	g
QS	mg	4	Acid citric, USP, anhydrous powder[a]	QS	mg
5.00	mg	5	Sodium citrate dihydrate, USP, ampoule granules	5.00	g
QS	mg	6	Sodium citrate dihydrate, USP, ampoule granules[a]	QS	mg
QS	–	7	Nitrogen gas, NF	QS	–
QS	mL	8	Water for injection, USP	QS to 1.00	L

[a] Use for pH adjustment only; use 80 mg of item 1 for 80-mg/mL label. Other ingredients remain the same.

Manufacturing Directions

1. Preparation.
   a. Add item 8 to ca. 110% of final volume into a suitable vessel.
   b. Heat item 8 to 90°C to 100°C and hold at that temperature for 10 minutes and commence bubbling N_2 gas through the solution. Continue N_2 gas protection through the remainder of solution manufacturing. Draw off 20% of final volume into another suitable vessel under N_2 protection and hold for solution QS. Lower the temperature to between 45°C and 55°C through solution QS.
   c. Add and dissolve items 2, 3, and 5. Mix well without excessive agitation.
   d. Add and dissolve item 1 with minimal agitation. To ensure an accurate pH measurement, allow the pH sample solution to cool to 20°C to 25°C. Minimize excessive agitation of solution with mixer. Supplement this stirring by bubbling N_2 gas into the solution. Do not allow solution to vortex.
   e. QS to final volume with previously boiled N_2-protected item 8.
   f. Place lid on mix tank and establish N_2 atmosphere in the tank headspace. Cool the solution to 25°C (range 20–30°C).
   g. Check the pH (range 3.2–3.5). If more than 3.5, adjust to pH 3.3 with item 4. If less than pH 3.2, adjust to pH 3.3 (range: 3.2–3.5) with item 6.
   h. Filter solution through a previously rinsed filtration setup by using an approved 0.45-μm or finer membrane and an approved prefilter into a clean glass-lined or 316 stainless steel tank, protected with N_2 gas by bubbling and flushing headspace. Sample.
2. Filling. Ampoule: Use type I 5-mL glass ampoules, USP.
   a. Fill specified amount into each clean, dry ampoule. Flush the headspace with filtered N_2 gas and seal the ampoule.
   b. Inspect. Sample.
3. Sterilization.
   a. Sterilize at 115°C at an F_0 range of 8 to 18. Use water spray cooling and terminal air overpressure to maintain autoclave pressure. Sample.

Doxapram Hydrochloride Injection, USP

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Doxapram hydrochloride	20.00	g
9.00	mg	2	Benzyl alcohol	9.00	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Adjust pH to 3.5 to 5.0 with item 3 or 4.
2. Fill 20-mL multiple-dose vial.
3. Sterilize by autoclaving.

Doxercalciferol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Doxercalciferol	2.00	mg
4.00	mg	2	Polysorbate 80	4.00	g
1.50	mg	3	Sodium chloride	4.00	g
10.00	mg	4	Sodium ascorbate	10.00	g
7.60	mg	5	Sodium phosphate dibasic	7.60	g
1.80	mg	6	Sodium phosphate monobasic	1.80	g
1.10	mg	7	Disodium edetate	1.10	g
QS	mL	8	Water for injection, USP	QS to 1.00	L

Description

A synthetic vitamin D analog that undergoes metabolic activation in vivo to form 1(alpha),25-dihydroxyvitamin D_2 (1(alpha),25-$(OH)_2$ D_2), a naturally occurring, biologically active form of vitamin D_2.

Doxorubicin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Doxorubicin hydrochloride	2.00	g
9.00	mg	2	Sodium chloride	9.00	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
10.00	mg	4	Lactose NF	10.00	g
0.20	mg	5	Methyl paraben	0.20	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	ft^3	7	Nitrogen gas, NF	QS	

Manufacturing Directions

1. In a suitable stainless steel vessel, take approximately 0.9 L of item 6. Heat to 70°C to 80°C and add and mix item 5. Dissolve completely.
2. Cool to room temperature. Begin purging item 7 and maintain cover throughout.
3. Add and dissolve items 2 and 4. Mix well.
4. Add item 1 and mix vigorously.
5. Check and adjust pH using item 3 to 3.0 (2.9–3.1).
6. Filter through a 0.22-μm membrane filter and fill into vials 5-mL (10-mg dose) or higher proportional volumes.
7. Lyophilize.

Doxycycline Hyclate Injection

Bill of Materials (Batch Size 50 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Doxycycline hyclate, 5% overage	1.3125[a]	kg
120.00	mg	2	Ascorbic acid USP, 5% overage	6.30	kg
75.00	mg	3	Mannitol, USP	3.75	kg
QS	mL	4	Water for injection, USP	QS to 50.00	L

[a] Actual quantity to be recalculated depending on the potency of the material.

Manufacturing Directions

1. Place approximately 35 L of item 4 into a suitable mixing tank, add item 2 into it, and mix thoroughly to a complete solution.
2. Add item 1 with constant mixing until clear.
3. Add item 3 to the mixing tank and mix to a complete solution.
4. QS to final volume with item 4. If the solution meets specifications, filter through a 0.22-μm filter into a sterile receiving jar.
5. Lyophilization. Chill the shelves to −40°C or less and load chamber with vials kept covered with clean, sterile covers. Let the product freeze. Proceed when thermocouples register −40°C or lower for a minimum of 4 hours. Start condenser, let it achieve a temperature of −50°C or lower, start vacuum pump, and let the chamber pressure drop to 200 μm or lower. Set shelf temperature to +25°C and let the product temperature rise to within 1°C of the set point. Mark time and let the cycle run for a minimum of an additional 48 hours. At the end of the cycle, bleed the chamber with air, open chamber, remove six representative vials (two from each of the top, middle, and bottom shelves), and close the door. Test samples for moisture. If all samples contain 2% or less, stopper the vial, terminate cycle, and remove vials for sealing. If not, then extend the cycle and record action.
6. Treat stoppers by adding rubber detergent to RO water with gentle agitation. Add stoppers, autoclave at 121°C (minimum) for not less than 20 minutes. Drain solution, rinse 3 times with 57°C±3°C water for injection. Add sufficient water to cover the stoppers during each rinse. Siliconize stoppers if needed by adding 118.2 mL of silicone solution; drain and autoclave at 121°C (minimum) for not less than 30 minutes. Dry for not less than 8 hours at 100°C; use additional time if necessary.

Doxycycline Hyclate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Doxycycline as doxycycline hyclate equivalent	100.00	g
480.00	mg	2	Ascorbic acid	480.00	g

Note: Use 960.00 mg of item 2 for 200 mg of doxycycline dose.

Doxycycline Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Doxycycline, use doxycycline hydrochloride	126.96	g
167.95	mg	2	Phosphoric acid (85%)	167.95	g
34.92	mg	3	Magnesium oxide	34.92	g
20.00	mg	4	Lidocaine	20.00	g
10.00	mg	5	Monothioglycerol	10.00	g
2.00	mg	6	Propyl gallate	2.00	g
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable quantity of item 7, add item 1 with stirring.
2. Add item 3 and mix.
3. Check and adjust pH to 2.5 (2.3–2.6) with item 2.
4. Add and mix items 4, 5, and 6.
5. Make up volume with item 7.
6. Filter and sterilize.

Ebselen Liposomal Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.11	mg	1	Ebselen	0.11	g
13.33	mg	2	DPPC (Dipalmitoylphosphatidylcholine)	13.33	g
1.33	mg	3	DPPG (Dipalmitoylphosphatidylglycerol)	1.33	g
6.45	mg	4	Cholesterol	6.45	g
0.025	mL	5	Methanol	0.25	L
0.025	mL	6	Chloroform	0.25	L
QS	mL	7	Acetate buffer pH 4.0 in water for injection, USP	QS to 1.00	L
QS	ft^3	8	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Dissolve items 1, 2, and 3 in items 5 and 6.
2. Remove solvents in step 1 under vacuum.
3. Hydrate the film with item 7 under item 8.
4. Add glass beads and stir to form liposomes.
5. Filter under sterile condition and fill into ampoules under cover of item 8.

Edetate Sodium, Polyvinyl Alcohol, Sodium Sulfacetamide, Sodium Thiosulfate Ophthalmic Drops with Thimerosal

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Qty	UOM
Part I					
		1	Water purified (distilled), USP, ca.	10.00	L
14.00	mg	2	Polyvinyl alcohol, 20–90	630.00	g
0.0001	mL/mL	3	Polysorbate 80, NF (use a 10% solution)	45.00	mL
Part II					
		4	Water purified (distilled), USP, ca.	250.00	L
0.6805	mg	5	Potassium phosphate monobasic, NF	30.62	g
5.3620	mg	6	Sodium phosphate dibasic heptahydrate, USP[a]	241.30	g
0.1274	mg	7	Disodium edetate, USP	5.73	g
306.00	mg	8	Sulfacetamide sodium, USP (2% overage)	13.77	kg
		9	5 N Hydrochloric acid, NF[b]	QS	mL
3.14	mg	10	Sodium thiosulfate pentahydrate, USP[c]	141.30	g
Part III					
		11	Water purified (distilled), USP, ca.	200.00	mL
0.05	mg	12	Thimerosal, USP[d]	2.25	g
		13	Water purified (distilled), USP	QS to 45.00	L

[a] Equivalent to 2.8393 mg/mL sodium phosphate dibasic anhydrous.
[b] Use for pH adjustment only.
[c] Equivalent to 2.0 mg/mL sodium thiosulfate anhydrous.
[d] The amount of thimerosal to be added must be calculated on the basis of the assay value of the raw material lot(s) used.
Assay Value:_____%
2.25 g × 100.0%/Assay Value (%) = ____ g of thimerosal required.

Manufacturing Directions

Part I

1. Measure out ca. 10 L of item 1 into a stainless steel pressure vessel.
2. Begin mixing with a suitable mixer.
3. Heat item 1 to 85°C to 90°C.
4. Begin mixing item 1 with a propeller mixer.
5. Add item 2 slowly to the vortex.
6. Mix for at least 90 minutes until item 2 is completely dissolved.
7. After mixing item 2 for at least 90 minutes, add item 3 and mix thoroughly.
8. Cool to room temperature, with force cooling.

Part II

1. Measure out ca. 25 L of item 4 into a suitable mixing tank calibrated for a final QS of 45 L. Begin mixing.
2. Add items 5 to 8, in order, allowing each to dissolve completely before adding the next.
3. After item 8 is completely dissolved, mix part II for at least 15 minutes.
4. Sample for pH (range 7.3–7.5). If necessary, adjust the pH to 7.3 to 7.5 with item 9.
5. Add item 10 and mix until it is dissolved.
6. Add part I to the mixing tank containing part II, while mixing part II.
7. Use 2 to 3 L of water purified (distilled) to rinse the part I kettle, pump, and hoses.
8. Add the rinsings to the mixing tank.

Part III

1. Weigh out item 12 and carefully transfer it to a suitable flask.
2. Add 200 mL of item 13 and mix until item 12 is dissolved.
3. Add part III to combined parts I and II while mixing.
4. Rinse the flask containing item 12 with ca. 200 mL of item 13 and add the rinsings to the batch.
5. Allow any foam to dissipate and QS the batch to 45 L with item 13.
6. Mix thoroughly for at least 15 minutes.

Sterile Filtration

1. Sterilize for 1 hour (range 45–60 minutes) at 121°C (−0, +5°C) in autoclave at 15 psi the filter and 100-L stainless steel pressure vessel. Transfer to the solution preparation area.
2. Attach the prefilter and final filter and hosing sterilization chart.
3. Mix the product for at least 10 minutes before filtration.
4. Connect the sterilized Pall filter and sterile filter with the aid of N_2 pressure (15–30 lb). Discard initial 10 L of filtrate, attach sterilized hose to sterilized filter holder, and connect to sterilized 100-L stainless steel pressure vessel. *Note*: Before sterile filtration to 100-L pressure vessel, perform the bubble point test at NLT 40 psi.
5. After completion of product filtration, disconnect Pall filter from pressure vessel. Flush the sterilized filter with at least 10 L of water purified (distilled) for the bubble point test (after filtration).
6. After filtration, decontaminate the outer surface of bulk holding pressure vessel and then transfer to filling cubicle. Sample.

Sterilization

Sterilize filling unit, 20-L surge bottle or manifold of filling unit, and uniforms at 121°C (−0, +2°C) at 15 psi for 1 hour.

Sterile Filling

1. Transfer the presterilized bottles, plugs, and caps to the filling cubicle after swabbing their outer polyethylene packing with filtered methylated spirit and keep under the laminar flow hood.
2. Transfer the sterilized assembly line to filling room. Aseptically connect the sterilized filling tubing and N_2 line from the 100-L pressure vessel to surge bottle.
3. Aseptically fill 15.40 mL of sterile solution through into sterilized container by using the automatic filling, plugging, and sealing machine and apply sterile closure components (plugs and caps). *Note*: Discard 50 to 100 bottles initially during volume adjustment. While filtering, N_2 pressure should not exceed 5 to 10 lb.
4. Perform the bubble point test on 0.22-μm inline gas filter before and after filtration at 18 psi. Sample.

Edetate Sodium, Polyvinyl Alcohol, Sodium Sulfacetamide, Sodium Thiosulfate Ophthalmic Drops With Benzalkonium Chloride

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Qty	UOM
Part I					
		1	Water purified (distilled), USP	6.00	L
14.00	mg	2	Polyvinyl alcohol, 20–90	630.00	g
0.10	mg	3	Polysorbate 80, NF (use a 10% Solution)	41.75	mL
Part II					
		4	Water purified (distilled), USP	30.00	L
2.68	mg	5	Sodium phosphate dibasic heptahydrate, USP	120.60	g
0.345	mg	6	Sodium phosphate monobasic monohydrate, USP	15.53	g
0.15	mg	7	Disodium edetate, USP	6.75	g
100.00	mg	8	Sodium sulfacetamide, USP	4.50	kg
QS	mL	9	5 N Hydrochloric acid, NF[a]	QS	mL
QS	mL	10	1 N Sodium hydroxide, NF[a]	QS	mL
3.14	g	11	Sodium thiosulfate pentahydrate, USP	141.30	g
0.05	mL	12	Benzalkonium chloride, NF (10% solution)[b]	22.50	mL
QS	mL	13	1 N Hydrochloric acid, NF[a]	QS	mL
QS	mL	14	1 N Sodium hydroxide, NF[a]	QS	mL
QS	mL	15	Water purified (distilled), USP	QS to 45.00	L

[a] Used for pH adjustment

[b] The amount of benzalkonium chloride, NF (10% solution), is calculated as follows: 22.50 mL × 10.0%/assay value (%) = mL benzalkonium chloride, 10% solution, required.

Manufacturing Directions

Part I

1. Measure out ca. 6 L of item 1 into a jacketed pressure vessel; measure the temperature (NMT 30°C).
2. Begin mixing and add item 2. Adjust the mixing to the minimum speed that will allow complete dispersion and agitation. Mix for 60 to 90 minutes.
3. Heat part I to 85°C to 90°C by circulating steam. Maintain the temperature of part I at 85°C to 90°C for 15 to 20 minutes.
4. Add item 3 and mix thoroughly. Cool part I to less than 30°C with force cooling.

Part II

1. Measure out ca. 30 L of item 4 into a suitable mixing tank. Begin mixing.
2. Add the items 5 to 8, in order, allowing each to dissolve completely before adding the next.
3. After item 8 is completely dissolved, mix part II for at least 30 minutes. If necessary, adjust pH to 7.3 to 7.5 with item 9 or 10.
4. Add item 11 and mix until it is completely dissolved. Transfer part I into the tank containing part II. Add item 12 and mix thoroughly. QS the batch to 45 L with item 15. If necessary, adjust the pH to 7.3 to 7.5 with item 13 or 14. Mix thoroughly for at least 30 minutes.
5. Sterile filter with the aid of N_2 pressure. Perform the bubble point test.
6. Aseptically fill sterile solution into sterilized containers. Perform the bubble point test. Sample.

Edrophonium Injectable

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Edrophonium	10.00	g
4.50	mg	2	Phenol liquefied	4.50	g
2.00	mg	3	Sodium sulfite	2.00	g
0.20	M	4	Citric acid anhydrous	0.20	M
0.20	M	5	Sodium citrate	0.20	M
QS	mL	6	Hydrochloric acid for pH adjustment	QS	
QS	mL	7	Sodium hydroxide for pH adjustment	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 5.4.

Electrolyte Maintenance Fluid (For Maintenance)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	%	1	Dextrose anhydrous, USP, 10% excess	55.00	g
0.28	%	2	Sodium acetate, 5% excess	2.94	g
0.09	%	3	Sodium chloride, 5% excess	0.96	g
0.15	%	4	Potassium chloride, 5% excess	1.575	g
0.13	%	5	Dibasic potassium phosphate, 5% excess	1.36	g
0.020	%	6	Sodium metabisulfite, 5% excess	0.22	g
QS		7	Glacial acetic acid, NF	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Dissolve items 2 to 6 in 0.9 L of item 4.
2. Adjust pH to 5.0 with item 7. Adjust with item 7 (ca. 1.1 mL); pH must not exceed 5.0.
3. Add item 1 and mix.
4. Filter using at least a 0.45-μm filter before final filtration with 0.22-μm filter and fill into type I 540-mL glass bottles.
5. Fill 540 mL while maintaining solution at 45°C to 50°C and seal immediately by using butyl gray rubber stoppers pre-washed and sterilized at 116°C for 30 minutes; use triple aluminum seals and suitable plastic hangers.
6. Sterilized filled bottle by autoclaving at 121°C for 20 minutes; do not exceed temperature by 3°C or time by 2 minutes either side of the limit. The autoclaving cycle should be fully validated to prevent excess 5-hydroxy methyl furfural test limits of USP.

Electrolyte Maintenance Fluid (For Rehydration)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.0	mg	1	Dextrose anhydrous, USP, 10% excess	55.00	g
3.70	mg	2	Sodium chloride NF, 5% excess	3.88	g
1.30	mg	3	Potassium chloride NF, 5% excess	1.60	g
3.70	mg	4	Ammonium chloride NF, 5% excess	3.88	g
0.15	mg	5	Sodium sulfite, NF, 5% excess	0.156	g
QS	mL	6	Hydrochloric acid for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS		8	Glacial acetic acid, NF, for pH adjustment	QS	

Manufacturing Directions

The general directions are common to all LVPs containing dextrose. Read directions for dextrose 5%.

1. To 0.8 L of item 7 add items 2, 3, and 4, and stir and dissolve.
2. Check and adjust pH to 4.8 to 5.0 with item 6. (Do not adjust if in this range.)
3. Add items 1 and 5 and make up volume.
4. Check and adjust pH again to 4.8 to 5.2 with item 8.
5. Filter using at least a 0.45-μm filter before final filtration with 0.22-(μm filter and fill into type I 540-mL glass bottles.
6. Fill 540 mL while maintaining solution at 45°C to 50°C and seal immediately by using butyl gray rubber stoppers prewashed and sterilized at 116°C for 30 minutes; use triple aluminum seals and suitable plastic hangers.
7. Sterilized filled bottle by autoclaving at 121°C for 20 minutes; do not exceed temperature by 3°C or time by 2 minutes either side of the limit. The autoclaving cycle should be fully validated to prevent excess 5-hydroxy methyl furfural test limits of USP.

Electrolyte Maintenance Fluid (Maintenance, Pediatric)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	%	1	Dextrose anhydrous, USP, 10% excess	55.00	g
0.315	%	2	Sodium acetate, 5% excess	3.30	g
0.13	%	3	Potassium chloride, 5% excess	1.365	g
0.031	%	4	Magnesium chloride, 5% excess	0.334	g
0.026	%	5	Dibasic potassium phosphate, 5% excess	0.273	g
0.021	%	6	Sodium metabisulfite, 5% excess	0.224	g
QS		7	Glacial acetic acid, NF	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Dissolve items 2 to 5 in 0.9 L of item 8.
2. Adjust pH to 5.0 using item 7.
3. Add item 1 and mix.
4. Make up the volume and check pH again and adjust between 4.8 and 5.0.
5. Filter by using at least a 0.45-μm filter before final filtration with 0.22-μm filter and fill into type I 540-mL glass bottles.

Electrolyte Maintenance Fluid: Maintenance (45 mEq)

1. Fill 540 mL while maintaining solution at 45°C to 50°C and seal immediately by using butyl gray rubber stoppers prewashed and sterilized at 116°C for 30 minutes; use triple aluminum seals and suitable plastic hangers.
2. Sterilized filled bottle by autoclaving at 121°C for 20 minutes; do not exceed temperature by 3°C or time by 2 minutes either side of the limit. The autoclaving cycle should be fully validated to prevent excess 5-hydroxy methyl furfural test limits of USP.

Electrolyte Maintenance Fluid

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Dextrose hydrous, USP (use 23.89 g if using anhydrous)	26.25	g
2.05	mg	2	Sodium chloride, USP	2.05	g
0.98	mg	3	Sodium citrate, USP	0.98	g
2.16	mg	4	Potassium citrate monohydrate	2.16	g
QS	mg	5	Citric acid, USP, anhydrous, for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

5 Electrolyte Maintenance Fluid Rehydration (75 mEq)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Dextrose hydrous, USP (use 23.89 g if using anhydrous)	26.25	g
3.80	mg	2	Sodium chloride, USP	3.80	g
0.98	mg	3	Sodium citrate, USP	0.98	g
2.16	mg	4	Potassium citrate monohydrate	2.16	g
QS	mg	5	Citric acid, USP, anhydrous, for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Electrolyte Maintenance Fluid Rehydration (90 mEq)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Dextrose hydrous, USP, (use 23.89 g if using anhydrous)	26.25	g
4.68	mg	2	Sodium chloride, USP	4.68	g
0.98	mg	3	Sodium citrate, USP	0.98	g
2.16	mg	4	Potassium citrate monohydrate	2.16	g
QS	mg	5	Citric acid, USP, anhydrous, for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Add item 1 to ca. 80% of item 6 in a previously cleaned mixing tank.
2. Add and dissolve items 3, 2, and 4, in order. Mix to dissolve.
3. Check pH to 6.0 to 6.5; adjust if necessary with item 5.
4. Filter using a 0.45-μm prefilter and 0.22-μm membrane filter.
5. Fill and steam sterilize.

Electrolytes, TPN Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
16.07	mg	1	Sodium chloride, USP	16.07	g
16.54	mg	2	Calcium chloride, USP	16.54	g
74.55	mg	3	Potassium chloride, USP	74.55	g
25.41	mg	4	Magnesium chloride, USP	25.41	g
121.00	mg	5	Sodium acetate, USP	121.00	g
QS	mL	6	Hydrochloric acid, reagent grade, for pH adjustment		
QS	mL	7	Water for injection, USP		

Manufacturing Directions

1. Prepare the solution in a glass-lined or 315 or higher temper-grade stainless steel tank.
2. Add item 7 to ca. 70% of the final volume into the tank.
3. Add and dissolve items 1 to 5 with mixing.
4. QS with item 7 and mix.
5. Check and record pH adjust with item 6 if necessary.
6. Filter the solution through a previously rinsed filtration setup, using an approved 0.45-μm membrane with an approved prefilter into a glass-lined or stainless steel tank.
7. Fill into clean vials by using the surge bottle.
8. Autoclave at 121°C for 20 minutes.
9. Inspect and finish.
10. Sample for testing.

Emetine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
30.00	mg	1	Emetine hydrochloride, USP	50.00	g
QS	mL	2	Sodium hydroxide for pH adjustment	QS	
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Dissolve item 1 in 0.9 L of item 4. Make up the volume.
2. Check and adjust pH to 3.0 (2.7–3.3) with items 2 and 3.
3. Filter through presterilized filtration assembly through a 0.45-μm prefilter and a 0.22-μm filter into a sterilized staging vessel.
4. Fill 1.1 mL into presterilized type I glass ampoule aseptically. *Do not* autoclave.

Enalaprilat Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Enalaprilat	5.40	g
11.40	mg	2	Sodium phosphate dibasic anhydrous	11.40	g
9.00	mg	3	Benzyl alcohol	9.00	g
QS	mL	4	Water for injection	QS to 1.00	L

Ephedrine and Pyrilamine Maleate Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Pyrilamine maleate, NF	25.00	g
10.00	mg	2	Ephedrine HCl, NF	10.00	g
3.00	mg	3	Chlorobutanol anhydrous, USP	3.00	g
QS	mL	4	Water for injection	QS to 1.00	L

Ephedrine Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Ephedrine sulfate, USP	50.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: The solution must be prepared in a glass-lined or a 316 or higher temper-grade stainless steel tank cleaned according to approved plant basic operating procedures.

1. Add item 2 to tank to ca. 90% of the final volume.
2. Add and dissolve item 1 with mixing.
3. QS with item 2 to final volume and mix until drug is dissolved and solution is uniform. Check pH (range 5–6.5).
4. Filter solution through a previously rinsed filtration setup, using an approved 0.45-μm or finer membrane with an approved prefilter. Filter solution into a clean glass-lined or 316 stainless steel holding tank. Sample.
5. With the 0.22-μm inline filter, fill specified dose into each clean, dry ampoule, and seal and sterilize in a steam autoclave at 121°C for 15 minutes. Sample.

Epinephrine Auto Injector Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Epinephrine	1.80	g
5.40	mg	2	Sodium chloride	5.40	g
1.50	mg	3	Sodium metabisulfite	1.50	g
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	ft^3	6	Nitrogen gas, NF	QS	

Manufacturing Directions

Note: This preparation requires strict control on exposure to light and air.

1. Take 0.9 L of item 5 and pass item 6 for 20 minutes, covered and protected from light.
2. Add and dissolve items 2 and 3.
3. Add item 1 and dissolve.
4. Check and adjust pH with item 4 to 2.2 to 5.0.
5. Filter through 0.22-μm membrane filter into emergency-use syringes.

Epinephrine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1	mg	1	Epinephrine, USP	1.00	g
9	mg	2	Sodium chloride, USP	9.00	g
5	mg	3	Chlorobutanol anhydrous, USP	5.00	g
2	mg	4	Sodium bisulfite, USP	2.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Hydrochloric acid for pH adjustment	QS	

Epoetin-Alpha for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2000	U	1	Epoetin alpha[a]	2000,000	U
2.50	mg	2	Albumin (human)	2.50	g
5.80	mg	3	Sodium citrate	5.80	g
5.80	mg	4	Sodium chloride	5.80	g
0.06	mg	5	Citric acid	0.06	g
QS	mL		Water for injection, USP	QS to 1.00	L

[a] Other strengths to 40000 U require adjustment of ingredients; adjust pH to 6.9 (range 6.6–7.2).

Epoprostenol Sodium for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.50	mg	1	Epoprostenol sodium equivalent to epoprostenol	0.50	g
3.76	mg	2	Glycine	3.76	g
2.93	mg	3	Sodium chloride	2.93	g
50.00	mg	4	Mannitol	50.00	g
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 10.2 to 10.8; freeze dry; diluent includes glycine; sodium hydroxide in water for injection.

Ergocalciferol Injection (Vitamin D)

Bill of Materials (Batch Size 2 L)					
Scale/mL		Item	Material	Qty	UOM
400.00	IU	1	Ergocalciferol, USP = $8 \times 10^5/40 \times 10^6$ potency of raw material	800000 20.00	IU mg
50.00	mg	2	Polysorbate 20, NF	100.00	g
500.00	mg	3	Glycerin, NF	1.00	kg
QS	mL	4	Water for injection, USP	2.00	L
QS	–	5	Nitrogen gas, NF	QS	–
QS	mL	6	Sodium hydroxide, 10%, for pH adjustment	QS	mL

Manufacturing Directions

1. Put item 2 into a clean compounding tank and place it on a hot plate, heat it to approximately 40°C and not exceeding 60°C, keep nitrogen blanket over tank throughout.
2. Add item 1 with constant stirring to step 1. Keep stirring until a clear solution is obtained.
3. Stop heating; while agitating, add in portions item 3 to the tank.
4. Bring within approximately 100 mL of the final volume with item 4. Mix thoroughly and check pH.
5. If necessary, adjust pH to between 5.0 and 7.0 with item 6. Do not adjust pH if within this range already.
6. Bring to final volume with item 4, check pH, and if approved, filter through a 0.22-μm filter into a sterile jar. Keep N_2 cover. Fill with N_2 postfill flush.

Ergonovine Maleate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.25	mg	1	Ergonovine maleate, USP, 7% excess	267.50	mg
0.20	mg	2	Acid maleic, BP	200.00	mg
QS	–	3	Nitrogen, NF	QS	–
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Precautions: Prepare solution in a clean glass-lined tank. Use N_2 protection throughout. Product is heat sensitive and must be refrigerated. Do not freeze.

1. Add item 4 to ca. 90% of the final volume into a glass-lined tank protected from light.
2. Bubble filter item 3 into item 4 for 10 minutes. Blanket with item 3.
3. Add and dissolve item 1 and 0.4% solution of item 2 (30 mL of a 0.4% item 2 solution needed for 1 L of final solution) with mixing.
4. Check pH (range 2.7–3.5). Adjust to pH 3 with remaining portion of 0.4% solution of item 2.
5. QS with item 4 to final volume. Sample.
6. Sterilize an approved 0.2- or 0.22-μm membrane filter with an approved prefilter.
7. Filter the solution through the sterilized filter unit into a sterile glass-lined holding container.
8. Sterilize sulfur-treated ampoules, using dry heat at 245°C for at least 3 hours and 25 minutes or an equivalent cycle.
9. Connect bulk solution container by using aseptic technique to the filling machines.
10. Aseptically fill the specified dose into each clean, sterile ampoule.
11. Flush the headspace of each ampoule with sterile-filtered item 3. Immediately seal. Sterilize and sample.

Ergonovine Maleate Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.20	mg	1	Ergonovine maleate, NF	0.20	g
0.50	mL	2	Liquefied phenol, USP	0.50	g
QS	mL	3	Water for injection, USP	1.00	L
QS	mL	4	Hydrochloric acid for pH adjustment	QS	

Erythromycin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Erythromycin, use erythromycin, USP, base special[a]	66.42	g
—	mL	2	Lactobionic acid, 12% w/v[b]	272.28	mL
QS	mg	3	Charcoal activated USP[c]	QS	g
9.00	mg	4	Benzyl alcohol, NF, for ampoules (15% excess)	12.38	g
QS	—	5	Nitrogen, NF	QS	—
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a] Qty based on a theoretical potency of 900 μg/mg; to be recalculated depending on actual potency.
[b] Include 5% excess for pH adjustment. The ratio between erythromycin base and lactobionic acid should remain constant.
[c] Amount of charcoal depends on area of filter. Use ca. 440 g/m^2 of filter surface area.

Manufacturing Directions

Note: Lactobionic acid is an irritant. Avoid contact with skin and eyes. Solution must be kept refrigerated prior to use.

1. Preparation of erythromycin lactobionate. *Note*: Total procedure for addition of lactobionic acid to erythromycin should not take less than 1.5 hours; all steps must be completed within a 12-hour period.
   a. Add ca. one-third of item 1 to 50% of the final volume of item 6 that has been previously cooled to 5°C to 10°C. Mix slowly; vigorous agitation will produce foaming and prevent adequate mixing. Maintain temperature of solution at 18°C or less throughout processing.
   b. To this item 1 slurry, slowly add 86 mL of item 2 solution, the addition taking approximately 20 minutes. Mix for an additional 10 minutes. item 2 must be added slowly in small amounts to prevent localized low pH in slurry and to give sufficient time for the reaction to occur. Reaction is completed when solution is almost clear.
   c. Add another one-third of item 1 followed by the slow addition of 86 mL of item 2 solution until the reaction is completed.
   d. Add remainder of item 1 followed by the slow and careful addition of the remaining item 2 solution until pH 7.4 is reached.
   e. Add item 6 to 88% of the final volume and mix until drug is dissolved.
   f. Check pH (range 7.0–7.5). If pH is more than 7.5, adjust down to pH 7.4 cautiously with item 2. Add in small quantities with thorough mixing and check pH after each addition. If pH falls less than 7.0, adjust up to 7.4 with small, careful additions of item 1 base. Stir at least 30 minutes after each addition and recheck pH after each addition.
   g. Make a slurry of item 3 and add to the solution. Discontinue cooling, but keep temperature less than 18°C at all times. Mix for 1 hour.
   h. Filter through a previously rinsed filter press or equivalent cellulose filters. Remove item 3 by recirculation through press. Recirculate for at least 15 minutes until solution is clear of item 3.
   i. Filter solution through a previously rinsed approved filtration setup by using a 0.45-μm or finer membrane filter connected in series prefilter. Recirculate for at least 15 minutes and filter into a glass-lined or 316 stainless steel tank.
   j. QS to final volume with item 6. Mix until ingredients are dissolved and solution is uniform. Sample.
   k. Store solution in refrigerator (2–6°C) until filled. Filling of this solution should be completed as soon as possible, but NMT 6 days after the solutions are prepared.
   l. Prepare a sterile 0.22-μm membrane filtration setup.
2. Preparation of bottles. Use type I glass, 50-mL bottles.
   a. Wash, dry, and stack bottles in a container suitable for sterilizing.
   b. Sterilize bottles by using dry heat at 200°C (–0, +50°C) bottle temperature for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for duration of the cycle.
3. Preparation of stoppers. Stopper: West, Faultless, or Selgas. Sterilize by autoclaving at 121°C for 60 minutes and vacuum dry at a temperature less than 90°C.
4. Filtration.
   a. Connect tank, sterile 0.22-μm membrane and sterile surge bottles to filling equipment by using aseptic technique.
   b. Apply N_2 gas pressure to tank to provide adequate filtration rate. (Do not apply more than 10 lb.) Sample.
5. Filling.
   a. Fill solution into each clean, dry sterile bottle and prestopper with lyophilization stoppers.
   b. Place filled bottles in sterile metal trays and introduce them into the previously sterilized chamber. Do not allow filled or bulk solution to warm to temperature. Freeze or refrigerate solution until lyophilized.
   c. Freeze product to −35°C to −38°C for blown vials or −25°C to −30°C when using tubing vials. Freezing temperature below those specified will cause excessive breakage.
   d. Apply 100 to 200 μm vacuum and set shelf temperature controller at 38°C. Set condenser temperature less than −50°C.
   e. Increase shelf temperature as product temperature approaches shelf temperature until product temperature reaches 38°C (±2°C). Hold at this temperature for at least 4 hours.
   f. Release vacuum with sterile N_2 gas and aseptically remove bottles from chamber. Aseptically apply stoppers and seal. Sample.

Esmolol Hydrochloride Injection Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Esmolol hydrochloride	10.00	g
5.90	mg	2	Sodium chloride	5.90	g
2.80	mg	3	Sodium acetate trihydrate	2.80	g
0.546	mg	4	Glacial acetic acid	0.546	g
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Hydrochloric acid for pH adjustment		
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 5.0 (4.5–5.5); package in nonlatex bags.

Concentrate

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
250.00	mg	1	Esmolol hydrochloride	250.00	g
250.00	mg	2	Propylene glycol	250.00	g
250.00	mg	3	Alcohol, USP	250.00	g
17.00	mg	4	Sodium acetate trihydrate	17.00	g
0.00715	mL	5	Glacial acetic acid	7.15	mL
QS	mL	6	Hydrochloric acid for pH adjustment		
QS	mL	7	Sodium hydroxide for pH adjustment		
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.5 to 5.5.

Estradiol Cypionate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Estradiol cypionate, USP	2.00	g
20.00	mg	2	Benzyl alcohol, NF	20.00	g
QS	mL	3	Cottonseed oil, USP	QS to 1.00	L

Note: Adjust fill volume for different strengths.

Estradiol Suspension Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.50	mg	1	Estradiol, NF	0.50	g
1.00	mg	2	Carboxymethylcellulose sodium, USP	1.00	g
1.00	mg	3	Sodium phosphate, USP	1.00	g
9.00	mg	4	Sodium chloride, USP	9.00	g
1:10	M	5	Benzalkonium chloride 50%, USP	1.10	M
QS	mL	6	Water for injection, USP	1.00	L
QS	mL	7	Acetic acid for buffering	QS	QS
QS	mL	8	Sodium acetate for buffering	QS	QS

Note: Adjust quantity of item 1 for 1 mg/mL strength.

Estradiol Valerate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Estradiol valerate, USP	10.00	g
20.00	mg	2	Benzyl alcohol, NF	20.00	g
QS	mL	3	Sesame oil, USP	QS to 1.00	L

Estrogenic Substances in Oil Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.50	mg	1	Estrone, NF	1.50	g
0.50	mg	2	Estrogenic substances, combined with item 1 = 2 mg	0.50	g
40.00	mg	3	Benzyl alcohol, NF	40.00	g
QS	mL	4	Sesame oil, USP	QS to 1.00	L

Estrone, Estradiol, and Cyanocobalamin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Estrone, NF	2.00	g
2.00	mg	2	Estradiol, NF	2.00	g
1000.00	mg	3	Cyanocobalamin, USP	1000.00	mg
1.00	mg	4	Carboxymethylcellulose sodium, USP	1.00	g
1.00	mg	5	Sodium phosphate, USP	1.00	g
9.00	mg	6	Sodium chloride, USP	9.00	g
15.00	mL	7	Benzyl alcohol, NF	15.00	g
QS	mL	8	Water for injection, USP	QS to 1.00	L
QS	mL	9	Hydrochloric acid for pH adjustment	QS	
QS	mL	10	Acetic acid for buffering	QS	
QS	mL	11	Sodium acetate for buffering; see item 10	QS	

Estrone Sterile Suspension Veterinary Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Estrone, NF	5.00	g
1.00	mg	2	Carboxymethylcellulose, USP	1.00	g
1.00	mg	3	Sodium phosphate, USP	1.00	g
9.00	mg	4	Sodium chloride, USP	9.00	g
1:10	M	5	Benzalkonium chloride, 50%, USP	1.10	M
QS	mL	6	Water for injection, USP	1.00	L
QS	mL	7	Acetic acid for buffering	QS	
QS	mL	8	Sodium acetate for buffering; see item 7	QS	

Etanercept Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Etanercept	25.00	g
40.00	mg	2	Mannitol	40.00	g
10.00	mg	3	Sucrose	10.00	g
1.20	mg	4	Tromethamine	1.20	g
5QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Lyophilized powder is reconstituted with 1.0 mL of water for injection containing 0.9% benzyl alcohol.

Etorphine Hydrochloride Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Etorphine hydrochloride (M-99)	1.00	g
3.40	mg	2	Sodium hydroxide, USP	3.40	g
0.50	mg	3	Disodium edetate	0.50	g
14.00	mg	4	Citric acid, USP	14.00	g
0.50	mg	5	Propylene glycol, USP	0.50	g
5.00	mg	6	Benzyl alcohol, NF	5.00	g
QS	mL	7	Water for injection, USP	QS to 1.00	L

Exemestane Aqueous Suspension Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Exemestane (micronized)	100.00	g
1.80	mg	2	Methyl paraben	1.80	g
0.20	mg	3	Propyl paraben	0.20	g
8.30	mg	4	Sodium chloride	8.30	g
30.00	mg	5	Polyethylene glycol 400	30.00	g
2.00	mg	6	Polysorbate 80 (Tween®)	2.00	g
1.50	mg	7	Methylcellulose	1.50	g
5.00	mg	8	Lecithin	5.00	g
1.00	mg	9	L-Methionine	1.00	g
0.50	mg	10	Edetate sodium	0.50	g
0.694	mg	11	Sodium phosphate monobasic hydrate	0.694	g
0.588	mg	12	Sodium phosphate dibasic dodecahydrate	0.588	g
QS	mL	13	Sodium hydroxide for pH adjustment		
QS	mL	14	Hydrochloric acid for pH adjustment		
QS	mL	15	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take 0.2 L of item 15 in a suitable vessel and add and disperse items 8 and 7 (adding in that order to the vessel). Mix to obtain a homogenous dispersion.
2. Autoclave at 121°C for 15 minutes the preparation in step 1.
3. In another vessel, take 0.8 L of item 15 and add and dissolve all other ingredients except item 1.
4. Pass the solution in step 3 through a 0.22-μm filter to sterilize.
5. Add preparation in step 4 to preparation in step 2 under aseptic conditions.
6. Check and adjust pH to 6.0 to 7.0 with item 13 or 14.
7. Add item 1 (presterilized by heat) and homogenize to form a smooth suspension.
8. Fill.

Famotidine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Famotidine	10.00	g
4.00	mg	2	L-Aspartic acid	4.00	g
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
20.00	mg	4	Mannitol	20.00	g
0.90	%	5	Benzyl alcohol[a]	0.90	%
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a]For multidose injection only. Adjust pH with item 2 or 3 to 5.7 to 6.4.

Fenoldopam Mesylate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Fenoldopam mesylate equivalent to fenoldopam	10.00	g
3.44	mg	2	Citric acid	3.44	g
518.00	mg	3	Propylene glycol	518.00	g
0.61	mg	4	Sodium citrate dihydrate	0.61	g
1.00	mg	5	Sodium metabisulfite	1.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Fentanyl Citrate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
78.55	mg	1	Fentanyl citrate, USP	78.55	mg
QS	mg	2	Sodium hydroxide, reagent-grade pellets	QS	mg
QS	mL	3	Hydrochloric acid, reagent-grade bottles	QS	mL
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Add item 4 to the stainless steel tank to ca. 95% of the final volume.
2. Add and dissolve item 1 with mixing. After drug addition, maintain protection from undue light exposure.
3. Check pH. Adjust to 4.5 if necessary (range 4.3–4.7) with item 2 or 3 (1% each).
4. QS to final volume with item 4 and mix well, check pH, and adjust as in step 3.
5. Filter through a previously rinsed filtration setup by using an approved 0.45-μm or finer membrane, with an approved prefilter, into a clean glass-lined or 316 stainless steel tank. Sample. Before starting to fill, flush 3 to 4 L to clean equipment of residual water and to set dosage. Discard.
6. Using an inline filter, fill specified amount into each clean, dry type I glass ampoule. Seal.
7. Sterilize in steam autoclave at 115°C and an F_0 range of 8 to 20. Cooling water rate should be controlled to minimize thermal shock. Alternatively, sterilize in steam autoclave at 122°C and an F_0 range of 8 to 20. Sample.

Filgrastim Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.30	mg	1	Filgrastim	0.30	g
0.59	mg	2	Sodium acetate	0.59	g
50.00	mg	3	Sorbitol	50.00	g
0.004	%	4	Polysorbate 80	0.004	%
0.035	mg	5	Sodium chloride	0.035	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Flosulide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Flosulide	10.00	g
50.00	mg	2	*N*-Methyl pyrrolidone	50.00	g
50.00	mg	3	Dimethylacetamide	50.00	g
300.00	mg	4	Polyethylene glycol 400	300.00	g
20.00	mg	5	Benzyl alcohol	20.00	g
0.50	mg	6	Alpha-tocopheryl acetate	0.50	g
QS	mL	7	Propylene glycol, USP	QS to 1.00	L

Fluconazole Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Fluconazole	2.00	g
9.00	mg	2	Sodium chloride	9.00	g
56.00	mg	3	Dextrose anhydrous, USP	56.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Use either item 2 or 3; packaged in plastic bags and sterilized by autoclaving.

Flumazenil Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.10	mg	1	Flumazenil	1.00	g
1.80	mg	2	Methyl paraben	1.80	g
0.20	mg	3	Propyl paraben	0.20	g
9.00	mg	4	Sodium chloride	9.00	g
0.10	mg	5	Disodium edetate	0.10	g
0.10	mg	6	Acetic acid, glacial	0.10	g
QS	mL	7	Sodium hydroxide for pH adjustment	QS	
QS	mL	8	Hydrochloric acid for pH adjustment	QS	
QS	mL	9	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 4.0 with item 7 or 8.

Folic Acid and Niacinamide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
15.00	mg	1	Folic acid, USP, 15% excess	19.16	g
150.00	mg	2	Niacinamide, USP, 15% excess	191.60	g
0.5	%	3	Liquefied phenol, NF	5.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS		7	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Maintain cover of item 7 throughout the manufacturing process.
2. Dissolve item 2 in 0.6 L of item 4.
3. Add item 1 into step 1 to make a suspension and dissolve it by slow addition of 40% of item 6 until dissolved; do not overadd item 6.
4. Dissolve item 3 in 0.1 L of item 4 and add this solution to that of step 2 slowly.
5. Make up volume. Check and adjust pH to 6.8 (6.5–7.0)
6. Filter through a 0.45-μm prefilter and 0.22-μm filter into a presterilized staging assembly.
7. Fill 10.5 mL into type I 10-mL amber glass vials presterilized aseptically under cover of item 7.

Follitropin-Beta for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
75.00	IU	1	Follitropin-beta	75,000	IU
25.00	mg	2	Sucrose	25.00	g
7.35	mg	3	Sodium citrate Dihydrate	7.35	g
0.10	mg	4	Polysorbate 80	0.10	g
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 7.0; 1 mL per vial lyophilized.

Furaltadone Injectable Solution (50 mg/mL)

Formulation

Furaltadone, 5.00 g; tartaric acid, 1.25 g; Kollidon 12 PF [1], 25.00 g; water of injectables, add 100 mL.

Manufacturing Directions

Dissolve the solid substances in water at approximately 50 °C.

The sterilization can be made by aseptic filtration or by heating (120°C, 20 minutes).

Remark

To prevent of discoloration of Kollidon in the solution during storage, 0.2% to 0.5% of cysteine could be added as antioxidant.

Furosemide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Furosemide, USP	10.00	g
7.50	mg	2	Sodium chloride, USP	7.50	g
1.34	mg	3	Sodium hydroxide, NF	1.34	g
QS		4	Sodium hydroxide, NF, for pH adjustment	QS	
QS		5	Hydrochloric acid, reagent grade, NF	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS		7	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Preparation of water. Check item 6 to be used for solution preparation and verify that it meets conductivity limit of NMT 1.0 mS/s and pH range of 5.0 to 7.0.
2. Preparation of solution. *Caution*: Product is light sensitive. Protect from light as much as possible throughout the processing.
   a. Put 900 mL of item 6 into the preparation vessel and bubble N_2 gas (item 7) to expel dissolved oxygen gas. Monitor the O_2 sensor display (O_2% limit = NMT 1).
   b. Put 300 mL of item 6 into another preparation vessel and bubble item 7 for 20 minutes.
   c. Add and dissolve items 2 and 3 into the step 2a preparation vessel.
   d. Add item 1 into step 2c solution and stir until it is completely dissolved and the solution is clear.
   e. Check pH (range 8.5–9.1).
   f. Adjust pH if necessary with 10% sodium hydroxide solution or 1 N hydrochloric acid solution.
   g. After adjusting pH, make up volume to 1 L by item 6 from step 2b and mix it for 15 minutes, followed by bubbling item 7 for 20 minutes.
   h. Check final pH (range 8.5–9.1).
   i. Take sample for assay.
3. Preparation of ampoules. Use sterilized type I 2-mL amber glass ampoules, USP.
4. Preparation of filtration assembly and machine parts for production. Clean and sterilize filtration assembly and machine parts in the autoclave as per USP 24.
5. Integrity testing. Before starting the sterile filtration, check the integrity of filter cartridge.
6. Aseptic filling. Fill 2.15 mL (range 2.1–2.2 mL) solution from the bulk into each sterile dry clean ampoule and seal it.
7. Terminal sterilization. Load the filled ampoules inside the autoclave chamber. Run the cycle at a sterilization temperature of 121.1°C and an exposure time of 20 minutes.
8. Ampoules leak test. Perform the leak test.
9. Optical checking. Check the ampoules under the optical checking machine.

Gentamicin and Prednisolone Ophthalmic Drops

Bill of Materials (Batch Size 42 L)					
Scale/mL		Item	Material	Qty	UOM
Part I					
		1	Water purified (distilled), USP	6.00	L
0.65[a]	mg	2	Hydroxypropyl methylcellulose, F-4M	39.90	g
Part II					
		3	Water purified (distilled), USP	10.00	L
4.50	mg	4	Polyvinyl alcohol, 20–90	918.80	g
0.50[b]	mg	5	Polysorbate 80, NF (use a 10% solution)	b	mL
Part III					
		6	Water purified (distilled), USP	40.00	L
4.50	mg	7	Sodium citrate, dihydrate, USP	295.30	g
3.30[c]	mg	8	Gentamicin sulfate, USP	216.60[d]	g
6.80[a]	mg	9	Sodium chloride, USP	441.30	g
0.15	mg	10	Disodium edetate, USP	9.80	g
0.05	mg	11	Benzalkonium chloride, NF (10% solution)	32.80[e]	mL
QS	mL	12	1 N Hydrochloric acid, NF[a]	QS[f]	mL
QS	mL	13	1 N Sodium hydroxide, NF[a]	QS[f]	mL
		14	Water purified (distilled), USP	60.00	L
		15	Sterile filtrate, QS parts I, II, and III	38.40	L
Part IV					
10.00	mg	16	Prednisolone acetate, USP	420.00	g
Part V					
		17	Water purified (distilled) USP	2.88	L

[a] Includes amount contained in hydroxypropyl methylcellulose micronizing diluent. It contains 0.5% hydroxypropylmethyl cellulose F-4M and 0.9% sodium chloride.
[b] Required amount is contained in the micronization of pred acetate, the specific gravity of polysorbate 80 is 1.08g/mL.
[c] The amount of gentamicin sulfate equivalent to 3.0 mg/mL of gentamicin base.
[d] The amount of gentamicin sulfate is calculated as follows: 216.6 g $\times$ 1000 mg/ mg/manufacturer's assay value $=$ g of gentamicin sulfate required.
[e] The amount of benzalkonium chloride, 10% solution, to be added must be calculated on the basis of the assay value of the raw material lot used as follows: 32.8 mL $\times$ 10.0%/assay value (%) $=$ mL benzalkonium chloride, 10% solution, required.
[f] For pH adjustment.

Manufacturing Directions

Part I

1. Measure out ca. 30 L of item 1 into a stainless steel pressure vessel. Begin mixing with a suitable mixer and heat it to 80°C to 90°C.
2. Measure out 3 L of heated item 1 into a stainless steel pressure vessel. Begin mixing it with a propeller mixer. Add item 2 slowly to the vortex and mix until it is thoroughly dispersed.
3. Transfer the dispersion to a glass bottle, rinse the container, and add the rinsings to the glass bottle. Place the glass bottle in the water sink and begin mixing.
4. Add item 1 to the bottle to bring the volume to ca. 6 L. Fill the water sink with cold water purified (distilled). Cool the dispersion to less than 30°C.
5. Cover the mouth of the bottle with two layers of aluminum foil. Secure the aluminum foil with two rubber bands. Place the bottle in the refrigerator, chill for at least 12 hours at 15°C or less until item 2 is completely hydrated.

Part II

1. Measure out ca. 30 L of item 3 into a stainless steel-jacketed pressure vessel. Heat it to 85°C to 90°C.
2. When the temperature reaches 85°C to 90°C, turn off the heat source and begin mixing vigorously. Measure out 10 L of heated item 3 into a 20-L glass bottle. Add item 4 slowly to the vortex. Mix for at least 90 minutes until all dissolved.
3. Add item 5 and mix well. Cool to room temperature with continuous agitation by placing in cold water bath.

Part III

1. Measure out ca. 40 L of item 6 into a mixing tank. Begin mixing. Add the items 7 to 11, in order, allowing each to mix thoroughly or dissolve completely before adding the next.
2. Mix thoroughly. Avoid excess foam formation. Add part I to the mixing tank containing part III, while mixing part III. Transfer part II into the mixing tank containing combined parts I and III.
3. Use 1 to 2 L of water purified (distilled) to rinse the part II kettle and any equipment used to transfer part II. Add the rinsings to the mixing tank.
4. Sample for pH. If necessary, adjust pH to 6.4 to 6.6 with item 12 or 13.
5. QS combined parts I, II, and III to 60 L with item 14. Mix parts I, II, and III (base) thoroughly for at least 15 minutes. Avoid excess foam formation. Sample.
6. Mix the product for at least 10 minutes before filtration. Sterile-filter with the aid of N_2 pressure (15–30 lb) into a sterilized 100-L stainless steel pressure vessel. Perform the bubble point test.

Part IV

Prednisolone acetate micronized.

Part V

1. Measure out and transfer item 17 into a suitable glass bottle. Seal the mouth of the bottle with two layers of aluminum foil paper and two layers of parchment paper.
2. Sterilize it by autoclaving for at least 80 minutes at 121°C. Remove the bottles from the autoclave and allow it to cool to room temperature.

Mixing Procedure

1. Grind the steroid for at least 6 hours before mixing.
2. Aseptically receive 38.4 L of sterile-filtered base (combined parts I, II, and III) into a sterilized glass bottle and place the glass bottle on a magnetic mixing table.
3. Place the bottle and magnetic mixer in front of a laminar air flow hood. Aseptically add a sterilized magnetic stirring bar to the glass bottle containing the base. Adjust the mixing speed such that a 0.5-in deep vortex is formed.
4. Aseptically pour the ground item 16 from the grinding jar, through a sterilized funnel, into the bottle containing the base. The volume of the suspension in the bottle should be 42 L.
5. Allow the product to mix with a 0.5-in deep vortex for at least 2 hours.
6. Homogenize the product suspension by using a sterilized homogenizer. Allow the product to mix in the receiving bottle after completion of homogenization for at least 2 hours. Sample.
7. Aseptically fill sterile solution through P2 sintered glass into sterilized container. Perform the bubble point test. Sample.

Gentamicin Injection (20 mg/2 mL)

Bill of Materials (Batch Size 10 L)					
Scale/mL		Item	Material	Qty	UOM
10	mg	1	Gentamicin base, 3% excess (use equivalent amount of gentamicin sulfate), USP	103.0	g
1.2	mg	2	Methyl paraben, USP	12.0	g
0.2	mg	3	Propyl paraben, USP	2.0	g
0.11	mg	4	Sodium edetate, USP	1.1	g
QS		5	Sulfuric acid, reagent-grade pellets, for pH adjustment	QS	
QS		6	Sodium hydroxide pellet for pH adjustment		
QS	mL	7	Water for injection, USP	QS	
QS		8	Nitrogen gas, NF	QS	

Gentamicin Injection (80 mg/2 mL)

Bill of Materials (Batch Size 10 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Gentamicin base, 3% excess (use equivalent amount of gentamicin sulfate), USP	412.00	g
1.80	mg	2	Methyl paraben, USP	18.00	g
0.20	mg	3	Propyl paraben, USP	2.00	g
0.11	mg	4	Sodium edetate, USP	1.10	g
QS		5	Sulfuric acid, reagent-grade pellets, for pH adjustment	QS	
QS		6	Sodium hydroxide pellets for pH adjustment		
QS	mL	7	Water for injection, USP	QS to 10.00	L
QS		8	Nitrogen gas, NF	QS	

Note: Qty of gentamicin sulfate = (1000 ∞ weight of gentamicin base)/(potency of gentamicin as base).

Manufacturing Directions

1. Preparation of water.
   a. Check the water for injection used for solution preparation and verify that it meets conductivity NMT 1 pS/cm.
   b. Take the sample for pH (range 5.0–7.0)
2. Preparation of solution.
   a. Put 3 L of water for injection into the first 20-L preparation vessel and bubble N_2 gas to expel dissolved O_2 for 20 minutes.
   b. Put 9 L of water for injection (hot water, 82–85°C) in a second 20-L preparation vessel. Check and record water temperature.
   c. Add and dissolve methyl paraben and propyl paraben in water for injection from step 2b with stirring until clear solution is obtained.
   d. Bubble N_2 gas through solution for 20 minutes and allow to cool to 30°C or less. Record temperature.
   e. Add and dissolve sodium EDTA into solution of step 2d. Mix until dissolved.
   f. Add and dissolve gentamicin sulfate into solution of step 2f and make a clear solution.
   g. Check and record pH (range 3.5–5.0).
   h. Adjust pH by 2 N H_2SO_4/2 N NaOH solution.
   i. Check pH after adjustment (range 3.5–5.0).
   j. Make volume up to 10 L by water for injection from step 2a and mix for 15 minutes.
   k. Take final pH (range 3.5–5.0).
   l. Bubble N_2 gas for 20 minutes.
   m. Request sample for assay.
   n. Transfer the preparation vessel to solution room.
3. Preparation of ampoules. Use type I 2-mL clear glass ampoules, USP.
   a. Assemble the machine parts (2-mL size) and set up the washing machine as per SOPs.
   b. Wash the ampoules according to SOPs.
   c. Sterilize the ampoules by using the dry heat tunnel.
   d. Set the temperature as per latest validation studies with revised cycle. Set temperature to 330°C.
4. Sterilization. Sterilize the filtration assembly and ampoule filling machine parts at 121°C for 30 minutes. Set the parameters according to current validated cycle. Sterilize the gowns at 121°C for 30 minutes. Set the parameters according to current validated cycle.
5. Integrity testing.
   a. Before starting the sterile filtration, check the integrity of filter cartridge according to SOPs.
   b. Record integrity test results of filter cartridge.
   c. Aseptically connect the N_2 line through sterile N_2 filter to inlet of the holding tank refer to SOPs.
6. Aseptic filling.
   a. Assemble the previously sterilized machine parts and set up the machine as per SOPs.
   b. Aseptically connect one end of previously sterilized filtration assembly with a 0.22-μm filtration cartridge to the outlet of the holding tank and the other end to the buffer holding tank.
   c. Operate the ampoules filling machine according to SOPs. Bleed the dosing system as described in the operating procedure. Adjust the fill volume to 2.15 mL.
   d. Fill 2.15 mL (range 2.1–2.2 mL) solution from the bulk into each sterile, dry clean ampoule and seal it.

Gentamicin Ophthalmic Drops

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Qty	UOM
Part I					
		1	Water purified (distilled), USP	10.00	L
14.00	mg	2	Polyvinyl alcohol, 20–90	630.00	g
Part II					
		3	Water purified (distilled), USP	25.00	L
8.00	mg	4	Sodium phosphate dibasic heptahydrate, USP	360.00	g
6.30	mg	5	Sodium chloride, USP	283.50	g
0.127	mg	6	Disodium edetate, USP	5.72	g
0.04	mL	7	Benzalkonium chloride, NF (10% solution)	18.00[a]	mL
3.30	g	8	Gentamicin sulfate, USP	148.50[b]	g
QS	mL	9	5 N Hydrochloric acid, NF[d]	QS	mL
QS	mL	10	1 N Sodium hydroxide, NF[d]	QS	mL
QS	mL	11	Water purified (distilled), USP	QS to 45.00	L

[a] The amount of benzalkonium chloride, 10% solution, to be added must be calculated on the basis of the assay value of the raw material lot used according to the following formula: 18 mL × 10.0%/assay value (%) = mL benzalkonium chloride, 10% solution, required.
[b] The amount of gentamicin sulfate calculated as follows: 148.5 g × 1000 mg/manufacturer's assay value = g of gentamicin sulfate required.

Manufacturing Directions

Part I

1. Measure out ca. 10 L of item 1 into a jacketed stainless steel pressure vessel. Heat it to 85°C to 90°C, turn off the heat source, and begin mixing it by a propeller mixer.
2. Add item 2 slowly to the vortex. Mix for at least 90 minutes until all of it is dissolved. Cool to room temperature, with continuous agitation, by running cold water through the kettle jacket.

Part II

1. Measure out ca. 25 L of item 3 into a mixing tank. Begin mixing and add items 4 to 7, in order, allowing each to dissolve completely before adding the next.
2. Rinse the container with water purified and add the rinsings to the batch.
3. Add item 8.
4. Pump part I into the tank containing part II and mix thoroughly for at least 30 minutes.
5. Sample for pH (range 7.4–7.5). If necessary, adjust the pH with item 9 or 10.
6. Allow any foam to dissipate and QS to 45 L with item 11. Mix thoroughly for at least 15 minutes.
7. Before filtration, mix the product for at least 10 minutes. Perform the bubble point test. Sample.
8. Aseptically fill sterile solution into sterilized containers. Perform the bubble point test.

Glycine Antagonist Injection Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.69	mg	1	Glycine antagonist[a]	1.69	g
0.72	mg	2	Tris (hydroxymethyl) aminomethane	0.72	g
7.68	mg	3	EDTA disodium salt dihydrate	7.68	mg
0.0194	mL	4	Propylene glycol	19.40	mL
50.00	mg	5	Dextrose anhydrous, USP	50.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a] (E)-3-Æ2-(phenylcarbamoyl) ethenyl-4,6-dichloroindole-2-carboxylic acid.

Manufacturing Directions

1. In sufficient quantity of item 6, add and dissolve items 2 to 5.

Bolus Injection

1. Add and dissolve item 1.
2. Add item 5 and dissolve.
3. Make up volume with item 6.
4. Filter aseptically and sterilize by autoclaving.

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
70.60	mg	1	Glycine antagonist[a]	70.60	g
1.30	mg	2	Tris (hydroxymethyl) aminomethane	1.30	g
10.00	mg	3	Polysorbate 80	10.00	g
300.00	mg	4	Glycofurol	300.00	g
50.00	mg	5	Mannitol	50.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a](E)-3Æ2-(phenylcarbamoyl) ethenyl!-4,6-dichloroindole-2-carboxylic acid.

Manufacturing Directions

1. In a suitable container, add item 5 to item 6 and dissolve.
2. Add and dissolve item 2.
3. In a separate container, add and mix item 1 with item 2 and item 4.
4. Add step 2 into step 3 gradually and slowly.
5. Filter through 0.2-μm membrane filter and autoclave at 131°C for 15 minutes.

Glycopyrrolate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.20	mg	1	Glycopyrrolate	0.20	g
9.00	mg	2	Benzyl alcohol	9.00	g
QS	mL	3	Hydrochloric acid for pH adjustment		
QS	mL	4	Sodium hydroxide for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH with item 3 or 4 to 3.0 to 4.0.

Gramicidin Ophthalmic Solution (1.3 mg/10 mL)

Formulation

1. Gramicidin, 13 mg; Cremophor RH 40 [1], 0.1 g.
2. Ethanol 96%, 1.0 g; preservatives, QS; water, 98.8 g.

Manufacturing Directions

Mix gramicidin and Cremophor RH 40, heat to approximately 65 °C, stir, and add slowly the heat solution II.

Granisetron Hydrochloride Injection Single Dose

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Granisetron, use granisetron hydrochloride	1.12	g
9.00	mg	2	Sodium chloride	9.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: pH 4.7 to 7.3; do not adjust.

Granisetron Hydrochloride Injection Multiple Dose

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Granisetron, use granisetron hydrochloride	1.12	g
9.00	mg	2	Sodium chloride	9.00	g
2.00	mg	3	Citric acid	2.00	g
10.00	mg	4	Benzyl alcohol	10.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: pH 4.0 to 6.0; do not adjust.

Guaiacol–Iodide Solution Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Potassium guaiacolsulfonate	40.00	g
50.00	mg	2	Sodium iodide, USP	50.00	g
1.00	mg	3	Sodium metabisulfite, NF	1.00	g
20.00	mg	4	Benzyl alcohol, NF	20.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Sodium hydroxide for pH adjustment	QS	

Haloperidol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Haloperidol, use haloperidol decanoate	70.52	g
12.00	mg	2	Benzyl alcohol	12.00	g
QS	mg	3	Sesame oil refined	QS to 1.00	L

Note: For higher strength of 100 mg, change only the quantity of active ingredient.

Hemin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
31.30	mg	1	Hemin	31.30	g
21.50	mg	2	Sodium carbonate	21.50	g
30.00	mg	3	Sorbitol	30.00	g
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Lyophilize 10 mL in each vial.

Heparin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
9.00	mg	1	Benzyl alcohol, NF	9.00	g
9.00	mg	2	Sodium chloride, USP	9.00	g
1000.00	U	3	Heparin sodium lyophilized, USP (NLT 120 U/g), adjust to specification	8.333	g
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Heparin sodium injection, USP, is a sterile solution. Each milliliter contains 1000, 2500, 5000, 7500, 10000, 15000, or 20000 USP U heparin sodium derived from porcine intestinal mucosa (standardized for use as an anticoagulant), in water for injection, and NMT 10 mg benzyl alcohol as a preservative. The pH range is 5.0 to 7.5. Heparin lock flush solution, USP, is a sterile solution. Each milliliter contains either 10 or 100 USP U heparin sodium derived from porcine intestinal mucosa (standardized for use as an anticoagulant), in normal saline solution, and NMT 10 mg benzyl alcohol as a preservative. The pH range is 5.0 to 7.5.

Manufacturing Directions

Note: Use only fresh pyrogen-free water for injection. Expensive solution; handle with care.

1. Preparation.
   a. Dissolve benzyl alcohol in ca. 80% of the final volume of water for injection.
   b. Add and dissolve sodium chloride and sodium heparin.
   c. Add water for injection, and QS to final volume. Mix thoroughly.
   d. Check and adjust pH (range 5.8–6.8) with 10% HCl or 10% NaOH.
   e. Sample for testing.
   f. Filter solution through a previously rinsed filtration setup, using an approved 0.45-μm membrane and an approved prefilter. Filter into a clean glass-lined or 316 stainless steel holding tank. If not filled within 24 hours, store at 2°C to 8°C. Allow to warm to room temperature before filling.
   g. Prepare for sterilization a 0.22-μm membrane filtration.
2. Preparation of bottles.
   a. Wash and dry type I glass bottles, 10 or 30 mL, and load into appropriate containers for sterilization.
   b. Sterilize at 200°C (−0°C, +50°C), bottle temperature for 225 minutes (−0, +360 minutes), while maintaining the oven temperature at 225°C (±10°C) for the duration of the cycle.
   c. Deliver the bottles to sterile filling area.
3. Preparation of stoppers. West Cpd 867 gray (92-046).
   a. Leach stoppers by boiling for 10 minutes in deionized water.
   b. Wash stoppers in a Prosperity (or equivalent) washer by using rubber cycle with 10 mL of Triton X-100.
   c. Dry in Huebsch (or equivalent) fast dryer at 55°C.
   d. Store in suitable containers until ready for use.
   e. Tray and inspect and rinse thoroughly. Wrap tray and identify properly.
   f. Sterilize at 121°C for 60 minutes.
   Note: Use completely aseptic technique in filling. This is an expensive solution.
4. Filling (10- or 30-mL vials).
   a. Connect bulk solution container, previously prepared sterile filter, and sterile surge bottle to filler by using aseptic technique.
   b. Aseptically fill either 10.5 or 31.0 mL of solution into each clean, sterile bottle. Stopper.
   c. Request sample.
   d. Apply seal and inspect.
   e. Request samples.

Hepatitis B Immune Globulin (Human)

Solvent/Detergent Treated and Filtered

Hepatitis B immune globulin (human) is a sterile solution of immunoglobulin (5±1% protein) containing antibodies to hepatitis B surface antigen (anti-HBs). The product is formulated in 0.075 M sodium chloride, 0.15 M glycine, and 0.01% polysorbate 80, pH 6.25. It contains no preservative and is intended for single use by the intramuscular (IM) route only.

Hexamethylmelamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Hexamethylmelamine	5.00	g
150.00	mg	2	Soybean oil, USP, superfine	150.00	g
12.00	mg	3	Egg phospholipid, parenteral grade	12.00	g
5.00	mg	4	Pluronic F-68®	5.00	g
22.50	mg	5	Glycerin, USP	22.50	g
QS	mL	6	Sodium hydroxide for pH adjustment		
QS	mL	7	Hydrochloric acid for pH adjustment		
QS	mL	8	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable container, dissolve item 1 in item 2 by propeller mixing.
2. Add to this solution slowly item 3 while continue mixing.
3. In another vessel, mix item 4 and 5 and 0.4 L of item 8 by propeller mixing.
4. Add the solution in step 3 to the solution in step 2 slowly and with continuous propeller mixing.
5. Check and adjust pH to 7.4 (range 7.2–7.6) with item 6 or 7.
6. Make up volume with item 8.
7. This is a coarse emulsion (2- to 25-μm droplets); pass it through a Microfluidizer® at 12000 psi pressure 3 times to droplet size of 0.22-μm with distribution of size to ±26%. The size is measured by the quasielastic laser light scattering particle size determination instrument.
8. Fill into suitable parenteral container.
9. Sterilize by autoclaving at 121°C for 15 minutes. 10. Measure particle size again.

Hydrochloric Acid

Bill of Materials (Batch Size 3 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mEq	1	Hydrochloric acid concentrated, NF (11.62 N), 2% excess	516.00	mL
QS	mL	2	Water for injection USP	QS to 3.00	L

Manufacturing Directions

Note: Use glass-lined compounding tanks only, special filtration and filling equipment, and proper safety (inhalation) equipment.

1. Take approximately 500 mL of item 2 in a clearly marked compounding vessel.
2. Measure required quantity of item 1 to the compounding vessel containing item 2.
3. Add item 2 close to QS. Mix thoroughly and allow the solution to cool to room temperature.
4. QS to volume with item 2 and mix thoroughly.
5. Sample for testing.
6. After approval, sterile filter through special filter compatible with formulation (0.22 μm) and fill (flint vials, Teflon-coated stoppers, 1888 gray).

Hydrocortisone Sodium Phosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Hydrocortisone equivalent hydrocortisone sodium phosphate	67.09	g
8.00	mg	2	Creatinine	8.00	g
10.00	mg	3	Sodium citrate	10.00	g
QS	mL	4	Sodium hydroxide for pH adjustment		
3.20	mg	5	Sodium bisulfite	3.20	g
1.50	mg	6	Methyl paraben	1.50	g
0.20	mg	7	Propyl paraben	0.20	g
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 7.5 to 8.5.

Hydrocortisone Sodium Succinate for Injection (Single-Unit System Lyophilized)

Bill of Materials (Batch Size 20 L)					
Scale/mL		Item	Material	Qty	UOM
63.80	mg	1	Hydrocortisone hemisuccinate, USP	1276.00	g
0.40	mg	2	Sodium phosphate monobasic anhydrous, USP	8.00	g
4.36	mg	3	Sodium phosphate dibasic anhydrous USP	87.20	g
5.25	mg	4	Sodium hydroxide, USP	110.40	g
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 20	L

Manufacturing Directions

1. Preparation of solution.
   a. Prepare a 10% solution of item 4 (110.4 g in 1104 mL) in item 6 in a clean container. Let the solution cool to room temperature.
   b. Prepare a 1 N solution of item 5 (20.0 g in 500 mL) in a clean container. Let the solution cool to room temperature.
   c. In another container, dissolve item 2 in 2000 mL of item 6. Mix to a homogenous solution.
   d. Add item 3 to the solution prepared in step 1c. Mix the tank contents to homogeneous solution.
2. Compounding.
   a. Place approximately 10 L of item 6 into a clear compounding tank. Cool to between 15°C and 18°C.
   b. Add item 1 to step 2a. Agitate to suspend the compound in water.
   c. Record temperature of suspension.
   d. Record pH of suspension.
   e. With constant stirring, carefully add solution in step 1a in small portions to the suspension. Monitor pH and temperature so that they do not rise more than 7.8 and 8°C, respectively. If they do, wait till they come down.
   f. At the end of the addition, the suspension should turn into a clear solution. If needed, add more item 4.
   g. When the solution has cleared, measure pH and temperature.
   h. Add phosphate solution to the compounding tank and mix to a homogenous solution. Check pH and temperature.
   i. Bring to final volume. Again check pH and temperature.
   j. Withdraw sample for laboratory test. After approval, filter through a sterile 0.22-μm filter protecting from light.
   k. Fill and determine fill volumes gravimetrically.
3. Lyophilization.
   a. Chill the shelves to −40°C or less.
   b. Load the chamber keeping vials covered with sterilized clean covers.
   c. Place thermocouple in representative vials on different shelves and record location.
   d. After loading, place washed sterilized center seals in the chamber and close chamber door.
   e. Product thermocouple should register −40°C or less for at least 4 hours.
   f. Start condenser and let it reach −55°C or less.
   g. Start vacuum and let chamber achieve vacuum level of 100 μm or less.
   h. Set the shelf temperature to +15°C; let it run for at least 12 hours.
   i. Raise shelf temperature to +30°C and run the cycle for an additional 36 hours at least.
   j. At the end of the cycle, bleed chamber to atmospheric pressure with sterile dry air or N_2.
   k. Withdraw six representative samples, two from each of the top, middle, and bottom shelves, and close the door.
   l. If all the samples contain moisture 2% or lower, stopper the vials and terminate the cycle, and remove vials for sealing (845 gray stopper).
   m. If any of the samples register more than 2% moisture, extend the cycle and record action.

Hydrocortisone Sodium Succinate for Injection (Nonlyophilized)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Hydrocortisone acetate	50.00	g
9.00	mg	2	Sodium chloride	9.00	g
4.00	mg	3	Polysorbate 80	4.00	g
5.00	mg	4	Carboxymethylcellulose	5.00	g
9.00	mg	5	Benzyl alcohol	9.00	g
QS	mL	6	Sodium hydroxide for pH adjustment		
QS	mL	7	Hydrochloric acid for pH adjustment		
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 5 to 7; 5-mL vials.

Twin-Unit System

This product comprises two solutions. Solution 1 is used in conjunction with Solution 2 for reconstitution. Each milliliter of the reconstituted solution contains 50 mg of hydrocortisone.

Hydrocortisone Sodium Succinate for Injection

Solution 1

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.46	mg	1	Sodium phosphate monobasic monohydrate, USP	0.46	g
4.37	mg	2	Sodium phosphate dibasic anhydrous, USP	4.37	g
50.0	mg	3	Hydrocortisone, use equivalent hydrocortisone hemisuccinate, USP, anhydrous (equivalent to hydrocortisone 50.0 g)	63.85	g
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Nitrogen gas, NF	QS	
QS	mL	7	Water for injection, USP	QS	

Manufacturing Directions

Caution: Hydrocortisone hemisuccinate is a potent drug. Avoid inhaling dust and contact with open sounds. Operators must wear face masks and rubber gloves and wash thoroughly after handling.

1. Preparation.
   a. Add water for injection to a clean 316 stainless steel mixing tank to ca. 60% of the final volume. (The tank should be equipped with baffles to insure better mixing.)
   b. Add and dissolve sodium phosphate monobasic and dibasic with mixing.
   c. Cool the sodium phosphate solution to 10°C to 14°C before proceeding and maintain this temperature range throughout solution preparation.
   d. Slowly add the hydrocortisone hemisuccinate while mixing to form a smooth dispersion.
   e. Add 2 N sodium hydroxide solution with mixing at a rate of NMT 100 mL/min until a pH of 7.5 to 7.6 is attained and the solution is essentially clear. Record pH and amount of 2 N sodium hydroxide added. *Note*: 2 N sodium hydroxide is prepared by dissolving 80 g of item 4 in 1 L water; ca. 80 mL of 2 N sodium hydroxide is needed per liter of hydrocortisone solution.
   f. Add water for injection to final volume and mix thoroughly for at least 45 minutes.
   g. Check and record pH (range 7.5–7.6). If more than 7.6, adjust with 10% hydrochloric acid (if below, use 2 N sodium hydroxide). Record pH and amount of hydrochloric acid or sodium hydroxide used.
   h. Filter solution through an approved 0.2-μm nylon filter into a clean 316 stainless steel portable tank. Use either N_2 pressure (NMT 10 psig) or a pump for filtration.
   i. Sample for testing.
   j. Store solution at 2°C to 8°C until ready for filling. Do not hold for more than 48 hours.
2. Preparation of bottles. Use type I 5-mL glass bottles.
   a. Wash, dry, and load bottles into a container suitable for sterilization.
   b. Sterilize bottles by using dry heat at 200°C bottle temperature for 225 minutes (or an equivalent cycle).
   c. Deliver bottles to the sterile filling area.
3. Preparation of stoppers. Use West Cpd No. 1811 stoppers.
   a. Wash by using rubber cycle and suitable detergents.
   b. Dry in fast dryer at 55°C.
   c. Inspect and wrap for autoclaving.

   d. Sterilize by autoclaving at 121°C for 60 minutes and vacuum dry with heat at a temperature not to exceed 90°C.
   e. Deliver to the sterile filling area.
4. Filtration.
   a. Sample for testing.
   b. Connect tank, sterile 0.2-μm filtration setup and sterile surge bottle to filling machine, using aseptic technique.
5. Filling.
   a. Aseptically fill 2.3 mL into each clean, dry sterile bottle.
   b. Place filled bottles in sterile metal trays and cover with sterile cover.
   c. Freeze product to −30°C (±5°C) and hold the product at this temperature range for at least 1 hour before increasing shelf temperature.
   d. Cool condenser to –50°C or less.
   e. Conduct vacuum level check.
   f. Control chamber pressure to 800 μm (±50 μm).
   g. Control shelf temperature at +20°C (±2°C).
   h. When product temperature reaches +10°C or higher, raise shelf temperature to 60°C (±2°C).
   i. When product temperature reaches +52°C or higher, control chamber pressure at less than 60 μm (full vacuum).
   j. Maintain product temperature greater than 50°C for 3.5 hours (±0.5 hours) before unloading. *Note*: The shelf temperature may be lowered to 25°C (±5°C) before unloading.
   k. Release vacuum with filtered N_2 gas and remove bottles from camber.
   l. Aseptically apply stoppers and seals.
   m. Inspect and send appropriate samples to QA for testing.
6. Finishing. Sample for testing.

Solution 2

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
9.54	mg	1	Benzyl alcohol, NF, for ampoule	9.54	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Nitrogen gas, NF	QS	

Manufacturing Directions

Caution: Use 316 or higher temper-grade stainless steel or steel-lined tank cleaned according to approved BOPs.

1. Preparation of solution.
   a. Collect ca. 95% of the final volume of water for injection in a tank.
   b. Add and dissolve with mixing benzyl alcohol.
   c. Add water for injection to final volume and mix thoroughly for ca. 45 minutes.
   d. Filter solution through a 0.2-μm filtration setup into a portable 316 stainless steel holding tank.
   e. Sample for testing.
   f. Store solution at room temperature before filling. *Note*: Do not hold solution more than 30 days before filling.
2. Preparation of ampoules. Use type I 2-mL glass ampoules.
   a. Wash, dry, and load ampoules in container suitable for sterilization.
   b. Sterilize ampoules by using dry heat at 200°C glass temperature for 225 minutes (or use an equivalent cycle).
   c. Deliver ampoules to the sterile filling area.
3. Filtration.
   a. Send appropriate samples for testing.
   b. Connect tank containing solution, sterile filtration setup, and sterile surge bottle to filling machine by using aseptic technique.
   c. Apply N_2 gas pressure to tank to provide adequate filtration rate (NMT 10 psig). If tank does not have a pressure heat, connect pump between tank and filter.
4. Filling.
   a. Sample for testing.
   b. Aseptically fill 2.3 mL of sterile-filtered solution into each sterile ampoule.
   c. Seal ampoules and inspect.

Hydromorphone Hydrochloride Injection Single Dose

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Hydromorphone hydrochloride	1.00	g
2.00	mg	2	Sodium citrate	2.00	g
2.00	mg	3	Citric acid	2.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: For 2- and 4-mg concentration, use the same formula.

Hydromorphone Hydrochloride Injection Multiple Dose

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Hydromorphone hydrochloride	2.00	g
0.50	mg	2	Disodium edetate	0.50	g
1.80	mg	3	Methyl paraben	1.80	g
0.20	mg	4	Propyl paraben	0.20	g
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Fill 20 mL into vials.

Hydroxycobalamin Injection

Bill of Materials (Batch Size 308 L)					
Scale/mL		Item	Material	Qty	UOM
1000.00	mg	1	Hydroxycobalamin, NF (as acetate, 344.96 × 100___% assay)	344.96[a]	g
0.204	mg	2	Sodium acetate trihydrate, USP	62.83	g
2.18	mg	3	Glacial acetic acid, USP, for pH adjustment	136.14	g
8.20	mg	4	Sodium chloride, USP	2525.60	g
1.50	mg	5	Methyl paraben, USP	462.00	g
0.20	mg	6	Propyl paraben, USP	61.60	g
QS	mL	7	Water for injection, USP	QS to 308.00	L
QS	mL	8	Nitrogen gas, NF	QS	

[a]Take the moisture content and the assay value of hydroxycobalamin (as acetate) into calculation.

Manufacturing Directions

1. Measure ca. 33 L of item 7 into a clean stainless steel container and heat to 90°C.
2. Add items 5 and 6 to the heated water and stir to dissolve. Cool to 25°C to 30°C.
3. Measure ca. 253 L of item 7 into another stainless steel clean mixing tank and mark it accordingly.
4. Add the solution from step 2 into the mixing tank with constant agitation.
5. Add items 2, 3, and 4 into the mixing tank with constant agitation until a clear solution is obtained.
6. Add item 1 into the mixing tank with constant agitation until a clear solution is obtained.
7. Bring to final volume with item 7; check pH and sample for in-process checks.
8. Bubble item 8 continuously into the mixing tank.
9. Sterile filter through a 0.22-μm filter into an appropriate reservoir for filling.
10. Use amber type I vials, 1888 gray stoppers, and appropriate aluminum seals.

Hydroxyprogesterone Caproate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
125.00	mg	1	Hydroxyprogesterone caproate, USP	125.00	g
460.00	mg	2	Benzyl benzoate, USP	460.00	g
20.00	mg	3	Benzyl alcohol, NF	20.00	g
QS	mL	4	Castor oil, USP	QS to 1.00	L

Hydroxypropylmethylcellulose Ophthalmic Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Hydroxypropylmethylcellulose	20.00	g
4.90	mg	2	Sodium chloride	4.90	g
0.75	mg	3	Potassium chloride	0.75	g
0.48	mg	4	Calcium chloride	0.48	g
0.30	mg	5	Magnesium chloride	0.30	g
3.90	mg	6	Sodium acetate	3.90	g
1.70	mg	7	Sodium citrate	1.70	g
QS	mL	8	Sodium hydroxide for pH adjustment	QS	
QS	mL	9	Hydrochloric acid for pH adjustment	QS	
QS	mL	10	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 6.8 to 7.6. Fill bottles and terminally sterilize.

Hyoscine Butylbromide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.0	mg	1	Hyoscin-*N*-butylbromide	20.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Hydrobromic acid, 1% solution	QS	mL
QS	mL	4	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Preparation of water. Check item 2 to be used for solution preparation and verify that it meets conductivity limit of NMT 1 mS/cm and pH range of 5 to 7.
2. Preparation of solution.
   a. Put 900 mL of item 2 into the preparation vessel and bubble N_2 gas (item 4) to expel dissolved O_2 gas. Monitor the O_2 sensor display (O_2% limit = NMT 1).
   b. Add and dissolve item 1 into step 2-a preparation vessel. Mix well with stirring to make clear solution.
   c. Check pH (range 4.0–5.2).
   d. Adjust pH if necessary with item 3 (range 4.0–5.2).
   e. After adjustment of pH, make up volume to 1 L by item 2 and mix during bubbling item 4 until oxygen % is less than 1.
   f. Check final pH (range 4.0–5.2).
   g. Take sample for assay.
3. Preparation of ampoules. Use type I 2-mL clear glass ampoules, USP. Sterilize the ampoules by using dry heat tunnel.
4. Preparation of filtration assembly and machine parts for production. Clean and sterilize filtration assembly and machine parts by autoclaving.
5. Prefiltration.
   a. Before starting the filtration, check the integrity of filter cartridge.
   b. Integrity test results of filter cartridge.
   c. Transfer the solution from the preparation vessel to mobile vessel through filtration assembly, containing a 0.45-μm filter cartridge.
   d. After filtration, transfer mobile vessel to solution room.
6. Final filtration.
   a. Before starting the final filtration, check the integrity of filter cartridge.
   b. Aseptically connect the N_2 line through sterile N_2 filter to the inlet of vessel.
   c. Aseptically connect one end of the previously sterilized filtration assembly with 0.22-μm pore-size filtration cartridge to the outlet of vessel and the other end to the buffer holding tank on the ampoule's filling machine parts.
   d. Filter the solution.
7. Aseptic filling. Fill 1.10 mL (range 1.05–1.15 mL) solution from the bulk into each sterile dry clean ampoule and seal it.
8. Terminal sterilization and leak test. Load the inverted ampoules inside the autoclave chamber and run the cycle as per following parameters: sterilization temperature 121.1°C and exposure time 20 minutes.
9. Optical checking. Check the ampoules under optical checking machine.

Ibuprofen Lysinate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Ibuprofen, use ibuprofen lysinate	12.00	g
9.33	mg	2	Sodium chloride	9.33	g
QS	mL	3	0.1 N Sodium hydroxide for pH adjustment	QS	
QS	mL	4	0.1 N Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take item 5 into a jacketed stainless steel vessel and maintain at 15°C to 30°C.
2. Begin mixing at 600 to 800 rpm and add item 2 to dissolve.
3. Add item 1 to vessel and dissolve. Add rinses. This ensures full dissolution of item 1.
4. Check and adjust pH to 7.2 to 7.6 with item 3 or 4.
5. Make up volume with item 5.
6. Transfer to filling area, filter, and autoclave at 123°C for 22 minutes.

Ibutilide Fumarate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.10	mg	1	Ibutilide fumarate (equivalent to 0.087 mg of base)	0.10	g
0.189	mg	2	Sodium acetate trihydrate	0.189	g
8.90	mg	3	Sodium chloride	8.90	mg
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 4.60 with item 4.

Idarubicin Hydrochloride Injections

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Idarubicin hydrochloride	1.00	g
25.00	mg	2	Glycerin	25.00	g
QS	mL	3	Hydrochloric acid for pH adjustment		
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.5; terminally sterilize.

Imiglucerase for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
21.20	U	1	Imiglucerase	21,200	U
17.00	mg	2	Mannitol	17.00	g
5.20	mg	3	Trisodium citrate	5.20	g
1.80	mg	4	Disodium hydrogen citrate	1.80	g
0.053	mg	5	Polysorbate 80	0.053	g
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Citric acid for pH adjustment	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: Fill 10 mL for 212 U and 20 mL for 424 U and lyophilize after adjusting pH.

Immune Globulin (Human) for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	IgG	50.00	g
30.00	mg	2	Albumin (human)	30.00	g
50.00	mg	3	Sucrose	50.00	g
5.00	mg	4	Sodium chloride	5.00	g
QS	mg	5	Citric acid for pH adjustment	QS	
QS	mg	6	Sodium carbonate for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: The heat treatment step employed in the manufacture of immune globulin IV (human) is pasteurization at 60°C for 10 hours in aqueous solution form with stabilizers. Lyophilized product to give 5% IgG per vial.

Infliximab Recombinant for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Infliximab	10.00	g
50.00	mg	2	Sucrose	50.00	g
0.05	mg	3	Polysorbate 80	0.05	g
0.22	mg	4	Sodium phosphate monobasic monohydrate	0.22	g
0.61	mg	5	Sodium phosphate monobasic dihydrate	0.61	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: 10 mL is lyophilized in each vial.

Insulin Aspart Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	U	1	Insulin aspart[a]	100,000	U
16.00	mg	2	Glycerin	16.00	g
1.50	mg	3	Phenol	16.00	g
1.72	mg	4	*M*-Cresol	1.72	g
19.60	mg	5	Zinc as zinc oxide	16.90	mg
1.25	mg	6	Disodium hydrogen phosphate dihydrate	1.25	g
0.58	mg	7	Sodium chloride	0.58	g
QS	mL	8	Hydrochloric acid 10% for pH adjustment		
QS	mL	9	Sodium hydroxide 10% for pH adjustment		
QS	mL	10	Water for injection, USP	QS to 1.00	L

[a] B28 asp regular human insulin analog; adjust pH to 7.2 to 7.6.

Insulin Glargine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3.637[a]	mg	1	Insulin glargine	3.673	g
30.00	mg	2	Zinc (as zinc oxide equivalent)	30.00	mg
2.70	mg	3	*M*-Cresol	2.70	g
20.00	mg	4	Glycerol, 85%	20.00	g
QS	mL	5	Hydrochloric acid, 10%, for pH adjustment		
QS	mL	6	Sodium hydroxide, 10%, for pH adjustment		
QS	mL	7	Water for injection, USP	QS to 1.00	L

[a] Equivalent to 100 U; adjust to pH 5.0 with item 5 or 6.

Insulin Human 70/30

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1000	U	1	Insulin human, USP, approximately 2% excess	1000,000	U
0.011	mg	2	Zinc oxide, USP; to give 0.025 mg/100 U	0.011	g
0.73	mg	3	Liquefied phenol, USP, equivalent to 0.65 mg/mL, calculated at 89% phenol	0.73	g
1.60	mg	4	Metacresol, USP	1.60	g
16.00	mg	5	Glycerin, USP (parenteral)	16.00	g
0.241	mg	6	Protamine sulfate, USP (purified) to provide 0.270 mg base/100 U in NPH crystallization part	0.241	g
3.78	mg	7	Sodium phosphate dibasic, USP	3.78	g
QS	mL	8	Water for injection, USP	QS	
QS	mL	9	Hydrochloric acid, 10% solution, for pH adjustment	QS	
QS	mL	10	Sodium hydroxide, 10% solution, for pH adjustment	QS	

Manufacturing Directions

This product is prepared by combining 70 parts by volume of human insulin NPH with 30 parts by volume of human insulin buffered regular.

Manufacture of NPH Insulin (Insulin Section)

1. Weigh the required amount of water for injection (775 kg) into a stainless steel manufacturing tank.
2. Add and mix accurately weighed quantities of liquefied phenol (617.9 g), metacresol (1.354 g), and glycerin (13.536 g) until adequately blended.
3. Add and mix a calculated amount of protamine sulfate purified (588.1 g) until completely dissolved.
4. Add and mix a calculated amount of insulin human (6.467 g based on potency of 25.7 U/mg and 0.9% excess) until all crystals are completely wetted.
5. Dissolve an accurately weighed amount of zinc oxide (21.49 g) in 10% hydrochloric acid solution (1.425 mL) and then add to a suitable container having a specified amount of water for injection.
6. Add the contents of the container to the insulin mixture. Mix the material until all crystals are dissolved. Determine the pH of the solution (7.35–7.55) and adjust, if necessary, to the proper range with 10% hydrochloric acid solution, or 10% sodium hydroxide solution.
7. Add additional water for injection to adjust the solution to final weight to give 846 L.

Buffer Section

1. Weigh the required amount of water for injection (800 kg) into a stainless steel manufacturing tank.
2. Add and mix accurately weighed quantities of liquefied phenol (655.2 g), metacresol (1.370 g), glycerin (13.696 kg), and sodium phosphate dibasic (6.471 kg) until all crystals are dissolved.
3. Add additional water for injection to adjust the solution to a final weight of 846 kg or 856 L.
4. Prepare a test sample representing a combination of equal volumes of insulin and buffer sections for NPH for pH determination.
5. If necessary, adjust pH of the buffer section with 10% hydrochloric acid solution or 10% sodium hydroxide solution, until the pH of an equal-parts mixture of the two bulk solutions is within proper range (7.35–7.55).
6. Separately sterilize each of the two solutions by membrane filtration.
7. Combine appropriate quantities of insulin and buffer sections for NPH aseptically and mixed in a suitable tank.
8. Aseptically adjust the pH of the resulting mixture to proper range, if necessary, by adding either 10%

hydrochloric acid solution, sterile, or 10% sodium hydroxide solution, sterile.
9. Allow the mixture to crystallize for at least 24 hours. Adjust the pH of the mixture aseptically to the proper pH range (7.35–7.55), if necessary, by adding either 10% hydrochloric acid solution, sterile, or 10% sodium hydroxide solution, sterile. After the NPH section is crystallized, take an in-process assay (to ensure 97–103% value).

Buffered Regular Insulin

1. Weigh the required quantity of water for injection (750 kg) into a stainless steel tank or glass container.
2. Add accurately weighed quantities of liquefied phenol (590.1 g), metacresol (1.293 g), glycerin (12.928 kg), and sodium phosphate dibasic (3.054 kg) and mix the contents until all components are dissolved.
3. While continuing to mix, add a calculated amount of insulin human (3.098 g based on 26.4 U/mg and 0.9% excess).
4. After the crystals are completely dissolved, dissolve the required amount of zinc oxide (10.27 g) in a measured volume of 10% hydrochloric acid solution (700 mL) and then add to a suitable container having a specified amount of water for injection (811 kg).
5. Add the contents of the container to the insulin solution.
6. Determine the pH of the solution and adjust, if necessary, to the proper pH range (7.35–7.55) with 10% hydrochloric acid solution or 10% sodium hydroxide solution.
7. Add additional water for injection to adjust the solution to final weight to yield a volume of 808 L.
8. If necessary, adjust the pH of the final solution (7.35–7.55) by adding either 10% hydrochloric acid solution or 10% sodium hydroxide solution.
9. Sterilize this solution by membrane filtration. Samples for in-process assays are routinely taken aseptically following the sterile filtration process. However, on occasion, samples may be taken prior to filtration.

NPH/Buffered Regular, Final Mixture

1. Combine aseptically the appropriate quantities of NPH insulin (70 parts) and buffered regular insulin (30 parts) and mixed in a suitable tank.
2. Aseptically adjust the pH of the final suspension to the proper pH range (7.35–7.55), if necessary, by adding either 10% hydrochloric acid solution, sterile, or 10% sodium hydroxide solution, sterile.
3. Fill the sterile suspension aseptically into sterile type I glass vials.
4. Keep the suspension homogeneous during transfer and filling operations. Fit the vials with rubber closures and sealed with aluminum seals.

Testing

Noncompendial tests include HPLC potency, nitrogen content, phenol and metacresol by HPLC, insulin by semiautomated Biuret method, endotoxins, zinc by atomic absorption, and pH determination.

Insulin Human Isophane Suspension (NPH)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	U	1	Insulin human, USP, approximately 2% excess	100,000	U
0.012	mg	2	Zinc oxide, USP, to give 0.025 mg/100 U	0.012	g
0.73	mg	3	Liquefied phenol, USP, equivalent to 0.65 mg/mL, calculated at 89% phenol	0.73	g
1.60	mg	4	Metacresol, USP	1.60	g
16.00	mg	5	Glycerin, USP (Parenteral)	16.00	g
0.35	mg	6	Protamine sulfate, USP (purified) to provide 0.025 mg base/100 U insulin; calculated at 77.5% base	0.35	g
3.78	mg	7	Sodium phosphate dibasic, USP	3.78	g
QS	mL	8	Water for injection, USP	QS	
QS	mL	9	Hydrochloric acid, 10% solution, for pH adjustment		
QS	mL	10	Sodium hydroxide, 10% solution, for pH adjustment		

Manufacturing Directions

A typical 5000-L batch will yield 483091 vials. It is prepared from two bulk solutions: an insulin section and a buffer section.

Insulin Section (2500 L)

1. Weigh the required quantity of water for injection (2380 kg) into a stainless steel manufacturing tank.
2. Add accurately weighed quantities of liquefied phenol (1.826 kg), metacresol (4.0 kg), and glycerin (40.0 kg) and mix the solution until homogeneous.
3. Sequentially add accurately weighed quantities of protamine sulfate purified (1.737 g; calculated at 77.5% protamine base; quantity required to yield 0.270 mg of protamine base/100 U of insulin) and insulin human (19.0 kg at the rate of 26.5 U/mg, including 0.7% excess).
4. Dissolve the required amount of zinc oxide (55.6 g) in a measured volume of 10% hydrochloric acid solution (4.5 L) and add to a stainless steel stockpot containing a specified amount of water for injection.
5. Add the contents of the stockpot to the insulin mixture.
6. When the insulin crystals are dissolved, determine the pH of the solution and adjust (7.0–7.5), if necessary, to the proper pH range with 10% hydrochloric acid solution or 10% sodium hydroxide solution.
7. Add additional water for injection to adjust the solution to final weight (QS to 2513 kg = 2500 L).

Buffer Section (2520 L, Includes Extra Amount over Batch Requirement)

1. Weigh the required quantity of water for injection (2450 kg) into a stainless steel manufacturing tank.
2. Add accurately weighed quantities of liquefied phenol (1.840 kg), metacresol (4.032 kg), glycerin (40.32 kg), and sodium phosphate dibasic (19.05 kg) and mix until all crystals are dissolved.
3. Volumetrically measure an amount of 10% hydrochloric acid solution (4.5 L) and add to the solution.
4. Add additional water for injection to adjust the solution to final weight (2538 kg = 2520 L; excess quantity of batch prepared to insure adequate quantity of full insulin solution).
5. Prepare a test sample for pH determination by mixing equal volumes of each bulk solution.
6. Determine pH. If necessary, adjust pH of the buffer section (to 7.0–7.5) with 10% hydrochloric acid solution or 10% sodium hydroxide solution, until the pH of an equal-parts mixture of the two bulk solutions is within proper range (7.0–7.5).
7. Routinely take samples for in-process assays following the sterile filtration process; however, on occasion samples may be taken prior to filtration.
8. Sterilize each of the two solutions by membrane filtration. Collect the two sterile solutions in separate sterile holding tanks.
9. Aseptically fill appropriate amounts of the two sterile solutions (1:1) into sterile type I glass vials. The vials are fitted with rubber closures and sealed with aluminum seals.
10. Maintain the filled vials at controlled room temperature for at least 24 hours to facilitate the crystallization process.
11. Alternatively, mix the two sterile solutions in a sterile filling tank. Maintain the mixture at controlled room temperature for at least 24 hours prior to filling to facilitate the crystallization process.
12. Aseptically take a control sample from the final mixture. The filled vials may be stored in a chill room until ready for finishing.

Testing

Noncompendial analytical methods include nitrogen content of insulin crystals and product by nitrogen analyzer, determination of zinc in insulin by atomic absorption, determination of phenol and metacresol by HPLC, high-molecular-weight protein content of crystals and product by size exclusion HPLC, insulin by Biuret method, and bacterial endotoxin tests.

Insulin Lispro Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	U	1	Insulin lispro[a]	100,000	U
0.28	mg	2	Protamine sulfate	0.28	g
16.00	mg	3	Glycerin	16.00	g
3.78	mg	4	Sodium phosphate dibasic	3.48	g
1.76	mg	5	*M*-Cresol	1.76	g
0.025	mg	6	Zinc ion (as zinc oxide equivalent)	0.025	g
0.715	mg	7	Liquefied phenol	0.715	g
QS	mL	8	Sodium hydroxide, 10% solution, for pH adjustment		
QS	mL	9	Hydrochloric acid, 10% solution, for pH adjustment		
QS	mL	10	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 7.0 to 7.8 with item 8 or 9.
[a] Lys (B28), Pro (B29) human insulin analog.

Insulin Regular

Bill of Materials (Batch Size 2500 L to give 241545 Vials)					
Scale/mL		Item	Material	Qty	UOM
100.00	U	1	Insulin human, USP, 2% excess, 26.5 U/mg	9.519	g
2.50	mg	2	Metacresol, USP	6.25	g
16.00	mg	3	Glycerin, USP	40.00	kg
1.00	mL	4	Water for injection, USP	QS	kg
QS	mL	5	Hydrochloric acid, 10% solution, for pH adjustment	2.215	mL
QS	mL	6	Sodium hydroxide, 10% solution, for pH adjustment	3.30	mL

Note: Adjust the quantity of insulin based on activity.

Manufacturing Directions

1. Put approximately 2400 kg of water for injection into a stainless steel manufacturing tank.
2. Add item 2 and 3 to the tank and mix well until contents are dissolved.
3. While mixing, add item 1. After the crystals are completely wetted, add item 5. When the crystals are dissolved, measure the pH; add item 6 or 5 to adjust the pH to between 7.0 and 7.8.
4. Add item 4 to make up the volume. Measure pH again.
5. Readjust pH with item 5 or 6 to between 7.0 and 7.8.
6. Sterilize the solution by membrane filtration. Sample and hold in sterile holding tank.
7. Fill aseptically into sterile type I glass vials fitted with rubber closure and sealed with aluminum seal.

Testing

Noncompendial analytical methods include nitrogen content of crystals and formulation by nitrogen analyzer, determination of zinc by atomic absorption, high-molecular-weight protein content by size exclusion HPLC, pH determination, and bacterial endotoxin test.

Interferon Injection 1: Interferon Alpha-2a

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3 MM	IU	1	Interferon alpha-2a	3 B	IU
7.21	mg	2	Sodium chloride	7.21	g
0.20	mg	3	Polysorbate 80	0.20	g
10.00	mg	4	Benzyl alcohol	10.00	g
0.77	mg	5	Ammonium acetate	0.77	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: The active concentration may range from 3 to 36 MM with no change in the quantity of other ingredients.

Interferon Injection 1: Interferon Alpha-2a (Prefilled Syringe)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3 MM	IU	1	Interferon alpha-2a	3B	IU
3.60	mg	2	Sodium chloride	3.60	g
0.10	mg	3	Polysorbate 80	0.10	g
5.00	mg	4	Benzyl alcohol	5.00	g
0.385	mg	5	Ammonium acetate	0.385	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: 11.1 mg/0.5 mL.

Interferon Beta-1b Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.30	mg	1	Interferon beta-1b	0.30	g
15.00	mg	2	Albumin human	15.00	g
15.00	mg	3	Dextrose	15.00	g
5.40	mg	4[a]	Sodium chloride	5.40	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

[a] This item is packaged separately as 0.54% solution (2 mL diluent for lyophilized product).

Interferon Beta-1a Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
33.00[a]	mg	1	Interferon beta-1a	33.00	mg
15.00	mg	2	Albumin (human)	15.00	g
5.80	mg	3	Sodium chloride	5.80	g
5.70	mg	4	Sodium phosphate dibasic	5.70	g
1.20	mg	5	Sodium phosphate monobasic	1.20	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a] Equivalent to 6.6 million IU.

Interferon Alpha-n3 Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5 MM	U	1	Interferon alpha-n3	5B	U
3.30	mg	2	Liquefied phenol	3.30	g
1.00	mg	3	Albumin (human)	1.00	g
8.00	mg	4	Sodium chloride	8.00	g
1.74	mg	5	Sodium phosphate dibasic	1.74	g
0.20	mg	6	Potassium phosphate monobasic	0.20	g
0.20	mg	7	Potassium chloride	0.20	g
QS	mL	8	Water for injection, USP	QS to 1.00	L

5: Interferon Alphacon-1 Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.03	mg	1	Interferon alphacon-1	0.03	g
5.90	mg	2	Sodium chloride	5.90	g
3.80	mg	3	Sodium phosphate	3.80	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Interferon Gamma-1b Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Interferon gamma-1b[a]	200.00	mg
40.00	mg	2	Mannitol	40.00	g
0.72	mg	3	Sodium succinate	0.72	g
0.10	mg	4	Polysorbate 20	0.10	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

[a] 0.5-mL fill gives 100 mg or 2 million IU.

Interleukin Eye drop

Manufacturing Directions

(per 100 mL) Interleukin-6 0.01 g, sodium chloride 0.9 g, sterilized purified water, QS.

Vitamin C Vaginal Ointment

Manufacturing Directions

A 12.5% by weight vitamin C containing vaginal ointment is produced in a 200 kg batch in the following manner.

1. The following components are melted in an ointment machine (dissolver) at 80°C: white Vaseline (petroleum jelly) 43750 g, cetyl stearyl alcohol (Lanette N) 52500 g, highly liquid paraffin 78750 g.
2. The melt is stirred and homogenized for 20 minutes and cooling is allowed to start. The dissolver is switched off at an internal temperature of 35°C. At an internal temperature of 30°C, 25,000 g of ascorbic acid is added and the dissolver is allowed to run for 15 minutes.
3. The mixture is cold stirred in a partial vacuum and then is introduced into a storage container via a homogenizer.

Interleukin for Injection (IL-2)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.25	mg	1	IL-2	0.25	g
0.70	mg	2	Sodium laurate	0.70	g
10.00	mM	3	Disodium hydrogen phosphate	10.00	M
50.00	mg	4	Mannitol	50.00	g
QS	mL	5	Hydrochloric acid, 1 M, for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take the IL-2 from the column and mix in a suitable container with items 2, 3, 4, and 6. Mix well.
2. Check and adjust pH to 7.5 (7.3–7.6) with item 5.
3. Filter and lyophilize.

Iodine IV Additive

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
118.00	mg	1	Sodium iodide (equivalent to 100 mg iodine)	118.00	mg
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Hydrochloric acid for pH adjustment		
QS	mL	4	Sodium hydroxide for pH adjustment		

Note: Sterile, nonpyrogenic solution for use as an additive to solutions for total parenteral nutrition (TPN).

Iron Copper Solution Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
30.00	mg	1	Sodium cacodylate (arsenic derivative)	30.00	g
0.522	mg	2	Ferric chloride	0.522	g
0.09	mg	3	Copper gluconate	0.09	g
3.00	mg	4	Thymol, USP	3.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Iron Dextran Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Elemental iron as iron dextran complex	50.00[a]	g
9.00	mg	2	Sodium chloride	9.00	g
QS	mL	3	Hydrochloric acid for pH adjustment		
QS	mL	4	Sodium hydroxide for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 5.2 to 6.2 with item 3 or 4.

[a] According to iron activity.

Iron Sucrose Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Element iron (polynuclear iron III) as iron sucrose[a]	20.00	g
60.00	mg	2	Sucrose	60.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: pH 10.5 to 11.1.
[a] Adjust according to available iron. Fill 5 mL into vial.

Isometheptene Hydrochloride Veterinary Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Isometheptene hydrochloride	100.00	g
55.00	mg	2	Hydrochloric acid, 37%	55.00	g
1.80	mg	3	Methyl paraben, USP	1.80	g
0.20	mg	4	Propyl paraben, USP	0.20	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Itraconazole Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Itraconazole, use itraconazole solubilized by hydroxypropyl (beta) cyclodextrin	400.00	mg
3.80	mL	2	Hydrochloric acid	3.00	mL
25.00	mL	3	Propylene glycol	25.00	mL
QS	mL	4	Sodium hydroxide for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: For dilution with 50 mL of 0.9% sodium chloride; each vial contains 200 mg itraconazole.

Ketoprofen Lysine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.50	mg	1	Citric acid	2.50	g
1.50	mg	2	Sodium hydroxide	1.50	g
80.00	mg	3	(R,S)-Ketoprofen salt of *d,l*-lysine	80.00	g
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	ft^3	5	Nitrogen gas, NF	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Make this preparation protected from light and continuously under cover of item 5.
2. Take 0.8 L of item 6 and bubble item 5 for 20 minutes protecting from light once the addition of drug begins.
3. Add items 1 and 2, mix, and dissolve.
4. Add item 3 and mix well.
5. Check and adjust pH to 7.0 to 7.5 with item 4. Keep bubbling item 5.
6. Using a pressurized source of item 5, filter through a 0.22-μm cartridge, and collect in a suitable staging vessel protected from exposure to ultraviolet light.
7. Fill type I 2-mL glass ampoule, with pre- and post-item 5 flush.
8. Sterilize.

Ketorolac Tromethamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
30.00	mg	1	Ketorolac tromethamine	30.00	g
100.00	mg	2	Alcohol USP	100.00	g
6.68	mg	3	Sodium chloride[a]	6.68	g
10.00	mg	4	Citric acid	10.00	g
QS	mL	5	Hydrochloric acid for pH adjustment		
QS	mL	6	Sodium hydroxide for pH adjustment		
QS	mL	7	Water for injection, USP	QS to 1.00	L

[a] Used in prefilled syringes; use only item 4 in vials.

Ketorolac Tromethamine Ophthalmic Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Ketorolac tromethamine	5.00	g
0.10	mg	2	Benzalkonium chloride	0.10	g
1.00	mg	3	Disodium edetate	1.00	g
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
0.1	mg	6	Octoxynol 40	0.1	g
QS	mL	7	Sodium chloride[a]	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 7.4.
[a] Adjust osmolality to 290 mOsm/kg.

Labetalol Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Labetalol hydrochloride	5.00	g
45.00	mg	2	Dextrose anhydrous, USP	45.00	g
0.10	mg	3	Disodium edetate	0.10	g
0.80	mg	4	Methyl paraben	0.80	g
0.10	mg	5	Propyl paraben	0.10	g
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Citric acid monohydrate for pH adjustment	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.0 to 4.0 with item 6 or 7.

Lactobionic Acid Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
120.00	mg	1	Lactobionic acid, powder	120.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Collect ca. 90% of final volume of item 2 in a clean glass-lined container or 316 stainless steel tank.
2. Add and dissolve item 1.
3. Sample for lactobionic acid concentration, silica content, and volume.
4. Based on step 3, calculate the final volume as follows: final volume = (solution volume × % concentration)/12%. Adjust volume.
5. Filter solution through previously rinsed and approved cellulose pads and papers. Recirculate until clear and essentially free of insoluble material into clean Pyrex tank or portable tank.
6. Sterile filter the solution through a sterile 0.22-μm membrane into a sterile Pyrex bottle.
7. Sample. Keep product refrigerated.

Lamotrigine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Lamotrigine	25.00	g
37.78	mg	2	Mannitol	37.78	g
9.37	mg	3	Methanesulfonic acid	9.375	g
QS	mL	4	Sodium hydroxide for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Dissolve mannitol in appropriate amount of water. The amount of mannitol needed is calculated to provide tonicity on reconstitution.
2. The mesylate salt of lamotrigine is formed in situ during the manufacturing process described in European patent 21121 and U.S. patent. no. 4486354 by addition of commercially available methanesulfonic acid.
3. When the appropriate amounts of lamotrigine and methanesulfonic acid are combined, the resulting solution pH ranges from ca. 2.8 to 3.5. Add sodium hydroxide and water to achieve the required pH and volumes as given in the protocol.
4. Adjust the solution pH to a range of 3.3 to 3.5 with sodium hydroxide solution or methane-sulfonic acid solution.
5. The final concentration of the lamotrigine calculated as free base in solution prior to freeze drying may vary from 1 to 50 mg/mL, preferably 25 mg/mL.
6. The solution is chemically and physically stable at room temperature for at least 7 days and may be held in suitable stainless steel/glass manufacturing tank for this period of time, if needed.
7. Sterile filter the solution and fill into appropriate vials to a fill volume of 10 mL.
8. Load the vials into a freeze drier that is pre-cooled to 5°C prior to loading.
9. Freeze the solution to −24°C for 4 to 5 hours. Initiate primary drying by ramping the shelf temperature to 0°C while maintaining the vacuum at 0.5 torr. After the product temperature reaches the shelf temperature, initiate and conduct secondary drying at a product temperature of 35°C for 6 to 8 hours. Maintain the chamber pressure at 0.5 torr during lyophilization.
10. Reconstitution of the lyophilized formulation with 12.5 mL of sterile water for injection provides an isotonic solution containing 20 mg lamotrigine free base/mL.

Lazaroid Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Lazaroid[a]	25.00	g
44.20	mg	2	Citric acid anhydrous, USP	44.20	g
5.88	mg	3	Sodium citrate anhydrous, USP	5.88	g
0.40	mL	4	Propylene glycol	0.40	L
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

[a] 2-[[4-(2,6)-bis(1-pyrrolidinyl)-4-pyrimidinyl-1-piperazinyl-16-alpha-methylpregna-1,4,9(11)-triene-3,20-dione mesylate]]; a 5× dose formulation for bolus injection has 100 mg/mL of active drug, and all other components are increased proportionally.

Manufacturing Directions

1. Add and dissolve items 1 and 2 in approximately 0.25 L of item 7.
2. Add and dissolve item 4 and mix well.
3. Check and adjust pH to 2.9 (2.7–3.0) with item 5 or 6.
4. Add item 1 and mix well.
5. Check and adjust pH again as in step 3.
6. Make up volume with item 7.
7. Filter and sterilize by autoclaving.

Lepirudin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Lepirudin	50.00	g
40.00	mg	2	Mannitol	40.00	g
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 7 with item 3.

Leucovorin Calcium Injection (50 mg/5 mL, 10-mL Vial Lyophilized)

Bill of Materials (Batch Size 5 L)					
Scale/mL		Item	Material	Qty	UOM
12.71	mg	1	Leucovorin calcium, $5H_2O$	63.51	g
5.60	mg	2	Sodium chloride	40.00	g
QS	mL	3	Water for injection, USP	QS to 5.00	L
QS	mL	4	Sodium hydroxide, 2%, for pH adjustment		
QS	mL	5	Hydrochloric acid, 2%, for pH adjustment		

Manufacturing Directions

1. Dissolve item 1 in 4 L of item 3 in a suitable vessel. Stir until a clear solution is obtained.
2. Add item 2 with constant agitation until clear solution is obtained.
3. Check pH and adjust to 8.1±0.1 with item 4 or 5.
4. QS to volume with item 3.
5. Sample for testing.
6. After approval, filter solution through a 0.22-μm filter and fill 10-mL flint vial with an 841 gray stopper without coating (applied later).
7. Load product into lyophilizer.
8. Set temperature to −40°C.
9. Product thermocouples should register −40°C or less for at least 4 hours before starting the drying cycle.
10. Start condenser and do not start vacuum until 100 μm or less.
11. Start vacuum to the chamber to achieve at least 100 μm or less.
12. Set to low heat and bring up temperature controller to +15°C. Hold at this temperature for at least 12 hours.
13. Bring up the temperature controller to +28°C. Hold at this temperature for at least 24 hours.
14. Bleed chamber slowly with sterile dry air or N_2 gas.
15. Stopper vials by using the internal stoppering mechanism or stopper the vials with depyrogenated cover in the laminar hood.
16. Withdraw the product from lyophilizer.

Leucovorin Calcium Injection (3 mg/mL, 2-mL Vial)

Bill of Materials (Batch Size 5 L)					
Scale/mL		Item	Material	Qty	UOM
3.81	mg	1	Leucovorin calcium, $5H_2O$	15.97	g
5.6	mg	2	Sodium chloride	28.00	g
9.0	mg	3	Benzyl alcohol, NF	45.00	g
QS	mL	4	Water for injection, USP	QS to 5	L
QS	mL	5	Sodium hydroxide, 2%, for pH adjustment		
QS	mL	6	Hydrochloric acid, 2%, for pH adjustment		

Manufacturing Directions

1. Dissolve item 1 in 4 L of item 4 in a suitable vessel. Stir until a clear solution is obtained.
2. Add item 2 and item 3, one by one, with constant agitation, until a clear solution is obtained.
3. Check pH and adjust to 8.4±0.05 with item 5 or 6.
4. QS to volume with item 4.
5. Sample for testing.
6. After approval, filter solution through 0.22-μm filter and fill a type I 2-mL amber vial, 1888 gray stopper without coating (sterilized after washing in disodium edetate).

Leuprolide Acetate Injection (5 mg/mL Injection)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Leuprolide acetate powder	5.00	g
9.00	mg	2	Benzyl alcohol, NF	9.00	g
QS		3	Sodium chloride, USP		
QS	mL	4	Sodium hydroxide for pH adjustment		
QS	mL	5	Glacial acetic acid, USP	QS	
QS	mL	6	Nitrogen gas, NF	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Warning: Leuprolide is a potent drug and a reproductive hazard. It is biologically active in very small quantities. May cause adverse effects on reproduction. Women of childbearing potential are restricted from working where leuprolide is expected. Use and store under well-ventilated conditions. Avoid direct contact. Wear the appropriate personal protective equipment as required by operating procedures. Periodic medical monitoring (blood test) may be requested to evaluate evidence of exposure.

First aid: Remove contaminated clothing. Wash affected area with plenty of soap and water. Report to employee first aid.

1. Preparation of leuprolide acetate solution. *Caution*: Handle with care. Eye protection required. Wear respirator or equivalent, rubber gloves, hood, coveralls, and shoe coverings when handling powder or preparing solution.
   a. Add benzyl alcohol, sodium chloride, and leuprolide acetate to ca. 900 mL of water for injection with mixing. Mix solution.
   b. Check and adjust pH to 5.7 to 6.3 with 2% acetic acid (made by adding 0.4 mL of glacial acetic acid q.s. to 10 mL water for injection) or 2% sodium hydroxide (prepared by adding 0.4 g QS to 10 mL water for injection).
   c. QS with water for injection to 1 L.
   d. Check and adjust pH again as in step 1b.
   e. Filter solution through a 0.22-μm or finer filter with an appropriate prefilter, if necessary, into a suitable glass or 316 stainless steel container.
   f. Sample for testing; adjust pH or ingredients if outside limits. Fill as soon as possible.
2. Preparation of bottles.
   a. Wash and dry type I 5-mL clear glass bottles and load into appropriate containers for sterilization.
   b. Sterilize by using dry heat at 200°C (−0, +50°C) glass temperature for 225 minutes (−0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for the duration of the cycle.
   c. Deliver to the sterile filling area.
3. Preparation of stoppers.
   a. Leach stoppers by boiling for 10 minutes in deionized water.
   b. Wash stoppers using rubber cycle (slow tumbling) with Triton X-100 or similar.
   c. Dry in a fast dryer at 55°C.
   d. Store in a suitable container until ready for use.
   e. Try, inspect, and rinse thoroughly. Wrap tray and identify properly.
   f. Sterilize in a steam autoclave for 121°C for 50 minutes.
4. Sterile filtration and setup.
   a. Connect storage container to a sterilized 0.22-μm or finer filter with an appropriate sterile prefilter.
   b. Filter enough solution into sterile container so as to wet filter.

c. Pressure test filter using N_2 at 40-lb pressure.
d. Filter solution into sterile container.
e. Commence filling.
f. Sample for testing.

5. Filling.
   a. Under aseptic conditions, fill 3.2 mL into each sterilized 5-mL vial.
   b. Sample for testing.
   c. Pressure test filter using N_2 at 40-lb pressure at end of filling run.
   d. Aseptically stopper each vial with a clean, sterile siliconized stopper.
   e. Apply overseal.
   f. Inspect each vial for defects.
   g. Sample for testing.

Leuprolide Acetate Injection: Depot Preparation (3.75 and 7.50 mg for Injecting Every Month)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
Chamber 1					
3.75	mg	1	Leuprolide acetate	3.75	g
0.65	mg	2	Purified gelatin	0.65	g
33.10	mg	3	*dl*-Lactic acid glycolic acids	33.10	g
6.60	mg	4	D-Mannitol	6.60	g
Chamber 2					
5.00	mg	1	Carboxymethylcellulose	5.00	g
50.00	mg	2	D-Mannitol	50.00	g
1.00	mg	3	Polysorbate 80	10.00	g
QS	mL	4	Glacial acetic acid for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: 3.75 or 7.50 mg active; same inactive ingredients.

Leuprolide Acetate Injection (11.25 and 22.50 mg for Injecting Every 3 Months)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
Chamber 1					
11.25	mg	1	Leuprolide acetate	11.25	g
99.30	mg	2	Polylactic acid	99.30	g
19.45	mg	3	D-Mannitol	19.45	g
Chamber 2					
7.50	mg	1	Carboxymethylcellulose	7.50	g
75.00	mg	2	D-Mannitol	75.00	g
1.50	mg	3	Polysorbate 80	1.50	g
QS	mL	4	Glacial acetic acid for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: 11.25 or 22.50 mg active; same inactive ingredients.

Leuprolide Acetate Injection (30 mg for Injecting Every 4 Months)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
Chamber 1					
30.00	mg	1	Leuprolide acetate	30.00	g
264.80	mg	2	Polylactic acid	264.80	g
51.90	mg	3	D-Mannitol	51.90	g
Chamber 2					
7.50	mg	1	Carboxymethylcellulose	7.50	g
75.00	mg	2	D-Mannitol	75.00	g
1.50	mg	3	Polysorbate 80	15.00	g
QS	mL	4	Glacial acetic acid for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Leuprolide Acetate Implant

Leuprolide acetate implant is a sterile, nonbiodegradable, osmotically driven miniaturized implant designed to deliver leuprolide acetate for 12 months at a controlled rate. It contains 72 mg of leuprolide acetate (equivalent to 65 mg leuprolide free base) dissolved in 104 mg dimethyl sulfoxide. The 4 mm × 45 mm titanium alloy reservoir houses a polyurethane rate-controlling membrane, an elastomeric piston, and a polyethylene diffusion moderator. The reservoir also contains the osmotic tablets, which are not released with the drug formulation. The osmotic tablets are composed of sodium chloride, sodium carboxymethyl cellulose, povidone, magnesium stearate, and sterile water for injection. Polyethylene glycol fills the space between the osmotic tablets and the reservoir. A minute amount of silicone medical fluid is used during manufacture as a lubricant. The weight of the implant is ca. 1.1 g.

Levorphanol Tartarate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Levorphanol tartarate	2.00	g
1.80	mg	2	Methyl paraben	1.80	g
0.20	mg	3	Propyl paraben	0.20	g
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 4.3 with item 4.

Levothyroxine Sodium for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Levothyroxine Sodium	20.00	mg
1.00	mg	2	Mannitol	1.00	g
0.07	mg	3	Tribasic Sodium Phosphate Anhydrous	0.07	g
QS	mL	4	Sodium Hydroxide for pH adjustment	QS	
QS	mL	5	Water for Injection, USP	QS to 1.00	L

Note: For 500-mg label, use 1.75 mg item 3. Fill 10 mL and lyophilize. Reconstitute with 5 mL of 0.9% sodium chloride injection.

Lidocaine Hydrochloride and Epinephrine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Lidocaine HCl, USP	10.00	g
6.00	mg	2	Sodium chloride, USP	6.00	g
1.00	mg	3	Methyl paraben, USP	1.00	g
0.50	mg	4	Disodium edetate	0.50	g
0.01	mg	5	Epinephrine, USP	0.01	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	mL	7	Glacial acetic acid, USP	QS	
QS	mL	8	Sodium acetate for buffering; see item 7	QS	

Note: Adjust item 1 for different strength.

Lidocaine Hydrochloride and Epinephrine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Lidocaine HCl, USP (lidocaine base 8.8 mg)	10.00	g
6.00	mg	2	Sodium chloride, USP	6.00	g
1.00	mg	3	Methyl paraben, USP	1.00	g
1.50	mg	4	Sodium metabisulfite, NF	1.50	g
0.01	mg	5	Epinephrine, USP	0.01	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	mL	7	Glacial acetic acid for buffering	QS	
QS	mL	8	Sodium acetate for buffering; see item 7	QS	
QS	mL	9	Sodium hydroxide for pH adjustment	QS	

Note: Adjust quantity of item 1 for different strengths.

Lidocaine Hydrochloride and Epinephrine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Lidocaine HCl, USP (lidocaine base 8.8 mg)	10.00	g
6.00	mg	2	Sodium chloride, USP	6.00	g
0.20	mg	3	Citric acid	0.20	g
0.50	mg	4	Sodium metabisulfite, NF	1.50	g
0.01	mg	5	Epinephrine, USP	0.01	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	mL	7	Sodium hydroxide for pH adjustment	QS	
QS	mL	8	Hydrochloric acid for pH adjustment		

Note: For a multiple-dose vial, add 1 mg methyl paraben. Adjust pH to 3.3 to 5.5.

Lidocaine Hydrochloride Injection (1% or 1.5% 20 mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
15.00	mg	1	Lidocaine hydrochloride, USP anhydrous, use lidocaine hydrochloride monohydrate, USP	16.00	g
6.50	mg	2	Sodium chloride, USP	6.50	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: For 1% strength, reduce the quantity accordingly; different fill volumes.

Manufacturing Directions

Note: The solution must be prepared in a glass-lined or a 316 or higher temper-grade stainless steel tank cleaned according to approved SOPs.

1. Preparation.
   a. Add water for injection to tank to ca. 90% of the final volume.
   b. Add and dissolve the lidocaine hydrochloride and the sodium chloride with mixing.
   c. Add water for injection to final volume and mix till ingredients are dissolved and solution is uniform.
   d. Check and record the pH. Adjust if necessary to pH 6.5 (6.2–6.7) with a 10% sodium hydroxide solution or 10% hydrochloric acid solution.
   e. Sample for testing.
   f. Filter solution through a previously rinsed filtration setup, using an approved 0.45-μm micrometer or finer membrane and an approved prefilter. Filter solution into a clean glass-lined or a 316 stainless steel holding tank.
   g. Prepare a 0.45-μm or finer membrane inline filter for the filling line.
2. Filling. Use type I 20-mL or other fill size glass ampoules, USP.
   a. Using the inline filter, fill specified amount into each clean, dry ampoule.
   b. Seal ampoules.
3. Sterilization. Sterilize at 115°C (+3°C, −0°C) and an F_0 range of 8 to 18. Use water spray cooling and terminal air pressure to maintain autoclave pressure.

Lincomycin Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
300.00	mg	1	Lincomycin, use lincomycin hydrochloride monohydrate for injectables (at the rate of 790 μ g/mg)	379.75[a]	g
9.45	mg	2	Benzyl alcohol, NF	9.45	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	mL
QS	mL	4	Sodium hydroxide reagent-grade pellets for pH adjustment	QS	mL
QS	mL	5	Nitrogen gas, NF	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a] Adjust weight of Lincomycin hydrochloride monohydrate to allow for variable potency: (379.746 × 790)/potency = g required for 1 L.

Manufacturing Directions

Caution: Lincomycin may cause an allergic reaction in some individuals. Avoid contact with skin. Wear appropriate personal protection gear.

1. Prepare 2% hydrochloric acid immediately prior to use by adding 0.4 mL of hydrochloric acid to ca. 10 mL of item 6. QS to 20 mL and mix.
2. Prepare 2% sodium hydroxide immediately prior to use by adding 0.4 g of pellets of item 4 into 10 mL of item 6. QS to 20.00 mL and mix.
3. Prepare the drug solution in a glass-lined or 316 or higher temper-grade stainless steel tank. Add ca. 50% of item 6. Add and dissolve item 1 and mix thoroughly.
4. With agitation, add item 2. Rinse residue from container by using item 6 and mix thoroughly until uniform solution is produced.
5. Check and record pH (range 3.0–5.5). Adjust if necessary as in step 2 or 3.
6. Make up volume with item 6. Sample for testing.
7. Filter solution through a previously rinsed filtration setup, using an approved 0.22-μm membrane filter with a 0.45-μm prefilter, into a clean glass-lined of 316 or higher temper-grade stainless steel tank.
8. Prepare type I glass ampoules by washing and drying and sterilizing at 200°C (−0, +50°C) glass temperature for 225 minutes (−0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for the duration of cycle.
9. Filter from the storage tank using 0.22-μm filter under aseptic condition 2.2 mL (or such other volumes as labeled into appropriate size ampoule) into ampoules. Seal immediately. Pressure test filter before and after filling. Sample (1 mL = 300 mg).

Liothyronine Sodium Injection (T_3)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Liothyronine sodium	10.00	mg
68.00	mL	2	Alcohol, USP	68.00	mL
0.175	mg	3	Citric acid anhydrous	0.175	mg
2.19	mg	4	Ammonia as ammonium hydroxide	2.19	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Lipid Emulsion 20% for Parenteral Nutrition

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Safflower oil winterized	200.00	g
12.00	mg	2	Egg phosphatides purified	12.00	g
25.00	mg	3	Glycerin, USP	25.00	g
QS	mL	4	Sodium hydroxide, reagent grade, for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Collect a volume of item 5 ca. equal to the final batch size. Heat and protect with item 6.
2. Maintain item 6 atmosphere in all containers and processing.
3. Add and disperse item 2 into a portion of the prepared water with agitation.
4. Add and dissolve item 3 previously filtered by using homogenizer to increase degree of dispersion.
5. Filter aqueous phosphatide dispersion phase.
6. Check pH and adjust accordingly.
7. Heat item 1. Unless previously filtered, filter and add to the aqueous phase with agitation to form a coarse emulsion concentrate.
8. Homogenize the coarse emulsion concentrate.
9. After homogenization, QS to final volume with prepared item 5.
10. Filter emulsion through a filter surface area to provide adequate flow.
11. Collect filtered emulsion with N_2 protection to surge tank.
12. Fill specified amount of emulsion into clean bottle.
13. Flush headspace of each bottle with filtered N_2; apply stopper.
14. Seal with ferrule.
15. Autoclave and then agitate to stabilize emulsion.
16. Visually inspect bottles and sample for testing.

Liver, Iron, and Cyanocobalamin with Procaine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
30.00	mg	1	Cyanocobalamin, USP	30.00	mg
0.10	mg	2	Liver injection (supplies 2 mg of cyanocobalamin activity), 20 mg/mL concentrate	0.10	g
50.00	mg	3	Ferrous gluconate, NF	50.00	g
1.50	mg	4	Riboflavin-5′-phosphate sodium	1.50	g
100.00	mg	5	Niacinamide, USP	100.00	g
16.40	mg	6	Citric acid, USP	16.40	g
23.60	mg	7	Sodium citrate, USP	23.60	g
20.00	mg	8	Procaine hydrochloride, USP	20.00	g
2.50	mg	9	Calcium pantothenate, USP	2.50	g
20.00	mg	10	Benzyl alcohol, NF	20.00	g
QS	mL	11	Water for injection, USP	QS to 1.00	L

Note: Protect from light.

Liver, Iron, and Vitamin B_{12} Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Thiamine HCl, USP	10.00	g
1.00	mg	2	Riboflavin-5′-phosphate sodium	1.00	g
1.00	mg	3	Pyridoxine HCl, USP	1.00	g
100.00	mg	4	Niacinamide, USP	100.00	g
1.00	mg	5	D-Panthenol	1.00	g
15.00	mg	6	Cyanocobalamin, USP	15.00	mg
33.00	mg	7	Ferrous gluconate, NF	33.00	mg
0.10	mL	8	Liver injection (20 mg/mL concentrate), supplies 2 mg of B_{12} activity	100.00	mL
10.00	mg	9	Sodium citrate, USP	10.00	g
1.00	mg	10	Liquefied phenol, USP	1.00	g
15.00	mg	11	Benzyl alcohol, NF	15.00	g
QS	mL	12	Water for injection, USP	QS to 1.00	L

Liver, Iron, and Vitamin B_{12} Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Cyanocobalamin, USP	50.00	mg
25.00	mg	2	Niacinamide, USP	25.00	g
0.50	mg	3	Riboflavin-5′-phosphate sodium	0.50	g
30.00	mg	4	Iron and ammonium citrate	30.00	g
0.10	mL	5	Liver injection (20 mg/mL concentrate), supplies 2 mg of B_{12}	100.00	mL
5.00	mg	6	Liquefied phenol, USP	5.00	g
10.00	mg	7	Benzyl alcohol, NF	10.00	g
QS	mL	8	Water for injection, USP	QS to 1.00	L

Lorazepam Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Lorazepam injection	2.00	g
0.18	mL	2	Polyethylene glycol 400	0.18	L
20.00	mg	3	Benzyl alcohol	20.00	g
QS	mL	4	Propylene glycol	QS to 1.00	L

Note: Increase the active ingredient to 4.00 mg for higher label product.

Magnesium Sulfate 50% Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
500.00	mg	1	Magnesium sulfate, USP	500.00	g
2.00	mg	2	Phenol, USP	2.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manganese Sulfate Injection (5-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.57	mg	1	Manganese sulfate monohydrate	21.95	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Sulfuric acid for pH adjustment	QS	

Manganese Sulfate Injection (10-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.308	mg	1	Manganese sulfate monohydrate	0.308	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Sulfuric acid for pH adjustment	QS	

Manganese Sulfate Injection (30-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.308	mg	1	Manganese sulfate monohydrate	4.39	g
0.90	%	2	Benzyl alcohol, NF	0.90	%
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Sulfuric acid for pH adjustment	QS	

Note: pH 4.0 to 7.0. Assay by atomic absorption 85% to 115%. Packaging commodity: Type I glass vials, West Co. 1888 gray stoppers, and West Co. flip-off aluminum seals.

Mechlorethamine Hydrochloride for Injection Trituration

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.10	mg	1	Mechlorethamine hydrochloride	0.10	g
QS	mg	2	Sodium chloride	QS to 1.00	kg

Note: This a triturate of drug with sodium chloride; when 100 mg is reconstituted with 10 mL water for injection, it yields 0.9% sodium chloride at pH 3 to 5 containing 1 mg of drug/mL.

Medroxyprogesterone Acetate Sterile Aqueous Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Medroxyprogesterone acetate (micronized)	200.00	g
0.85	mg	2	Myristyl gamma picolinium chloride	0.85	g
11.00	mg	3	Sodium sulfate	11.00	g
20.30	mg	4	Polyethylene glycol 3350	20.30	g
2.50	mg	5	Polyvinylpyrrolidone K17	2.50	g
0.694	mg	6	Sodium phosphate monobasic hydrate	0.694	g
0.588	mg	7	Sodium phosphate dibasic dodecahydrate	0.588	g
1.50	mg	8	L-Methionine	1.50	g
QS	mL	9	Hydrochloric acid for pH adjustment	QS	
QS	mL	10	Sodium hydroxide for pH adjustment	QS	
QS	mL	11	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable container (stainless steel), dissolve items 2 to 8 with aggressive mixing in item 11.
2. Sterilize the step 1 preparation by autoclaving at 121°C for 15 minutes.
3. Sterilize item 1 separately and add to step 2 under aseptic conditions.
4. Homogenize in a homogenizer.
5. Make up volume with item 11.
6. Check and adjust pH to 6.0 to 7.0 with item 8 or 9.
7. Filter and sterile fill.

Medroxyprogesterone Acetate Sterile Aqueous Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
140.00	mg	1	Medroxyprogesterone acetate (micronized)	200.00	g
1.80	mg	2	Methyl paraben	1.80	g
0.20	mg	3	Propyl paraben	0.20	g
8.00	mg	4	Sodium chloride	8.00	g
28.75	mg	5	Polyethylene glycol 3350	28.75	g
3.00	mg	6	Polysorbate 80	3.00	g
5.00	mg	7	Polyvinylpyrrolidone K17	5.00	g
0.694	mg	8	Sodium phosphate monobasic hydrate	0.694	g
0.588	mg	9	Sodium phosphate dibasic dodecahydrate	0.588	g
1.50	mg	10	L-Methionine	1.50	g
QS	mL	11	Hydrochloric acid for pH adjustment	QS	
QS	mL	12	Sodium hydroxide for pH adjustment	QS	
QS	mL	13	Water for injection, USP	QS to 1.00	L

Note: Use the same method as given previously, except that in step 1, first preheat item 13 to between 70°C and 90°C to dissolve items 2 and 3 and then cool.

Medroxyprogesterone Acetate Sterile Aqueous Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
150.00	mg	1	Medroxyprogesterone acetate	150.00	g
28.90	mg	2	Polyethylene glycol 3350	28.90	g
2.41	mg	3	Polysorbate 80	2.41	g
8.68	mg	4	Sodium chloride	8.68	g
1.37	mg	5	Methyl paraben	1.37	g
0.15	mg	6	Propyl paraben	0.15	g
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	mL	8	Hydrochloric acid for pH adjustment	QS	
QS	mL	9	Sodium hydroxide for pH adjustment	QS	

Note: Fill 1 mL into syringe; terminally sterilize.

Medroxyprogesterone and Estradiol Sterile Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Medroxyprogesterone acetate (micronized)	50.00	g
10.00	mg	2	Estradiol cypionate (micronized)	10.00	g
1.80	mg	3	Methyl paraben	1.80	g
0.20	mg	4	Propyl paraben	0.20	g
8.00	mg	5	Sodium chloride	8.00	g
28.75	mg	6	Polyethylene glycol 3350	28.75	g
1.90	mg	7	Polysorbate 80	1.90	g
2.50	mg	8	Polyvinylpyrrolidone K17	2.50	g
0.694	mg	9	Sodium phosphate monobasic hydrate	0.694	g
0.588	mg	10	Sodium phosphate dibasic dodecahydrate	0.588	g
1.50	mg	11	L-Methionine	1.50	g
QS	mL	12	Hydrochloric acid for pH adjustment	QS	
QS	mL	13	Sodium hydroxide for pH adjustment	QS	
QS	mL	14	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable stainless steel container, add item 14 and heat to 70°C to 90°C.
2. Add and dissolve items 3 and 4.
3. Cool to room temperature.
4. Add and dissolve items 5 to 11. Mix well.
5. Check and adjust pH to 6.0 to 7.0 with item 12 or 13.
6. Add items 1 and 2 and make a smooth slurry by using a homogenizer.
7. Filter and sterile fill.

Melphalan Hydrochloride for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Melphalan hydrochloride	5.00	g
2.00	mg	2	Povidone	2.00	g
QS	mL		Water for injection, USP	QS to 1.00	L
Diluent					
0.02	mg	1	Sodium citrate	0.02	g
0.60	mL	2	Propylene glycol	0.60	L
0.052	mL	3	Ethanol (96%)	52.00	mL
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Fill 10 mL into vials and lyophilize. Reconstitute with 10 mL of diluent.

Menadione Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Menadione	25.00	g
30.00	mg	2	Benzyl alcohol	30.00	g
QS	mL	3	Sesame oil, USP	QS to 1.00	L

Menadione Sodium Bisulfite Injection Veterinary (50 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Menadione sodium bisulfite	50.00	g
10.00	mg	2	Sodium bisulfite, USP	10.00	g
10.00	mg	3	Benzyl alcohol, NF	10.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium acetate for buffering	QS	
QS	mL	7	Glacial acetic acid for buffering; see item 6	QS	

Menadione Sodium Bisulfite Injection Veterinary (5 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Menadione sodium bisulfite	5.00	g
5.00	mg	2	Sodium chloride, USP	5.00	g
20.00	mg	3	Sodium bisulfite, USP	20.00	g
10.00	mg	4	Benzyl alcohol, NF	10.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Sodium acetate for buffering	QS	
QS	mL	7	Glacial acetic acid for buffering; see item 6	QS	

Menotropins for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
7.50	IU	1	Follicle-stimulating hormone	7,500	IU
7.50	IU	2	Luteinizing hormone	7,500	IU
1.05	mg	3	Lactose hydrous	1.05	g
0.025	mg	4	Monosodium phosphate monohydrate	0.025	g
0.025	mg	5	Disodium phosphate anhydrous	0.025	g
QS	mg	6	Phosphoric acid for pH adjustment	QS	
QS	mL	7	Sodium hydroxide for pH adjustment		
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: Fill 10 mL into each vial and lyophilize; reconstitute before administration. Menotropins for injection, USP, is a purified preparation of gonadotropins. Menotropins are extracted from the urine of postmenopausal females and possess follicle-stimulating hormone (FSH) and luteinizing hormone (LH) activity. The ratio of FSH bioactivity and LH bioactivity in menotropins is adjusted to approximate unity by the addition of human chorionic gonadotropin purified from the urine of pregnant women.

Meperidine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Meperidine hydrochloride, USP	50.00	g
QS	mL	2	Hydrochloric acid for pH adjustment	QS	
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: Use a clean, glass-lined tank. Protect from light.

1. Preparation.
   a. Add water for injection ca. 65% of the final volume into glass-lined tank protected from light.
   b. Add and dissolve meperidine hydrochloride with mixing.
   c. Check and record pH of the solution; adjust to 4 to 5 with 1 N hydrochloride acid solution.
   d. QS with water for injection to final volume.
   e. Sample for testing.
   f. Sterilize an approved 0.2- or 0.22-μm membrane filter with an approved prefilter.
   g. Filter the solution through the sterilized filter unit into a sterile glass-lined holding container.
2. Preparation of ampoules.
   a. Wash and dry type I 1-mL sulfur-treated ampoules and load into appropriate containers for sterilization.
   b. Sterilize using dry heat at 245°C for at least 3 hours and 25 minutes (or use an equivalent cycle).
   c. Deliver to sterile filling area.
3. Filling.
   a. Connect bulk solution container by using aseptic technique to the filling machines.
   b. Aseptically fill 1.2 mL (range 1.1–1.3 mL) into each clean, sterile ampoule.
   c. Immediately seal each ampoule.
4. Sterilization.
   a. Autoclave at 121°C for 20 minutes.
   b. Sample for testing.

Meperidine Hydrochloride and Promethazine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Meperidine hydrochloride	25.00	g
25.00	mg	2	Promethazine hydrochloride	25.00	g
0.10	mg	3	Edetate sodium	0.10	g
0.04	mg	4	Calcium chloride	0.04	g
0.75	mg	5	Sodium formaldehyde sulfoxylate	0.75	g
0.25	mg	6	Sodium metabisulfite	0.25	g
5.00	mg	7	Phenol liquefied	5.00	g
QS	mg	8	Acetic acid for buffering	QS	
QS	mg	9	Sodium acetate for buffering	QS	
QS	mL	10	Water for injection, USP	QS to 1.00	L

Note: Fill 2- and 10-mL vials.

Mepivacaine Hydrochloride Injection Single-Dose Vials

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Mepivacaine hydrochloride	1.00	g
6.60	mg	2	Sodium chloride	6.60	g
0.30	mg	3	Potassium chloride	0.30	g
0.33	mg	4	Calcium chloride	0.33	g
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: This formula is for 1%, 1.5%, and 2.0% solutions. Reduce quantity of sodium chloride only to 5.6 and 4.6 mg, respectively. Fill volumes are 20 or 30 mL. Adjust pH to 4.5 to 6.8 with item 5 or 6. Autoclave at 15-lb pressure 121°C for 15 minutes. May be reautoclaved.

Mepivacaine Hydrochloride Injection Multidose Vials

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Mepivacaine hydrochloride	1.00	g
7.00	mg	2	Sodium chloride	7.00	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: This formula is for a 1% (50-mL) vial; for 2% concentration, reduce sodium chloride to 5.0 mg. Adjust pH to 4.5 to 6.8 with item 5 or 6. Autoclave at 15-lb pressure 121°C for 15 minutes. May be reautoclaved.

Meropenem for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Meropenem	100.00	g
9.02	mg	2	Sodium as sodium carbonate (3.92 mEq)	9.02	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: For 1-g strength, fill 10 mL into vials and lyophilize; reconstitute with water for injection, USP. Fill 5 mL and lyophilize for 500-mg strength. pH of freshly constituted solution is between 7.3 and 8.3.

Mesoridazine Besylate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Mesoridazine as mesoridazine besylate	25.00	g
0.50	mg	2	Edetate sodium	0.50	g
QS	lb	3	Carbon dioxide, dried	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Fill under CO_2 environment.

Metaraminol Bitartrate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Metaraminol as equivalent metaraminol bitartrate	10.00	g
4.40	mg	2	Sodium chloride	4.40	g
1.50	mg	3	Methyl paraben	1.50	g
0.20	mg	4	Propyl paraben	0.20	g
2.00	mg	5	Sodium bisulfite	2.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Methandriol Dipropionate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Methandriol dipropionate	50.00	g
50.00	mg	2	Benzyl alcohol, NF	50.00	g
QS	mL	3	Sesame oil, USP	QS to 1.00	L

Methocarbamol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Methocarbamol	100.00	g
0.50	mL	2	Polyethylene glycol 300	0.50	L
QS	mL	3	Hydrochloric acid for pH adjustment		
QS	mL	4	Sodium hydroxide for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.5 to 6.0; fill 10 mL into single-dose vials.

Methohexital Sodium for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
500.00	mg	1	Methohexital sodium	500.00	g
60.00	mg	2	Sodium carbonate anhydrous	60.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: Fill 1 mL to 10 m for 0.5- to 5.0-g strengths and lyophilize. The pH of the 1% solution in water for injection is between 10 and 11; the pH of the 0.2% solution in 5% dextrose is between 9.5 and 10.5.

Methylprednisolone Acetate Suspension Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Methylprednisolone acetate, USP	20.00	g
29.60	mg	2	Polyethylene glycol 4000, USP	29.60	g
8.90	mg	3	Sodium chloride, USP	8.90	g
0.20	mg	4	Benzalkonium chloride 50%, USP	0.20	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Glacial acetic acid for buffering	QS	
QS	mL	7	Sodium acetate for buffering; see item 6	QS	

Note: For higher strength, use 40 or 80 mg as item 1.

Methylprednisolone Acetate Suspension Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Methylprednisolone acetate	20.00	mg
29.50	mg	2	Polyethylene glycol 3350	29.50	g
1.97	mg	3	Polysorbate 80	1.97	g
6.90	mg	4	Sodium phosphate monobasic	6.90	g
1.44	mg	5	Sodium phosphate dibasic	1.44	g
9.30	mg	6	Benzyl alcohol	9.30	g
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	mL	8	Hydrochloric acid for pH adjustment		
QS	mL	9	Sodium hydroxide for pH adjustment		

Note: For higher strengths, use 40 or 80 mg without adjusting tonicity with sodium chloride. Adjust pH to between 3.5 and 7.0 with item 8 or 9.

Metoclopramide Injection: Preservative Formula

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Metoclopramide HCl, USP; based on assay	5.00	g
7.00	mg	2	Sodium chloride, USP	7.00	g
1.50	mg	3	Sodium metabisulfite, USP	1.50	g
20.00	mg	4	Benzyl alcohol, NF	20.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Nitrogen gas, NF	QS	

Manufacturing Directions

Note: The product is light sensitive. Protect from light throughout.

1. Preparation of water. Check item 5 to be used for solution preparation and verify that it meets the following requirements: conductivity limit of NMT 1.0 mS/cm and pH range of 5.0 to 7.0.
2. Preparation of solution.
   a. Take 900 mL of item 5 in the preparation vessel and bubble item 6 to expel dissolved oxygen gas. Monitor the O_2 sensor display (O_2% limit = NMT 1).
   b. Add and dissolve item 4 and item 2 into step 2a preparation vessel. Mix well with stirring. After that add and dissolve item 1 and make clear solution by mixing.
   c. Add and dissolve items 3 and 2 into step 2b.
   d. Check pH (range 3.5–5.5).
   e. Adjust pH if necessary with 1 N HCl solution or 10% NaOH solution (range 3.5–5.5).
   f. After adjustment of pH, make up volume to 1 L with item 5 and mix during bubbling item 6 until O_2% is less than 1.
   g. Check final pH (range 3.5–5.5).
3. Preparation of prefiltration assembly. Clean and sterilize filtration assembly by autoclaving at 121.5°C for 30 minutes according to the current validated cycle.
4. Prefiltration.
   a. Transfer the solution from the preparation vessel to mobile vessel through filtration assembly containing the 0.45-μm filter cartridge.
   b. After filtration, check the integrity of filter cartridge.
   c. After filtration, transfer the mobile vessel to the solution room.
5. Preparation of ampoules. Use type I 2-mL clear glass ampoules, USP.
   a. Wash the ampoules in the washing machine as per following parameters and their limits:
      DI water pressure: 2 bar min
      WFI pressure: 2 bar min
      Compressed air pressure: 6 bar
      Machine speed: 100%
   b. Sterilize the ampoules by using dry heat.
   c. Set the temperature at 330°C.
6. Final filtration.
   a. Clean and sterilize filling machine parts by autoclaving at 122°C for 30 minutes (or as per latest validation studies).
   b. Before starting the final filtration, check the integrity of filter cartridge.
   c. Aseptically connect the N_2 line through sterile N_2 filter to the inlet of mobile vessel. Check the validity of the N_2 filter.
   d. Aseptically connect one end of previously sterilized filtration assembly with the 0.22-μm pore-size filtration cartridge to the outlet of mobile vessel and the other end to the buffer holding tank.
   e. Filter the solution.
7. Aseptic filling.
   a. Operate the previously sterilized ampoules-filling machine as per machine parameters. Adjust the fill volume to 2.15 mL.
   b. Fill 2.15 mL (range 2.1–2.2 mL) metoclopramide injection from the bulk into each sterile dry clean ampoule and seal it.
8. Terminal sterilization and leak test. Load the inverted ampoules inside the autoclave chamber, run the cycle as per following parameters (as per latest validation studies): Sterilization temperature of 121.1°C, exposure time of 20 minutes.

Metoclopramide Injection: Preservative-Free Formula

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Metoclopramide base as metoclopramide monohydrochloride monohydrate	5.00	mg
8.50	mg	2	Sodium chloride	8.50	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Metolazone Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Metolazone	10.00	g
100.00	mg	2	Ethanol, USP, 95%	100.00	g
650.00	mg	3	Propylene glycol	650.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable vessel, add item 3 and begin mixing.
2. Add item 1 with stirring and begin heating vessel to 50°C until dissolved.
3. Cool the solution to 25°C.
4. Add item 2 with stirring.
5. Make up volume with item 4.
6. Filter and sterilize.

Metronidazole Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Metronidazole	5.00	g
8.50	mg	2	Sodium chloride, USP	8.50	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Dissolve items 1 and 2 in approximately 0.8 L of item 3 in a stainless steel 316 or higher temper-grade vessel. Perform all processing aseptically and protected from light.
2. Make up volume with item 3.
3. Check pH 5.0 to 6.0; do not adjust.
4. Filter the solution through a 0.22-μm membrane filter and fill immediately into bags at a filling volume of 105 mL. Check filter integrity before and after filling.
5. Seal the PVC bags and autoclave at 115°C for 40 minutes starting from the moment temperature has reached 115°C inside the bag.
6. Individually seal bag into further PVC bag. Sample for complete testing.

Metronidazole Injectable Solution (500 mg/10 mL)

Formulation

I. Metronidazole, 5.0 g.
II. Kollidon 12 PF [1], 25.0 g; propylene glycol [1], 25.0 g; Lutrol E 400 [1], 25.0 g; water for injectables, 20.0 g.
III. Hydrochloric acid 0.1 N, QS.

Manufacturing Directions

Suspend I in the solution II, adjust pH 4.4 with III, and heat until metronidazole is dissolved.

Properties of the Solution

A clear solution was obtained. It can be diluted with water without precipitation.

Remark

To prevent of discoloration of Kollidon in the solution during storage, 0.2% to 0.5% of cysteine could be added as antioxidant.

Metronidazole Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Metronidazole	5.00	g
0.48	mg	2	Sodium phosphate dibasic anhydrous	476.00	mg
0.23	mg	3	Citric acid anhydrous	229.00	mg
7.90	mg	4	Sodium chloride	7.90	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: The solution must be prepared in a 315 or higher temper-grade stainless steel or glass-lined tank cleaned according to approved plant BOPs.

1. Preparation of solution.
   a. Obtain a sample from the water for injection source to be used for rinsing and mixing and certify that it meets the conductivity requirements of NMT 3.0 mS/s and pH range of 5 to 7. Record values.
   b. Test the rinse draining from the tank for conductivity and oxidizable substances prior to batch preparation. Record values (conductivity NMT 3).
   c. Record pH, conductivity, and temperature of water for injection.
   d. Add water for injection to tank to ca. 95% of the final volume.
   e. Add and dissolve the sodium phosphate dibasic, citric acid, and sodium chloride.
   f. Check and record pH (range 5.4–6). *Note*: Solution is buffered to fall into this pH range.
   g. Add and dissolve the metronidazole with mixing.
   h. Check and record pH (range 5.6–6). Solution is buffered to fall into this pH range.
   i. Add water for injection to final volume and mix until ingredients are completely dissolved and solution is uniform.
   j. Send first sample for testing.
   k. Filter solution through a Sparkler or equivalent prefilter and recirculate until clear. Then filter through an approved 0.45-μm or finer membrane connected in series to the prefilter. Recirculate until sparkling clear. *Note*: Perform the bubble point test on the membrane before and after filtration.
2. Filling.
   a. Fill a specified volume into each clean container.
   b. Send a second sample for testing.
3. Sterilization.
   a. Sterilize by using standard autoclave cycle.
   b. Send final sample for testing.

Metronidazole and Dextrose Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Metronidazole, USP, 5% excess	2.10	g
50.00	mg	2	Dextrose anhydrous, 5% excess	52.50	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Use freshly prepared item 3 stored for NMT 24 hours at 80°C. Add items 1 and 2 to item 3 at 60°C and mix for 15 minutes.
2. Filter using at least a 0.45-μm filter before final filtration with a 0.22-μm filter and fill into type I 540-mL glass bottles.
3. Fill 540 mL while maintaining solution at 45°C to 50°C and seal immediately by using butyl gray rubber stoppers prewashed and sterilized at 116°C for 30 minutes; use triple aluminum seals and suitable plastic hangers.
4. Sterilize filled bottle by autoclaving at 121°C for 20 minutes. Do not exceed temperature by 3°C or time by 2 minutes either side of the limit. The autoclaving cycle should be fully validated to prevent excess 5-hydroxy methyl furfural test limits of USP.
5. Check pH of solution (4.0–4.3). Before autoclaving, pH is 5.5 to 6.5.

Midazolam Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Midazolam as midazolam hydrochloride equivalent	1.00	g
8.00	mg	2	Sodium chloride	8.00	g
0.10	mg	3	Edetate sodium	0.10	g
10.00	mg	4	Benzyl alcohol	10.00	g
QS	mL	5	Hydrochloric acid for pH adjustment		
QS	mL	6	Sodium hydroxide for pH adjustment		
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 2.9 to 3.2 with items 5 and 6. The same formula is used for 5-mg strength.

Milrinone Lactate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.20	mg	1	Milrinone as milrinone lactate equivalent	0.20	g
49.40	mg	2	Dextrose anhydrous, USP	49.40	g
QS	mg	3	Lactic acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.2 to 4.0 with item 3 or 4. The nominal concentration of lactic acid is 0.282 mg/mL.

Mineral Complex Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
6.43	mg	1	Sodium chloride, USP	6.43	g
0.176	mg	2	Calcium chloride dihydrate, USP	0.176	g
3.253	mg	3	Magnesium chloride hexahydrate, USP	3.253	g
1.193	mg	4	Potassium chloride granules, USP	1.193	g
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Add ca. 95% of the final volume of water for 5. injection into a glass-lined or 316 or higher temper-grade stainless steel tank.
2. Bubble N_2 gas through the water and maintain N_2 gas protection throughout the remainder of the solution preparation.
3. Add and dissolve sodium chloride, calcium chloride, magnesium chloride, and potassium chloride while mixing.
4. QS with water for injection to final volume and mix until solution is uniform.
5. Check and record pH. Adjust with hydrochloric acid or sodium hydroxide if needed.
6. Filter solution with a prefilter.
7. Filter solution through a 0.45-μm membrane filter.
8. Fill correct volume into each flexible container.
9. Seal, overwrap, and autoclave.
10. Inspect and finish.
11. Sample for testing.

Miconazole Injectable Solution (1%)

Formulation

1. Miconazole, 1.0 g; Cremophor EL [1], 12.0 g.
2. Parabens, QS; water for injectables, add 100 mL.

Manufacturing Directions

Heat mixture I to approximately 65 °C, stir well, and add slowly the hot solution II.

After the ampoules have been heat-sterilized, they should be shaken for a short time, while they are still hot, to eliminate any separation of the phases that may have occurred. Sterilization can also be performed by membrane filtration under pressure.

Mitoxantrone for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Mitoxantrone base as mitoxantrone hydrochloride equivalent	2.00	g
8.00	mg	2	Sodium chloride	8.00	g
0.05	mg	3	Sodium acetate	0.05	g
0.46	mg	4	Glacial acetic acid	0.46	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: pH 4.0 to 4.5; must be diluted prior to administration.

Morphine Sulfate Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Morphine sulfate	10.00	g
8.00	mg	2	Sodium chloride	8.00	g
QS	mL	3	Sodium hydroxide for pH adjustment		
QS	mL	4	Sulfuric acid for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 4.5 with item 3 or 4. Sterile fill; do not heat-sterilize. A 10-mL fill provides a 100-mg dose for infusion; for 500-mg strength use 6.25 mg/mL of sodium chloride instead and label quantity of 8.00 mg/mL.

Morphine Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Morphine sulfate, USP, pentahydrate	25.00	g
QS		2	Nitrogen gas, NF	QS	
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Precaution: Prepare solution in a clean glass-lined tank or stainless steel container. This product requires N_2 gas and light protection during solution preparation. This product is a narcotic drug.

1. Preparation.
   a. Add water for injection to ca. 90% of the final volume into a glass-lined or stainless steel container; protect from light. Heat to 70°C (65–75°C). Pass bubble-filtered sterile N_2 gas for 10 minutes. Cool the water to 25°C (range 22–30°C).
   b. Add and dissolve morphine with mixing. Check and record pH (2.7–5.8). QS with water to final volume and mix thoroughly. Sample for testing.
   c. Sterilize an approved 0.2- or 0.22-μm membrane filter with an approved prefilter. Filter the solution by using N_2 pressure through the sterilized filter unit into a sterile glass-lined, light-protected container blanketed with N_2.
2. Preparation of ampoules. Use type I amber sulfur-treated ampoules. Wash, dry, and load into appropriate containers for sterilization. Use dry heat at 245°C to 330°C for 2 hours and 45 minutes to 3 hours and 30 minutes or equivalent cycle. Deliver to sterile filling area.
3. Filling. Connect bulk solution container with an aseptic technique to the filling machines. Aseptically fill each clean, sterile ampoule. Flush headspace with sterile filtered N_2. Immediately seal. This product is not terminally sterilized.

Moxidectin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.50	mg	1	Moxidectin	10.50	g
100.00	mg	2	Sucrose monolaurate	100.00	g
200.00	mg	3	Ethanol, USP	200.00	g
678.50	mg	4	Propylene glycol[a]	670.50	g

[a] Or QS to 1 L.

Manufacturing Directions

1. In a suitable vessel, add item 3 at room temperature and add to it item 1, stir, and mix.
2. In a separate vessel, add item 4 and dissolve in it item 2. Mix vigorously to dissolve.
3. Add solution of step 1 into solution of step 2 and mix vigorously.
4. Filter and sterilize.

Multiple Electrolytes and Dextrose Injection (Elliott's B Solution)

Bill of Materials (Batch Size 10.5 L)					
Scale/mL		Item	Material	Qty	UOM
7.50	mg	1	Sodium chloride, USP	76.65	g
1.90	mg	2	Sodium bicarbonate, USP	19.95	g
0.80	mg	3	Dextrose hydrous, USP	8.40	g
0.30	mg	4	Magnesium sulfate, USP	3.15	g
0.30	mg	5	Potassium chloride, USP	2.10	g
0.20	mg	6	Calcium chloride-$2H_2O$, USP	2.10	g
0.20	mg	7	Sodium phosphate dibasic.$7H_2O$	2.10	g
0.10	mg	8	Phenolsulfonphthalein, USP	1.05	mg
QS	mL	9	Water for injection, USP	10.50	L
QS	–	10	Carbon dioxide, NF, to adjust pH	QS	–

Manufacturing Directions

1. Dissolve 42 mg of item 8 in 1 L of item 9; warm gently if necessary to approximately 40°C to make a stock solution.
2. Place 9 L of item 9 into a suitable mixing tank. Add items 2, 7, 1, 6, 4, 5, and 3, in order, one by one with constant stirring; allow each ingredient to dissolve completely before adding the next one.
3. Pipe 25 mL of the stock solution in step 1 to mixing tank and mix well. Check pH, QS the volume with item 9, keep a cover with item 10, and flush with item 10 to adjust the pH to 6.2 to 6.4.
4. Sample, filter through 0.22-μm filter, and transfer to clean vessel and fill. *Caution*: The solution should be filtered and filled as soon as possible after compounding because the pH may not be stable.
5. Rinse stoppers with purified water and autoclave in a solution of EDTA (62.5 g in 2.5 L) at 121°C for 1 hour; rinse at least 3 times with purified water.

Muromonab-CD3 Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Muromonab-CD3	1.00	g
0.45	mg	2	Sodium phosphate monobasic	0.45	g
1.80	mg	3	Sodium phosphate dibasic	1.80	g
0.80	mg	4	Sodium chloride	0.80	g
0.20	mg	5	Polysorbate 80	0.20	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Fill 5 mL into each vial, pH 6.5 to 7.5; buffered preparation. The proper name, Muromonab-CD3, is derived from the descriptive term *murine monoclonal antibody*. The CD3 designation identifies the specificity of the antibody as the Cell Differentiation (CD) cluster 3 defined by the First International Workshop on Human Leukocyte Differentiation Antigens.

Nalbuphine Hydrochloride

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Nalbuphine hydrochloride	10.00	g
2.00	mg	2	Sodium chloride	2.00	g
9.40	mg	3	Sodium citrate	9.40	g
12.60	mg	4	Citric acid	12.60	g
1.80	mg	5	Methyl paraben	1.80	g
0.20	mg	6	Propyl paraben	0.20	g
QS	mL	7	Hydrochloric acid for pH adjustment	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: pH adjusted to 3.5 to 3.7 with item 7. A 20-mg/mL strength has the same formula.

Naloxone Hydrochloride Injection (1 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Naloxone hydrochloride	1.00	g
8.35	mg	2	Sodium chloride	8.35	g
1.80	mg	3	Methyl paraben	1.80	g
0.20	mg	4	Propyl paraben	0.20	g
QS	mL	5	Hydrochloric acid for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.0 to 4.0 with item 5. Also available as paraben-free formula.

Naloxone Hydrochloride Injection (0.04 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.04	mg	1	Naloxone hydrochloride	0.04	g
8.60	mg	2	Sodium chloride	8.60	g
1.80	mg	3	Methyl paraben	1.80	g
0.20	mg	4	Propyl paraben	0.20	g
QS	mL	5	Hydrochloric acid for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.0 to 4.0 with item 5.

Naloxone Hydrochloride Injection (0.02 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.02	mg	1	Naloxone hydrochloride	0.02	g
9.00	mg	2	Sodium chloride	9.00	g
QS	mL	3	Hydrochloric acid for pH adjustment		
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.0 to 4.0 with item 3.

Nandrolone Decanoate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Nandrolone decanoate, USP, 5% excess	105.00	g
100.00	mg	2	Benzyl alcohol, NF, 5% excess	105.00	g
QS	mL	3	Sesame oil, USP	QS to 1.00	L

Manufacturing Directions

Note: Use clean, dry equipment for compounding and filling the product.

1. Heat approximately 0.8 L of item 3 to approximately 40°C. Use this preheated oil for the compounding of product.
2. Add item 1 to step 1; agitate until dissolved. Add a small amount of sesame oil, if necessary.
3. Add item 2 to the mixing tank and continue stirring.
4. QS to volume with sesame oil.
5. Filter through a 0.22-μm membrane filter into a sterile reservoir for filling.
6. Fill into type I 2-mL amber vials (presterilized at 330°C for at least 240 minutes) and 1888 gray stopper without coating and appropriate aluminum seal.

Nandrolone Phenylpropionate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Nandrolone phenylpropionate	25.00	g
0.40	mL	2	Ethyl oleate	0.40	L
0.60	mL	3	Arachis oil	0.60	L

Manufacturing Directions

1. Place items 2 and 3 in a suitable stainless steel 316 or higher temper-grade vessel, mix and filter through an appropriate system, and sterilize by dry heat at 160°C for 2 hours; allow to cool to 80°C.
2. In a separate vessel, add item 1 and portions of step 1 to dissolve item 1 completely. Add oil mixture from step 1 to make up the volume.
3. Filter through a presterilized assembly and fill 1.2 mL into type I flint ampoules.

Naphazoline Ophthalmic Drops

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
17.71	mg	1	Acid boric granular	17.71	g
1.50	mg	2	Hydroxypropyl methylcellulose 4000, cps	1.50	g
0.36	mg	3	Borax, sodium borate	0.36	g
1.00	mg	4	Edetate sodium	1.00	g
0.114	mg	5	Naphazoline hydrochloride, 5% excess	0.12	g
0.586	mL	6	Benzalkonium chloride, 17%, 7% excess	0.63	mL
QS	mL	7	Water for injection, USP	QS to 0.95	L

Manufacturing Directions

Use a thoroughly cleaned and rinsed steam-jacketed, glass-lined, or stainless steel tank (No. 304 or better) equipped with a speed-controlled agitator. Tank should have a cover. Foaming occurs due to benzalkonium chloride, which concentrates in foam; processing and filling systems should be designed to minimize foaming and allow rapid dissipation of foaming.

1. Bulk solution.
   a. Charge 80% of final volume of water into mixing tank.
   b. If using methylcellulose, heat deionized water to 90°C. While agitating, add and disperse methylcellulose by slowly sprinkling onto the surface of solution; mix to avoid excessive foaming. Allow 15 minutes for hydration of methylcellulose before discontinuing heating and allowing to cool to 40°C.
   c. While agitating, add and dissolve disodium edetate, benzalkonium chloride, boric acid, and sodium borate; continue cooling to 30°C (25–30°C); discontinue agitation and QS to 950 mL with deionized water. Start agitator and mix for at least 15 minutes at 30°C. Discontinue agitation and cooling. Sample.
2. Naphazoline hydrochloride concentrate solution. Dissolve naphazoline hydrochloride in 50 mL of deionized water, and sterile filter solution through a previously sterilized Millipore® filter unit containing a 0.22-μm membrane. Hold naphazoline solution under aseptic conditions for addition to bulk solution (after it has been autoclaved and cooled).
3. Prefiltration. Methylcellulose solutions filter at a slow rate. Recirculate solution until clear and transfer to holding or sterilization.
4. Sterilization and filling. Use either heat sterilization or sterile filtration. In heat sterilization, sterilize at 112°C to 115°C for 60 minutes, cool the solution to 25°C to 30°C, aseptically add the sterile naphazoline solution, and mix well. Set up a previously sterilized filter and transfer line with 10-μm stainless steel filter. Aseptically fill sterile solution into sterilized containers and apply sterile closure components. Sample. In sterile filtration, use Pall cartridge with Sartorius cartridge. Prepare and steam-sterilize the recommended filter units and aseptically fill the sterilize solution to which naphazoline solution has been added into each sterilized container and apply sterile closure. Sample.

Natamycin Ophthalmic Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Natamycin	50.00	g
0.20	mg	2	Benzalkonium chloride	0.20	g
QS	mL	3	Hydrochloric acid for pH adjustment		
QS	mL	4	Sodium hydroxide for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill into 15-mL glass bottles with dropper assembly.

Natural Estrogenic Substances Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.50	mg	1	Estrone, NF	1.50	g
0.50	mg	2	Estrogenic substances; items 1 and 2 combined, 2 mg	0.50	g
1.00	mg	3	Carboxymethylcellulose sodium, USP	1.00	g
9.00	mg	4	Sodium chloride, USP	9.00	g
1.00	mg	5	Sodium phosphate, USP	1.00	g
1:10	M	6	Benzalkonium, 50%, USP	1:10	M
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	mL	8	Acetic acid for buffering	QS	
QS	mL	9	Sodium acetate for buffering; see item 8	QS	

Note: For 5-mg strength, adjust fill volume.

Nedocromil Sodium Ophthalmic Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Nedocromil sodium	20.00	g
0.10	mg	2	Benzalkonium chloride	0.10	g
0.50	mg	3	Edetate sodium	0.50	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: pH 4 to 5.5; fill into 5-mL natural LDPE round eye drop bottle with controlled dropper tip and a natural polypropylene cap.

Neomycin and Prednisolone Acetate Ophthalmic Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
Part I					
5.50	mg	1	Borosilicate beads		
247.50	g	2	Prednisolone acetate, USP (10% overage)		
0.0066	mL	3	Water purified (distilled), USP	300.00	mL
0.0055	mL	4	P VA micronizing diluent	250.00	mL
0.0177	mL	5	Water purified (distilled), USP, ca.	800.00	mL
Part II					
0.3333	mL	6	Water purified (distilled), USP, ca.	15.00	L
14.00[a]	mg	7	Polyvinyl alcohol, 20–90	941.30	g
0.0003[a]	mL	8	Polysorbate 80, NF (use 10% solution)	141.00	mL
Part III					
0.8222	mL	9	Water purified (distilled), USP, ca.	37.00	L
0.01	mL	10	Propylene glycol, USP	675.00	mL
8.33	mg	11	Sodium acetate trihydrate, USP	562.30	g
3.85[b]	mg	12	Neomycin sulfate, USP (10% overage)	259.90[c]	g
11,500	U	13	Polymyxin B sulfate, USP (15% overage)	92.37[d]	g
Part IV					
0.0044	mL	14	Water purified (distilled), USP, ca.	200.00	mL
0.01	mg	15	Thimerosal, USP[e]	0.675	g
QS	mL	16	Water purified (distilled), USP, ca.; QS add parts II, III, and IV	60.00	L
QS	mL	17	Sterile filtrate QS parts II, III, IV	40.00	L
Part V					
0.0811	mL	18	Water purified (distilled), USP	3.65	L

[a] Includes amount contained in polyvinyl alcohol micronizing diluent. Polyvinyl alcohol micronizing diluent contains 1.0% polyvinyl alcohol 20–90 and 1.65% polysorbate 80, NF.
[b] Equivalent to 3.85 mg/mL neomycin base.
[c] The amount of neomycin sulfate to be added must be calculated on the basis of the manufacturer's assay value of the raw material lot used as per the following formula: 259.9 g neomycin base ∞ 1000 mg/mg/manufacturer's assay value (mg/mg) = g of neomycin sulfate required.
[d] The amount of Polymyxin B sulfate to be added must be calculated on the basis of the manufacturer's assay value of the raw material lot used as per the following formula: 776250000 U Polymyxin B sulfate/manufacturer's assay value (U/mg $\times$ 1000 mg/g = g of Polymyxin B sulfate required. (Assuming assay = 8403 U/mg.)T
[e] The amount of thimerosal to be added must be calculated on the basis of the manufacturer's assay value of the raw material lot used as per the following formula: 0.675 g $\times$ 100.0%/assay value(%) = g thimerosal required.

Manufacturing Directions

Caution: Hazardous handling of prednisolone and neomycin; observe protection and precaution. Protect the preparation from light after adding neomycin and Polymyxin B.

Part I

1. Add item 2 into a 2-L grinding jar filled to approximately half with glass beads; add 300 mL of item 5 to it and then 250 mL of item 4.
2. Seal the jar with a Teflon stopper and mix until the steroid has been wetted; remove the stopper and wrap the mount of jar with a double layer of aluminum foil and a double layer of parchment paper and secure it with steel wires.
3. Sterilize the jar by autoclaving for at least 2 hours and 30 minutes at 121°C; remove the jar from the autoclave and allow it to cool to room temperature.
4. Transfer 800 mL of item 5 into a 1-L flask; wrap the mouth of the flask with a double layer of aluminum foil and a double layer of parchment paper and secure the two rubber bands.
5. Sterilize item 5 by autoclaving for 30 minutes minimum at 121°C; remove the flask from the autoclave and allow it to cool to room temperature.
6. Wrap a Teflon stopper that will fit the mouth of the grinding jar with two layers of aluminum foil; sterilize the Teflon stopper by autoclaving for at least 30 minutes at 121°C.
7. Aseptically (under a laminar flow hood, with appropriate gowning) add as much of the 800 mL of sterile item 5 as it takes to fill the grinding jar to the neck. Seal the grinding jar with the sterilized Teflon stopper, cover the Teflon stopper with double layers of aluminum and double

layers of parchment paper, and secure the parchment paper and aluminum foil with two steel wires.
8. Place the grinding jar on the mill and grind until the particle size is approved by QC.

Part II
1. Measure out ca. 20 L of item 6 into a container suitable for heating. Begin mixing with a suitable mixer. Heat the item 5 to 85°C to 90°C.
2. Measure out 15 L of heated item 6 into a 20-L container; begin mixing with a propeller mixer.
3. Add item 7 slowly to the vortex. Avoid formation of excessive foam. Mix for at least 90 minutes until it is completely dissolved (mixing time not less than 90 minutes).
4. Add item 8, 10% solution, and mix well; cool to room temperature.

Part III
1. Measure out ca. 37 L of item 9 into a mixing tank suitably calibrated for a final QS of 60 L; begin mixing.
2. Add items 10, 11, 12, and 13, in order, allowing each to mix thoroughly or dissolve completely before adding the next.
3. Add part II to the mixing tank containing part III while mixing part III.
4. Use 3 to 4 L of item 9 to rinse the part II container, add the rinsings to the mixing tank, mix thoroughly.

Part IV
1. Weigh out item 15 and carefully transfer it to a suitable flask.
2. Add 200 mL of item 14 and mix until item 15 is dissolved.
3. Add part IV to combined parts II and III and mix thoroughly.
4. Rinse the part IV flask with ca. 200 mL of item 16 and add the rinsings to the mixing tank.
5. Allow any foam to dissipate and QS the combined solution of parts II, III, and IV (product base) to 60 L with item 16; mix thoroughly for at least 15 minutes.
6. Take a 60-mL sample of combined parts II, III, and IV product base for bulk assay.

Sterile Filtration
Note: Sterile filter 40-L of combined parts II, III, and IV base, using an approved 0.2-μm filter.

1. Sterilize for 1 hour (range 45–60 minutes) at 121°C (−0, +5°C) in an autoclave at 15 psi in a 100-L stainless steel pressure vessel. Transfer to solution preparation area.
2. Mix the product for at least 10 minutes before filtration.
3. Connect the sterilized filter and sterile filter with the aid of N_2 pressure (15–30 lb) into the sterilized 100-L stainless steel pressure vessel. *Note*: Before sterile filtration to the 100-L pressure vessel, perform the bubble point test at NLT 40 psi and on a 0.22-Lim in-line gas filter at 18 psi.
4. After completion of product filtration, flush the sterilizing filter with at least 10 L of water purified (distilled).
5. After filtration, decontaminate the outer surface of the bulk holding the pressure vessel and then transfer to filling cubicle; discard NLT 10 L through the sterilized filter prior to connecting on the sterile filling lead line.
6. QA sample for bulk assay. Discard any remaining base portion, after keeping 40 L of the combined parts II, III, and IV.

Sterilization
Sterilize filling unit, 20-L surge bottle, P2 sintered glass filter, and uniforms at 121°C (−0°, +2°C) and 15 psi for 1 hour.

Part V
1. Measure out and transfer item 18 into a suitable glass bottle. Seal the mouth of the bottle with two layers of aluminum foil and two layers of parchment paper; secure the aluminum foil and parchment paper with two rubber bands.
2. Sterilize item 18 by autoclaving for at least 60 minutes at 121°C. Remove the bottle from the autoclave and allow it to cool to room temperature.

Mixing Procedure
Note: Perform all mixing of steroid under aseptic conditions. Product is light sensitive.

1. Grind the steroid (part I) for at least 6 hours before mixing.
2. Aseptically receive 40.0 L of sterile filtered product base (combined parts II, III, and IV) into a sterilized glass bottle calibrated at 40.0 and 45.0 L.
3. Place the glass bottle containing the product base (combined parts II, III, and IV) on a magnetic mixing table.
4. Place the bottle and magnetic mixer in front of a laminar air flow hood.
5. Aseptically add a sterilized magnetic stirring bar to the glass bottle containing the product base. Adjust the mixing speed such that a 10.5-in. deep vortex is formed.
6. Aseptically pour the ground prednisolone acetate, part I, from the grinding jar through a sterilized polyethylene Buchner funnel into the bottle containing the product base. Rinse the grinding jar and the funnel with the sterilized water purified (distilled) (part V).
7. Add the rinsings to the bottle containing parts II, III, and I V. The volume of the suspension in the bottle should now be 45 L. Remove the Buchner funnel and insert a sterilized closing stopper into the mouth of the bottle containing combined parts I to V.
8. Allow the product to mix with a 0.5-in deep vortex for at least 2 hours. Continue mixing at this setting.

Homogenization Procedure
Homogenize the product suspension in a sterilized homogenizer. Filter the suspension through filter into an empty 45-L sterilized glass bottle located in the filling room. Aseptically add a sterilized magnetic stirring bar to the empty 45-L sterilized glass bottle located in the filling room. Place the empty 45-L sterilized glass bottle onto a magnetic mixing table. Adjust the homogenizer controls while cycling the suspension from the bottle through the sterilized homogenizer back to the bottle.

Sterile Filling
1. Transfer the radiation-sterilized bottles, plugs, and caps to the filling cubicle after swabbing their outer polyethylene packing with filtered methylated spirit and keep under the laminar flow hood.
2. Transfer the sterilized assembly line to the filling room; wear surgical gloves and uniforms. Aseptically connect the sterilized filling tubing and N_2 line from the 100-L pressure vessel to the surge bottle.
3. Aseptically fill 5.4 mL of sterile solution through P2 sintered glass into the sterilized container by using the automatic filling, plugging, and sealing machine and apply sterile closure components (plugs and caps). *Note*: While filtering, do not exceed to N_2 pressure of 5 to 10 lb.
4. Perform the bubble point test on a 0.22-μm inline gas filter before and after filtration at 18 psi.

Neomycin Sulfate–Polymyxin B Sulfate for Irrigation

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Neomycin base	40.00	g
200,000	U	2	Polymyxin B sulfate	2 MM	U
10.00	mg	3	Methyl paraben	10.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Fill 1 mL per ampoule.

Neostigmine Methylsulfate Injection Single-Dose Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.50	mg	1	Neostigmine methylsulfate	0.50	g
1.80	mg	2	Methyl paraben	1.80	g
0.20	mg	3	Propyl paraben	0.20	g
QS	mL	4	Sodium hydroxide for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to ca. 5.9 with item 4.

Neostigmine Methylsulfate Injection Multidose Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.50	mg	1	Neostigmine methylsulfate	0.50	g
1.80	mg	2	Glacial acetic acid	1.80	g
0.20	mg	3	Sodium acetate	0.20	g
4.50	mg	4	Phenol liquefied	4.50	g
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to ca. 5.9 with item 5.

Nesiritide for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.15	mg	1	Nesiritide, 5% excess	0.158	g
2.00	mg	2	Mannitol	2.00	g
0.21	mg	3	Citric acid monohydrate	0.21	g
0.294	mg	4	Sodium citrate dihydrate	0.294	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill 10 mL into each vial and lyophilize.

Netilmicin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Netilmicin, use netilmicin sulfate	12.00	g
4.00	mg	2	Sodium sulfite	4.00	g
1.30	mg	3	Methyl paraben	1.30	g
0.20	mg	4	Propyl paraben	0.20	g
5.40	mg	5	Sodium chloride	5.40	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take 0.9 L of item 6 into a jacketed stainless steel vessel; heat it to 70°C to 90°C.
2. Add and dissolve items 3 and 4 to complete solution.
3. Cool to room temperature.
4. Add item 2 and dissolve.
5. Add item 5 and dissolve.
6. Add item 1 and dissolve.
7. Check pH to 6.7 to 6.9; do not adjust.
8. Filter and sterilize.

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.50	mg	1	Netilmicin, use netilmicin sulfate	3.00	g
1.20	mg	2	Sodium sulfite	1.20	g
2.10	mg	3	Sodium metabisulfite	2.10	g
1.30	mg	4	Methyl paraben	1.30	g
0.20	mg	5	Propyl paraben	0.20	g
2.60	mg	6	Sodium sulfate	2.60	g
0.10	mg	7	Disodium edetate	0.10	g
QS	mL	8	Water for injection, USP	QS to 1.00	L

Niacinamide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Niacinamide, USP	100.00	g
5.00	mg	2	Liquefied phenol, USP	5.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Hydrochloric acid for pH adjustment	QS	

Nicardipine Hydrochloride for Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.50	mg	1	Nicardipine hydrochloride	2.50	g
48.00	mg	2	Sorbitol	48.00	g
0.525	mg	3	Citric acid monohydrate	0.525	g
0.09	mg	4	Sodium hydroxide	0.09	g
QS	mg	5	Citric acid monohydrate for pH adjustment	QS	g
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to around 3.5 with item 5 or 6. Fill into 10-mL ampoules for infusion after dilution.

Nicardipine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Nicardipine hydrochloride	1.00	g
48.90	mg	2	Sorbitol	48.90	g
0.09	mg	3	Sodium hydroxide	0.09	g
0.525	mg	4	Citric acid monohydrate	0.525	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Nikethamide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
250.00	mg	1	Nikethamide	250.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Place item 2 in a suitable stainless steel vessel, add item 1, and dissolve.
2. Check pH to 7.2 (7.0–7.3); do not adjust.
3. Filter the solution in step 1 into a staging vessel, using a 0.45-μm prefilter and 0.22-μm filter.
4. Fill 2 mL presterilized (e.g., 200°C for 4 hours) type I flint ampoules.
5. Autoclave at 121°C for 30 minutes.
6. Sample for clarity and sterility.

Nimesulide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Nimesulide	5.00	g
20.00	mg	2	Benzyl alcohol	20.00	g
10.00	mg	3	Lecithin (Lipoid E-80®)	10.00	g
100.00	mg	4	Dimethylacetamide	100.00	g
20.00	mL	5	Water for injection	20.00	mL
QS	mL	6	Propylene glycol	QS to 1.00	L

Nimodipine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.20	mg	1	Nimodipine	0.20	g
200.00	mg	2	Ethanol USP, 95%	200.00	g
170.00	mg	3	Polyethylene glycol 400	170.00	g
2.00	mg	4	Tertiary sodium citrate	2.00	g
0.30	mg	5	Citric acid	0.30	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Nystatin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Nystatin	50.00	g
50.00	mg	2	Pluronic F-68®	50.00	g
50.00	mg	3	Dimethylsulfoxide	50.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: The concentration of nystatin can be varied; the concentration of Pluronic and DMSO should be proportional to it. Store at 0°C. Lyophilized powder for reconstitution.

Octreotide Acetate Injection Single-Dose Ampoule

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Octreotide as octreotide acetate	50.00	mg
3.40	mg	2	Lactic acid	3.40	g
45.00	mg	3	Mannitol	45.00	g
QS	mg	4	Sodium carbonate for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to between 3.9 and 4.7 with item 4; a 1-mg/mL concentration is also available.

Octreotide Acetate Injection Multidose Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Octreotide as octreotide acetate	50.00	mg
3.40	mg	2	Lactic acid	3.40	g
45.00	mg	3	Mannitol	45.00	g
5.00	mg	4	Phenol liquefied	5.00	g
QS	mg	5	Sodium carbonate for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to between 3.9 and 4.7 with item 5; a 1-mg/mL concentration is also available.

Octreotide Acetate Injection Depot

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Octreotide base as octreotide acetate[a]	11.20	mg
188.80	mg	2	DL-Lactic and glycolic acid copolymer	188.80	g
41.00	mg	3	Mannitol	41.00	g
Diluent					
5.00	mg	1	Carboxymethylcellulose sodium	5.00	g
6.00	mg	2	Mannitol	6.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

[a] Equivalent to labeled quantity of 10, 20, or 30 mg octreotide base. Fill powder into 5-mL vial; provide 2 mL of diluent.

Ofloxacin Otic Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3.00	mg	1	Ofloxacin	3.00	g
0.025	mg	2	Benzalkonium chloride	0.025	g
9.00	mg	3	Sodium chloride	9.00	g
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 6.0 to7.0 with item 4 or 5. Fill 5 mL or 10 mL into plastic dropper bottle.

Ondansetron Hydrochloride Injection Single-Dose Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Ondansetron as ondansetron hydrochloride dihydrate equivalent	2.00	g
9.00	mg	2	Sodium chloride	9.00	g
0.50	mg	3	Citric acid monohydrate	0.50	g
0.25	mg	4	Sodium citrate dihydrate	0.25	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill 2 mL into each vial. pH 3.3 to 4.0.

Ondansetron Hydrochloride Injection Multidose Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Ondansetron as ondansetron hydrochloride dihydrate equivalent	2.00	g
8.30	mg	2	Sodium chloride	8.30	g
0.50	mg	3	Citric acid monohydrate	0.50	g
0.25	mg	4	Sodium citrate dihydrate	0.25	g
1.20	mg	5	Methyl paraben	1.20	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Fill 20 mL into each vial. pH 3.3 to 4.0.

Ondansetron Hydrochloride Injection Premixed for Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.64	mg	1	Ondansetron as ondansetron hydrochloride dihydrate equivalent	0.64	g
50.00	mg	2	Dextrose	50.00	g
0.52	mg	3	Citric acid monohydrate	0.50	g
0.23	mg	4	Sodium citrate dihydrate		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill 50 mL into each flexible plastic container specially formulated, nonplasticized, thermoplastic copolyster; pH 3.3 to 4.0.

Oprelvekin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Oprelvekin (interleukin IL-11)[a]	1.00	g
4.60	mg	2	Glycine	4.60	g
0.32	mg	3	Sodium phosphate dibasic heptahydrate	0.32	g
0.11	mg	4	Sodium phosphate monobasic monohydrate	0.11	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

[a] Specific activity ca. 8×10^6 U/mg; adjust for activity. Fill 5 mL into each 5-mL vial and lyophilize. On reconstitution with 5 mL water for injection, the pH is around 7.0.

Orphenadrine Citrate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
30.00	mg	1	Orphenadrine citrate, NF	30.00	g
1.00	mg	2	Sodium bisulfite, USP	1.00	g
2.90	mg	3	Sodium chloride, USP	2.90	g
0.10	mg	4	Benzethonium chloride, NF	0.10	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Sodium hydroxide for pH adjustment	QS	

Oxacarbazepine-10 Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.50	mg	1	Oxacarbazepine-10	2.50	g
47.50	mg	2	Dextrose anhydrous, USP	47.50	g
QS	ft^3	3	Nitrogen gas, NF	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable vessel, take approximately 0.9 L of item 4. Bubble with item 3 for 20 minutes.
2. Heat to 60° to 80°C and add item 1, mix, and dissolve.
3. Cool to room temperature.
4. Add item 2, mix, and dissolve.
5. Filter through a 0.22-μm membrane filter and fill into type I glass vials.
6. Sterilize by autoclaving at 121°C for 15 minutes.

Oxazepine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4] oxazepine base	63.00	g
0.70	mL	2	Propylene glycol	2.10	L
QS	mL	3	Hydrochloric acid, 10%, for pH adjustment, ca.	51.00	mL
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Add and dissolve item 1 into item 2.
2. Add 800 mL of item 4 and mix well.
3. Check and adjust pH to 6.1 to 6.3 with item 3 and heating to 60°C.
4. Make up volume with item 4.
5. Sterile filter through a 293-mm Selas filter or equivalent with a 0.22-μm membrane.
6. Fill into glass ampoules or vials, 2.0 mL (each unit containing 40 mg of item 1).

Oxendolone Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Oxendolone	100.00	g
5.00	mg	2	Sodium carboxymethylcellulose	5.00	g
80.00	mg	3	Sorbitol, NF, crystalline powder nonpyrogenic	80.00	g
10.00	mg	4	Benzyl alcohol, NF	10.00	g
1.40	mg	5	Methyl paraben, NF	1.40	g
0.14	mg	6	Propyl paraben, NF	0.14	g
2.00	mg	7	Polysorbate 80, NF	2.00	g
QS	mL	8	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Preparation of sterile bulk suspension.
   a. Take sufficient quantity of item 8 and heat to 80°C; add and dissolve items 5 and 6 and cool to room temperature.
   b. Add item 2 slowly with gentle stirring until smoothly dispersed.
   c. Add item 3 and stir to dissolve.
   d. In a separate container, heat sufficient quantity of item 8 to 50°C and add item 1 and disperse evenly; cool to room temperature and add items 4 and 7 and mix gently to avoid air entrapment.
   e. Add the two suspensions above and mix for 2 to 3 minutes.
   f. Add item 3, stir, and make up the volume.
2. Preparation of vials. Use type I 5-mL borosilicate vials.
   a. Wash and dry vials and load into suitable containers for sterilization.
   b. Sterilize by using dry heat at 200°C (–0, +500°C) vial temperature for 225 minutes (–0, +360 minutes) while maintaining the oven temperature at 225°C (±10°C) for the duration of the cycle.
   c. Deliver to the sterile filling area.
3. Preparation of stoppers. Use type isobutylene isoprene rubber-Daikyo F713 stoppers.
   a. Wash by using the rubber cycle (slow tumbling) with Triton X-100 detergent.
   b. Dry in dryer at 55°C.
   c. Rack, inspect, and wrap the stoppers for autoclaving.
   d. Sterilize in an autoclave for 1 hour at 121°C and vacuum dry with heat for a minimum of 4 hours at a temperature not exceeding 90°C.
   e. Deliver to the sterile filling area.
4. Filling.
   a. Using aseptic technique, connect bulk suspension container to a suitable filling machine.
   b. With continuous gentle stirring of bulk suspension, aseptically fill 2.2 mL of suspension into each clean, sterile vial.
   c. Insert a sterile rubber stopper into each filled vial and apply overcap.
   d. Remove from sterile area and pack into bulk container and label each container with product lot number.
   e. Sample for testing.

Oxymorphone Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Oxymorphone hydrochloride	1.00	g
8.00	mg	2	Sodium chloride	8.00	g
1.80	mg	3	Methyl paraben	1.80	g
0.20	mg	4	Propyl paraben	0.20	g
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Fill into vials; delete items 3 and 4 for ampoule filling.

Oxytetracycline Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Oxytetracycline, use oxytetracycline dihydrate	65.00	g
3.34	mg	2	Sodium formaldehyde sulfoxylate	3.34	g
0.20	mg	3	Propyl gallate	0.20	g
11.00	mg	4	Monothioglycerol	11.00	g
0.64	mL	5	Propylene glycol	0.64	L
0.005	mL	6	Propylene glycol	5.00	mL
0.05	mL	7	Propylene glycol	50.00	mL
0.026	mL	8	Propylene glycol, QS to ca.	26.00	mL
0.029	mL	9	Monoethanolamine	29.00	mL
25.00	mg	10	Magnesium chloride	25.00	g
10.00	mg	11	Citric acid	10.00	g
20.00	mg	12	Lidocaine HCl	20.00	g
0.114	mL	13	Water for injection, USP	114.00	mL
0.025	mL	14	Water for injection, USP	25.00	mL
0.002	mL	15	Water for injection, USP	2.00	mL
0.008	mL	16	Water for injection, USP	8.00	mL
QS		17	Nitrogen gas, NF		

Manufacturing Directions

Note: Use glass-lined container. Provide N_2 cover throughout. Be careful about the order of steps and intermediate times required.

1. Put item 13 into a suitable vessel and bubble item 17 for 20 minutes.
2. Add item 2 to step 1 and dissolve by stirring.
3. In a separate container, dissolve item 3 in item 6 and mix to step 2.
4. Add item 4 slowly over a 5-minutes period. Ensure complete dissolution.
5. Concurrently with step 4, add item 1 and stir to dissolve.
6. Take item 5 in a separate tank and keep under cover of item 17; maintain at 15°C by circulating chilled water through walled stainless steel vessel.
7. Dissolve item 10 into item 14 and add to step 6.
8. Transfer step 2 solution to step 6 and mix vigorously.
9. Dissolve item 12 into item 7 and add to step 6; wait for 10 minutes.
10. Dissolve item 11 into item 15 and add to step 6. Check pH; it should be around 7.0
11. Add item 9 to step 6 to get a final pH of 8.5 to 8.6. Use item 16 for washings.
12. Make up volume with item 8.
13. Filter the solution under pressure of item 17 using a 0.45-μm prefilter and 0.22-μm filter into a staging glass tank.
14. Fill aseptically into type I 30-mL flint glass vials.

Oxytetracycline Injectable Solution for IM + IV Veterinary Application (500 mg/10 mL)

Formulation

I. Oxytetracycline hydrochloride, 5.7 g;.
II. Kollidon 17 PF [1], 10.0 g; reducing agent, 0.5 g; (e.g. Rongalite® C, BASF); water for injectables, add 100 mL.
III. Magnesium oxide, 0.46 g.
IV. Ethanolamine to adjust pH 8.8.

Manufacturing Directions

Suspend III in solution II, pass continuously nitrogen through the solution to avoid oxidation, and add slowly I to the well-stirred solution. Adjust the pH with IV.

Properties of the solution

Yellow, clear solution.

Remarks

The absence of oxygen during manufacturing and in the final packaging and a good quality of oxytetracycline HCl are essential to avoid the oxidation (= dark solution).

The function of Kollidon 17 PF not only is the solubilization of oxytetracycline but also the reduction of its local toxicity.

The reducing agent must be selected in accordance with the legislation of the corresponding country.

Oxytetracycline Sustained-Release Injectable for IM Veterinary Application (2.2 g/10 mL)

(According to U.S. Patent 4.018.889 (1976)

Formulation

Oxytetracycline, 22.65 g; magnesium oxide, 1.92 g; Soluphor P [1], 40.00 g; Kollidon 17 PF [1], 5.00 g; sodium formaldehyde sulfoxylate, 0.44 g; 2-aminoethanol, 3.84 g; water of injectables, QS, add 100.00 mL.

Manufacturing Directions

Mix the water and the Soluphor P and dissolve the Kollidon 17 PF in the mixture. Heat the solution to 75°C. Add the sodium formaldehyde sulfoxylate and stir until dissolved. After the magnesium oxide has been suspended, slowly stir in the oxytetracycline until a clear solution is obtained. After the solution has cooled, set to pH 8.5 with aminoethanol.

Remarks

The quality of the oxytetracycline and the complete absence of oxygen during the manufacturing and packaging of the solution is essential to obtain a acceptable chemical stability and no dark color.

The reducing agent, sodium formaldehyde sulfoxylate (rongalite, C, BASF), must be selected in accordance with the legislation of the corresponding country.

Oxytocin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Sodium acetate trihydrate USP	2.00	g
5.10	mg	2	Sodium chloride, USP	5.10	g
10.00	U	3	Oxytocin acetate powder (300 U/mg)	33.333[a]	mg
5.00	mg	4	Chlorobutanol, NF, anhydrous crystals	5.00	g
2.20	mg	5	Glacial acetic acid, USP, for pH adjustment	2.20	g
QS	mL	6	Nitrogen gas, NF	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

[a] Adjust according to potency.

Manufacturing Directions

Note: Oxytocin is a potent drug, which can be absorbed by the nasal and buccal administration route. It is particularly hazardous for women, especially during the last trimester of pregnancy. Prepare solution in a clean glass-lined tank or a 316 stainless steel tank, cleaned according to approved SOPs.

1. Preparation of water. Collect ca. 90% to 95% of final volume of water for injection in a suitable tank. Determine pH (range 5.5–6.5). Sample for testing.
2. Preparation of solution.
   a. Bubble sterile-filtered N_2 into water in the tank; continue bubbling throughout the preparation.
   b. Add sodium acetate, acetic acid glacial, sodium chloride, and chlorobutanol, in order, with mixing. Check and record pH of the solution. Adjust to pH 3.9 to 3.95 by adding acetic acid. Adjust pH with acetic acid.
   c. While bubbling N_2 gas, add the oxytocin acetate. Mix well. Adjust pH to 3.9 to 3.95 with 1 N acetic acid freshly prepared by 6.0 mL glacial acetic acid and 94 mL water for injection.
3. Preparation of sterile apparatus.
   a. Prepare a 0.2-μm filter and sterilize in autoclave at 121°C for 30 to 35 minutes slow exhaust.
   b. Sterilize all Pyrex bottle fittings in an autoclave at 121°C for 30 to 35 minutes.
   c. Sterilize a sufficient number of Pyrex bottles with dry heat (oven) at 245°C to 330°C for 2 hours and 445 minutes to 3 hours and 30 minutes.
   d. Aseptically filter through a 0.2-μm membrane assembly with an approved filter in an N_2 atmosphere.
4. Preparation of ampoules. Wash and dry ampoules and load into appropriate containers for sterilization. Sterilize by using a dry-heat oven at 245°C to 330°C for 2 hours and 45 minutes to 3 hours and 30 minutes. May use equivalent cycle to assure sterility, pyrogen-free ampoules. Deliver to sterile filling area.
5. Filling.
   a. Connect bulk solution container by using aseptic technique to the filling machines. Fill aseptically specified amount in clean, dry sterile ampoule.
   b. Displace headspace air with sterile N_2 aseptically and immediately seal each ampoule. Sample for testing. Do not autoclave.

Oxytocin Injection, USP (20 U/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	U	1	Oxytocin, USP	20,000	U
5.00	mg	2	Chlorobutanol anhydrous, USP	5.00	g
0.25	%	3	Acetic acid	0.25	%
QS	mL	4	Water for injection, USP	QS to 1.00	L

Paclitaxel Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
6.00	mg	1	Paclitaxel	6.00	g
527.00	mg	2	Cremophor® EL purified (polyoxyetylated castor oil)[a]	527.00	g
0.497	mL	3	Dehydrated alcohol[b]	497.00	mL

[a] Paclitaxel is dissolved in an organic solvent as the primary vehicle, that is, dimethylacetamide (DMA) or dimethylsulfoxide (DMSO), and then followed with a secondary solvent, such as polyethyleneglycol 400 (PEG), to stabilize the drug in solution for subsequent (final) dilution in an aqueous solvent. A preferred final solvent is an aqueous lipid emulsion such as emulsified soybean oil (e.g., Intralipid® or Liposyn®, Soyacal®, or Travemulsion®).
[b] Paclitaxel injection without Cremophor: 49.7% v/v final preparation. Fill 5, 16.7, or 50 mL into each vial.

Palivizumab for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Palivizumab	100.00	g
47.00	mM	2	Histidine	47.00	mM
3.00	mM	3	Glycine	3.00	mM
56.00	mg	4	Mannitol	56.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill 1 mL and lyophilize; dilute concentrations for higher volume fill for lyophilization.

Pancuronium Bromide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.20	mg	1	Sodium acetate anhydrous, USP	1.20	g
3.20	mL	2	Glacial acetic acid, USP, for pH adjustment	3.20	mL
QS	mL	3	Glacial acetic acid, USP, for tonicity adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
10.00	mg	5	Benzyl alcohol, NF	10.00	g
2.00	mg	6	Pancuronium bromide	10.00	g
QS	mg	7	Sodium chloride, USP, for tonicity adjustment	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Prepare the solution in a glass-lined or 316 stainless steel tank.
2. Add water for injection to ca. 95% of the final volume into tank. If necessary, cool the water to within the temperature range of 20°C to 30°C.
3. Add and dissolve the sodium acetate with mixing.
4. Check and record the pH. Adjust to pH 4.0 (range 3.9–4.1) with the slow addition of either glacial acetic acid or 10% sodium hydroxide.
5. With mixing, add benzyl alcohol. Mix until the solution is uniform.
6. With mixing, add and dissolve sodium chloride to adjust tonicity.
7. Using extreme care in handling, add and dissolve the pancuronium bromide with mixing.
8. QS to final volume with water for injection.
9. Check pH. Readjust to 4.0 (range 3.9–4.1), with either glacial acetic acid or 10% sodium hydroxide, if necessary.
10. Aseptically filter the solution through a 0.22-μm (or finer) membrane.
11. Aseptically fill solution into ampoules.
12. Inspect and label container.
13. Sample for testing.

Parenteral Nutrition Fat Emulsion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Safflower oil, winterized	50.00	g
50.00	mg	2	Soybean oil, winterized	50.00	g
9.00	mg	3	Egg phosphate, purified, reduced electrolytes	9.00[a]	g
25.00	mg	4	Glycerin, USP	25.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Nitrogen gas, NF	QS	
QS	mL	7	Sodium hydroxide for pH adjustment	QS	

[a] Range 9.0 to 12.0 g.

Manufacturing Directions

1. Take the amount of item 5 that is equal to the final volume, heat to 70°C to 90°C, and protect with item 6. Maintain this atmosphere throughout processing.
2. Add and disperse item 3 into a portion of item 5 in step 1 with agitation, keeping temperature at 50°C to 90°C.
3. Add and dissolve item 4 previously filtered through a 0.8-μm membrane filter, using a homogenizer to increase degree of dispersion.
4. Filter the dispersion through a cellulose acetate (Millipore®) 0.45-μm or equivalent membrane.
5. Check pH and adjust to 8.5 to 9.5 with item 7 and maintain this pH throughout the process.
6. Filter oils (items 1 and 2) through a 0.45-μm filter and heat to 65°C to 95°C and add to the aqueous phase with agitation to form a coarse emulsion.
7. Homogenize in a homogenizer at a pressure of 5000 psi (range 4000–8000 psi) with a minimum of 10 passes or equivalent.
8. Check pH and adjust again to 8.5 to 9.5.
9. Filter emulsion through a 0.8-μm cellulose acetate filter (Millipore) into a holding tank.
10. Homogenize again with at least three passes at the above specification, and make up volume with item 5. Check and adjust pH again.
11. Fill by using a displacement filler into syringes maintained to reduce foaming; add rubber plunger, add cap, and autoclave. Alternative filling is in a bottle.
12. Sample.

Paricalcitol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	μg	1	Paricalcitol	5.00	mg
0.30	mL	2	Propylene glycol	0.30	L
0.20	mL	3	Alcohol	0.20	L
QS	mL	4	Water for injection, USP	QS to 1.00	L

Pegademase Bovine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
250.00	U	1	Pegademase bovine	250,000	U
1.20	mg	2	Sodium phosphate monobasic	1.20	g
5.58	mg	3	Sodium phosphate dibasic	5.58	g
8.50	mg	4	Sodium chloride	8.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: One unit of activity is defined as the amount of ADA that converts 1 μM of adenosine to inosine per minute at 25°C and pH 7.3. Fill 1.5 mL into each ampoule for single use.

Pegaspargase Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
750.00	IU	1	PEG-L-Asparaginase[a]	750,000	IU
5.58	mg	2	Sodium phosphate dibasic	5.58	g
1.20	mg	3	Sodium phosphate monobasic	1.20	g
8.50	mg	4	Sodium chloride	8.50	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

[a] 750 IU±20%. Fill 5 mL per vial.

Peginterferon Alpha-2b for Injection

Bill of Materials (Batch Size 1000 vials L)					
Scale/mL		Item	Material	Qty	UOM
74.00	mg	1	Peginterferon alpha-2b	74.00	mg
1.11	mg	2	Dibasic sodium phosphate anhydrous	1.11	g
1.11	mg	3	Monobasic sodium phosphate dihydrate	1.11	g
59.20	mg	4	Sucrose	59.20	g
0.074	mg	5	Polysorbate 80	0.074	g

Note: Fill into 2-mL vials; reconstitute with 0.7 mL of sterile water for injection; other strengths include 118.4, 177.6, and 222 μg per vial.

Penicillin G Benzathine and Penicillin G Procaine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
150,000	U	1	Penicillin G as the benzathine salt	150 MM	U
150,000	U	2	Penicillin G as the procaine salt	150 MM	U
0.012	mg	3	Citric acid	0.012	g
0.006	mg	4	Sodium citrate	0.006	g
5.00	mg	5	Lecithin	5.00	g
5.50	mg	6	Carboxymethylcellulose	5.50	g
5.50	mg	7	Povidone	5.50	g
1.00	mg	8	Methyl paraben	1.00	g
0.10	mg	9	Propyl paraben	0.10	g
QS	mL	10	Water for injection, USP	QS to 1.00	L

Penicillin G Benzathine Injectable Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
600,000	U	1	Penicillin G as the benzathine salt	600 MM	U
3.00	mg	2	Polyvinylpyrrolidone	3.00	g
6.00	mg	3	Sodium citrate	6.00	g
0.01	mg	4	Lecithin	0.01	g
3.00	mg	5	Carboxymethylcellulose	3.00	g
1.00	mg	6	Methyl paraben	1.00	g
0.10	mg	7	Propyl paraben	0.10	g
QS	mL	8	Water for injection, USP	QS to 1.00	L

Pentobarbital Sodium Solution Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Pentobarbital sodium	50.00	g
0.40	mL	2	Propylene glycol	0.40	L
0.10	mL	3	Alcohol, USP	0.10	L
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to ca. 9.5 with item 4 or 5. Other strengths, 1- and 2.5-g/vial in multidose vials. Do not use if any precipitate appears.

Pentostatin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Pentostatin	10.00	g
50.00	mg	2	Mannitol	50.00	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill 1 mL per vial and lyophilize; for higher fill volume, adjust levels accordingly. Adjust pH to 7.0 to 8.5 with item 3 or 4.

Pentylenetetrazol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Pentylenetetrazol	100.00	g
1.80	mg	2	Methyl paraben, USP	1.80	g
0.20	mg	3	Propyl paraben, USP	0.20	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Sodium hydroxide for pH adjustment	QS	

Pheniramine Maleate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
22.50	mg	1	Pheniramine maleate	22.50	g
QS	mL	2	Sodium hydroxide for pH adjustment		
QS	mL	3	Hydrochloric acid for pH adjustment		
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Dissolve item 1 in item 4 in a suitable 316 or higher temper-grade stainless steel vessel.
2. Check pH and adjust to between 4.5 and 5.0 with item 2 or 3.
3. Filter solution through presterilized assembly by using a 0.45-μm prefilter and a 0.22-μm filter into a sterilized staging vessel.
4. Fill 2.15 mL into presterilized type I amber ampoules (presterilized at 200°C for 4 hours).
5. Autoclave filled ampoules at 116°C for 30 minutes.
6. Sample for assay, sterility, and clarity testing.

Phenol Saline Diluent

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
9.00	mg	1	Sodium chloride, USP	9.00	g
4.00	mg	2	Liquefied phenol, USP	4.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Phenylbutazone and Dipyrone Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
150.00	mg	1	Phenylbutazone	150.00	g
150.00	mg	2	Dipyrone	150.00	g
20.00	mg	3	Lidocaine	20.00	g
20.00	mg	4	Sodium hydroxide, USP	20.00	g
2.00	mg	5	Sodium metabisulfite	2.00	g
1.00	mg	6	Disodium edetate	1.00	g
0.25	mL	7	Propylene glycol	0.25	L
QS	mL	8	Water for injection, USP	QS to 1.00	L
QS	mL	9	Sodium hydroxide for pH adjustment	QS	
QS		10	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Dissolve item 4 in ca. 0.2 L of item 8. Add item 1 with stirring.
2. Check and adjust pH to 13 to 14 with item 9; continue stirring.
3. Dissolve item 3 in item 7 in a separate vessel and stir to a clear solution.
4. Add step 3 to step 2.
5. Dissolve item 2 in 0.2 L (or a suitable amount) of item 8 and add to step 4.
6. Dissolve item 5 and 6 in small amount of item 9 and add to above solution. Make up the volume with item 9.
7. Check and adjust pH to 10 (9.5–10.5) with item 9.
8. Filter through a presterilized filtration assembly by using a 0.45-μm prefilter and a 0.22-μm filter into a staging sterilized vessel.
9. Fill 3 mL solution into type I amber ampoules with pre- and postflush with item 10; presterilize ampoules at 200°C for 4 hours.
10. Autoclave at 121°C for 30 minutes.
11. Sample for testing assay, clarity, and sterility.

Phenylbutazone Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
200	mg	1	Phenylbutazone, USP (use sodium salt in equivalent quantity)	200.00	g
15.00	mg	2	Benzyl alcohol, NF	15.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Sodium hydroxide for pH adjustment	QS	

Phenylephrine and Zinc Sulfate Ophthalmic Drops

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Qty	UOM
Part I					
		1	Water purified (distilled), USP	10.00	L
14.00	mg	2	Polyvinyl alcohol, 20–90	0.63	kg
Part II					
		3	Water purified (distilled), USP	30.00	L
2.00	mg	4	Sodium citrate dihydrate, USP	90.00	g
1.10	mg	5	Sodium metabisulfite	49.50	g
7.10	mg	6	Sodium chloride, USP	319.50	g
1.32	mg	7	Phenylephrine hydrochloride, USP (10% overage)	59.40	g
2.75	mg	8	Zinc sulfate, USP (10% overage)	123.75	g
0.533	mg	9	Sodium hydroxide, NF	23.99	g
QS	mL	10	1 N Sodium hydroxide, NF[a]	QS	mL
Part III					
		11	Water purified (distilled), USP	100.00	mL
0.05	mg	12	Thimerosal, USP	2.25[b]	g
QS	mL	13	Water purified (distilled), USP	QS to 45.00	L

[a]For pH adjustment only.
[b]The amount of thimerosal to be added must be calculated on the basis of the assay value of the raw material lot used according to the following formula: 2.25 g × 100.0%/assay value (%) = g thimerosal required.

Manufacturing Directions

Part I

1. Measure out ca. 10 L of item 1 into a jacketed stainless steel pressure vessel. Begin mixing with a suitable mixer and heat it to 85°C to 90°C.
2. When the temperature reaches 85°C to 90°C, turn off the heat source. Begin mixing item 1 with a propeller mixer.
3. Add item 2 slowly to the vortex. Avoid formation of excessive foam. Mix for at least 90 minutes until it is completely dissolved. Cool with force cooling to room temperature.

Part II

1. Measure out ca. 30 L of item 3 into a mixing tank suitably calibrated for a final QS of 45 L. Begin mixing.
2. Add items 4 to 9, in order, allowing each to dissolve completely before adding the next. Mix well.
3. Sample for pH (range 6.8–7.0). If necessary, adjust the pH to 6.8 to 7.0 with item 10.
4. Add part I to part II while mixing part II. Use 2.5 to 4.0 L of water purified (distilled) to rinse the part I container, pump, and hoses. Add the rinsings to the mixing tank.

Part III

1. Dissolve item 12 in ca. 100 mL of item 11. Add part III to combined parts I and II and mix thoroughly.
2. Rinse the flask containing item 12 with ca. 100 mL of item 13 and add the rinsings to the batch.
3. Allow any foam to dissipate and QS the batch to 45 L with item 13. Sample.
4. Mix thoroughly for at least 15 minutes.
5. Before filtration, mix the product for at least 10 minutes.
6. Sterile-filter with the aid of N_2 pressure (15–30 lb). Before sterile filtration, perform bubble point test at NLT 40 psi. Sample.
7. Aseptically fill sterile solution into sterilized containers. Sample.

Phenylpropanolamine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
75.00	mg	1	Phenylpropanolamine hydrochloride	75.00	g
5.00	mg	2	Chlorobutanol anhydrous, USP	5.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Phenytoin Sodium Injection

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
100.00	mg	1	Polyvinylpyrrolidone, USP	100.00	g
1.00	mL	2	Sodium hydroxide, 1 N solution	10.00	mL
50.00	mg	3	Phenytoin sodium[a]	50.00	mg
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	ft^3	6	Nitrogen gas, NF	QS	

[a]Adjusted to 100% purity assay basis.

Manufacturing Directions

1. Put 0.75 L of item 5 into a jacketed stainless steel vessel; heat it to 40°C to 45°C. Provide item 6 cover throughout.
2. Add item 1 with vigorous mixing until completely dissolved.
3. Cool to room temperature.
4. Add item 2 in small portions and mix well.
5. Add item 3 and dissolve.
6. Check and adjust pH to 12.1 to 12.3 with item 4.
7. Make up volume to 0.98 L with item 5.
8. Check and adjust pH again as in step 6 to 12.2.
9. Make up volume with item 5.
10. Filter with Pall membrane in a Millipore® assembly presterilized under N_2 pressure.
11. Fill under item 6 pre- and postflush into type I glass ampoules aseptically.

Phytonadione (Vitamin K_1) Injection

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
10.00	mg	1	Phytonadione, USP (vitamin K)	10.00	g
200.00	mg	2	Polysorbate 20, NF (sp. gr. 1.08)	200.00	g
500.00	mg	3	Glycerin, USP (sp. gr. 1.249)	500.00	g
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide 10% for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Weigh item 2 into a clean compounding tank and bring temperature to approximately 45°C (not to exceed 50°C). Take a small portion of polysorbate 20 out and put it in a smaller container. Keep N_2 blanket over the contents of the vessel.
2. Weigh phytonadione under subdued light into another vessel. Pour warm polysorbate 20 from the compounding tank. Mix and pour into the compounding tank and give two more rinses with warm polysorbate 20.
3. Stir to a homogenous mixture.
4. Add approximately 600 mL of water for injection to the compounding tank and mix thoroughly by stirring.
5. Add glycerin to the compounding tank. Mix thoroughly.
6. Check pH, and if necessary adjust with item 5 to between 6.0 and 7.0. Do not adjust pH if it is already within this range.
7. Bring to final volume with water for injection and mix well.
8. Withdraw a 10-mL sample for testing.
9. If approved, filter batch through a sterile 0.22-μm filter into a receiving vessel in the clean room. Keep an N_2 blanket over contents of the receiving vessel.
10. Fill with a postfill flush of N_2. Use type I flint vials sterilized and red uncoated stoppers.

Phytonadione (Vitamin K_1) Injection

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
9.00	mg	1	Benzyl alcohol, NF	9.00	g
41.21	mg	2	Dextrose monohydrate, USP, use dextrose, Powder anhydrous, USP	37.50	g
2.10	mg	3	Phytonadione, USP, 5% excess	2.10	g
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
70.00	mg	5	Polysorbate 80, NF	70.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Preparation.
   a. Add water for injection to ca. 75% of the final volume into glass-lined, light-protected tank.
   b. Add and dissolve dextrose. Add in portions of benzyl alcohol. Mix in another container polysorbate 80 and phytonadione. Add the dextrose solution.
   c. Check and adjust pH to 6.5 (range 6–7) with 1 N sodium hydroxide solution. Record volumes of each used.
   d. QS with water for injection to final volume.
   e. Sample for testing.
   f. Sterilize an approved 0.2- or 0.22-μm membrane filter with an approved prefilter.
   g. Filter the solution through the sterilized filter unit into a sterile, glass-lined holding container.
2. Preparation of ampoules.
   a. Wash and dry type 1 1-mL sulfur-treated ampoules and load into appropriate containers for sterilization.
   b. Sterilize using dry heat at 245°C for at least 3 hours and 25 minutes or an equivalent cycle to ensure sterile, pyrogen-free bottles.
   c. Deliver to the sterile filling area.
3. Filling.
   a. Connect bulk solution container by aseptic technique to the filling machines.
   b. Aseptically fill 0.65 mL (range 0.6–0.7 mL) into each clean, sterile ampoule.
   c. Immediately seal each ampoule.
   d. Sample for testing.
   e. Finishing. Sample for testing.

Phytonadione Injection—Aqueous Colloidal Solution of Vitamin K_1

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
10.00	mg	1	Phytonadione	10.00	g
70.00	mg	2	Polyoxyethylated fatty acid derivative	70.00	g
37.50	mg	3	Dextrose	37.50	g
9.00	mg	4	Benzyl alcohol	9.00	g
QS	mL	5	Hydrochloric acid for pH adjustment		
QS	mL	6	Sodium hydroxide for pH adjustment		
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 5 to 7; lower strength of 2 mg/mL.

Piperacillin Sodium and Tazobactam Sodium Injection

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
40.00	mg	1	Piperacillin as piperacillin sodium	40.00	g
10.00	mg	2	Tazobactam	10.00	g
20.00	mg	3	Dextrose hydrous, USP	20.00	g
2.00	mg	4	Sodium citrate dihydrate	2.00	g
QS	mL	5	Hydrochloric acid for pH adjustment		
QS	mL	6	Sodium bicarbonate for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Fill 50 mL into a PL2040 plastic container; keep frozen until administered. Adjust pH to 4.5 to 6.8 with item 5 or 6. Other strengths: 3.375 g/50 mL (item 3, 350 mg and item 4, 150 mg per bag) and 4.50 g/100 mL (item 3, 2 g and item 4, 300 mg per bag).

Plicamycin for Injection

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
0.25	mg	1	Plicamycin	0.25	g
10.00	mg	2	Mannitol	10.00	g
QS	mg	3	Disodium phosphate to adjust pH	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Fill 10 mL and lyophilize. Adjust pH to 7 with item 3.

Polyvinyl Alcohol Ophthalmic Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
14.00	mg	1	Polyvinyl alcohol	14.00	g
6.00	mg	2	Povidone, USP (*K* value 29–32)	6.00	g
2.00	mg	3	Potassium chloride granules, USP	2.00	g
4.33	mg	4	Sodium chloride, USP	4.33	g
0.50	mg	5	Sodium bicarbonate, USP	0.50	g
0.009	mg	6	Sodium citrate, USP, dihydrate powder	9.00	mg
0.65	mg	7	Dextrose anhydrous, USP, powder	0.65	g
0.50	mg	8	Disodium edetate, USP	0.50	g
5.33	mg	9	Sodium phosphate dibasic, USP, granules	5.33	g
1.05	mg	10	Sodium phosphate monobasic, USP, monohydrate	1.05	g
0.13	mg	11	Sodium hydroxide	0.13	g
QS	mg	12	Sodium hydroxide	QS	
0.10	mg	13	Benzalkonium chloride, use benzalkonium chloride solution, USP, 17% (with 7% excess)	0.63	mL
QS	mL	14	Water purified (deionized), USP		

Manufacturing Directions

1. Use steam-jacketed, glass-lined, or 316 or higher temper-grade stainless steel tank equipped with agitator. Wear suitable mask when handling item 1.
2. Put 0.4 L of item 14 into the mixing tank, maintaining the temperature at 20°C to 30°C. Add item 1 with mixing. Rinse the tank walls and agitator shaft with 35 mL of item 14. Continue mixing for 10 minutes. Raise the temperature to 82°C to 85°C and hold at this temperature for 30 to 45 minutes. (Do not exceed 85°C.) Continue mixing and cool to 25°C to 35°C.
3. Put 0.3 L of item 14 into another mixing tank at 20°C to 30°C and add item 2 slowly with mixing, using rinsing of tank and shaft to 0.4-L total. (Adding item 2 too rapidly will cause clumping that may be difficult to disperse.)
4. Slowly add items 3 to 10.
5. In a separate container, dissolve item 11 in ca. 3 mL of item 14 with mixing (ca. 5% solution).
   Slowly add while mixing this solution to solution in step 5 (approximately 0.2 mL/min; if added too rapidly, Povidone may precipitate out). Continue mixing with rinsing tank for another 30 minutes.
6. When solution in step 2 has cooled to 20°C to 30°C, transfer solution in step 3 into it slowly and rinse the tank. (Avoid foaming by keeping transfer line below the surface of solution.)
7. Continue mixing and bring to volume with item 14 to 0.98 L.
8. Check and record pH (7.4–7.5); adjust pH with 1% of item 12 solution by slow addition.
9. While mixing, add item 13 slowly and mix for at least 30 minutes.
10. Make up volume to 1 L.
11. Check and record pH (7.3–7.5); again adjust as above if necessary.
12. Prepare and sterilize a nylon filter Pall 0.2 μm and aseptically fill the sterile solution into sterilized container and apply sterile closure components.
13. Sample for testing.

Potassium Estrone Sulfate Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
4.00	mg	1	Potassium estrone sulfate	4.00	g
8.00	mg	2	Sodium phosphate, USP	8.00	g
15.00	mg	3	Benzyl alcohol, NF	15.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Hydrochloric acid for pH adjustment	QS	

Potassium Estrone Sulfate Suspension Injection

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
1.00	mg	1	Potassium estrone sulfate	1.00	g
2.00	mg	2	Estrone, NF	2.00	g
1.00	mg	3	Carboxymethylcellulose sodium, USP	1.00	g
1:10	M	4	Benzalkonium chloride, 50%, USP	1:10	M
1.00	mg	5	Polysorbate 80, USP	1.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Potassium Phosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
224.00	mg	1	Potassium phosphate monobasic, NF	224.00	g
236.00	mg	2	Potassium phosphate dibasic anhydrous, USP	236.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: Use clean glass-lined tank.

1. Preparation.
   a. Add water for injection to ca. 80% into tank and heat to 70°C (65–75°C). Add and dissolve potassium phosphate monobasic with mixing, add and dissolve potassium phosphate dibasic with mixing, and cool to 25°C (20–30°C). QS with water to 1 L and mix until completely dissolved. Sample. Allow to stand overnight and filter (do not recirculate) by using an approved 0.22-μm membrane filter with an approved prefilter into a glass-lined tank.
   b. Prepare for sterilization a 0.22-μm membrane filtration setup.
2. Preparation of bottles. Use type I or type II 20-mL bottles.
   a. Wash and dry bottles and sterilize using dry heat at 200°C (–0, +50°C) glass temperature for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for the duration of cycle.
   b. Deliver to sterile filling area.
3. Preparation of stoppers.
   a. Leach stoppers by boiling for 10 minutes in deionized water. Wash stoppers by using the rubber cycle (slow tumbling) with Triton X-100.
   b. Dry in fast dryer at 55°C. Store in a suitable container until ready for use.
   c. Tray, inspect, and rinse thoroughly. Wrap, try and identify properly, and sterilize in a steam autoclave at 121°C for 60 minutes.
4. Filling.
   a. Connect the bulk solution container, previously prepared sterile filter, and sterile surge bottle to filler by aseptic technique.
   b. Aseptically fill 15.5 mL (15.2–15.8 mL) of solution into each clean, dry sterile bottle. Stopper aseptically, apply seal, and inspect. Sample.

Prednisolone and Neomycin Ophthalmic Suspension

Bill of Materials (Batch Size 45 L)					
Scale		Item	Material	Qty	UOM
Part I					
5.50	mg	1	Borosilicate beads prednisolone acetate, USP (10% overage)	247.50	g
0.0066	mL	2	Water purified (distilled), USP	300.00	mL
0.0055	mL	3	PVA micronizing diluent	250.00	mL
0.0177	mL	4	Water purified (distilled), USP, ca.	800.00	mL
Part II					
0.3333	mL	5	Water purified (distilled), USP, ca.	15.00	L
14.00[a]	mg	6	Polyvinyl alcohol 20–90	941.30	g
0.0003[a]	mL	7	Polysorbate 80, NF (use 10% solution)	141.00	mL
Part III					
0.8222	mL	8	Water purified (distilled), USP, ca.	37.00	L
0.01	mL	9	Propylene glycol, USP	675.00	mL
8.33	mg	10	Sodium acetate trihydrate, USP	562.30	g
3.8500[b]	mg	11	Neomycin sulfate, USP (10% overage)	259.90[c]	g
11,500	U	12	Polymyxin B sulfate, USP (15% overage)	92.37[d]	g
Part IV					
0.0044	mL	13	Water purified (distilled) USP, ca.	200.00	mL
0.01	mg	14	Thimerosal USP[e]	0.675	g
QS	mL	15	Water purified (distilled) USP, approx; QS add parts II, III, and IV	60.00	L
QS	mL	16	Sterile filtrate QS parts II, III, IV	40.00	L
Part V					
0.0811	mL	17	Water purified (distilled) USP	3.65	L

[a] Includes amount contained in polyvinyl alcohol micronizing diluent. Polyvinyl alcohol micronizing diluent contains 1.0% polyvinyl alcohol 20–90 and 1.65% polysorbate 80, NF.
[b] Equivalent to 3.85 mg/mL neomycin base.
[c] The amount of neomycin sulfate to be added must be calculated on the basis of the manufacturer's assay value of the raw material lot used according to the following formula: 259.9 g neomycin base $\times$ 1000 mg/mg/manufacturer's assay value (μg/mg) = g of neomycin sulfate required.
[d] The amount of Polymyxin B sulfate to be added must be calculated on the basis of the manufacturer's assay value of the raw material lot used according to the following formula: 776250000 U Polymyxin B sulfate/manufacturer's assay value (U/mg $\times$ 1000 mg/g) = g of Polymyxin B sulfate required. (Standard 8403 U/mg.)
[e] The amount of thimerosal to be added must be calculated on the basis of the manufacturer's assay value of the raw material lot used according to the following formula: 0.675 g $\times$ 100.0%/assay value (%) = g thimerosal required.

Manufacturing Directions

Part I

1. Add item 1 into a 2-L grinding jar filled approximately half with glass beads. Add 300 mL of item 4 to it and then 250 mL of item 3.
2. Seal the jar with a Teflon stopper and mix until the steroid has been wetted. Remove the stopper and wrap the mount of jar with a double layer of aluminum foil and a double layer of parchment paper, and secure it with steel wires.
3. Sterilize the jar by autoclaving for at least 2 hours and 30 minutes at 121°C. Remove the jar from the autoclave and allow it to cool to room temperature.
4. Transfer 800 mL of item 4 into a 1-L flask. Wrap the mouth of the flask with a double layer of aluminum foil and a double layer of parchment paper and secure with two rubber bands.
5. Sterilize item 4 by autoclaving for 30 minutes minimum at 121°C. Remove the flask from the autoclave and allow it to cool to room temperature.
6. Wrap a Teflon stopper that will fit the mouth of the grinding jar with two layers of aluminum foil. Sterilize the Teflon stopper by autoclaving for at least 30 minutes at 121°C.
7. Aseptically (under a laminar flow hood, with appropriate gowning) add as much of the 800 mL of sterile item 4 as it takes to fill the grinding jar to the neck. Seal the grinding jar with the sterilized Teflon stopper. Cover the Teflon stopper with double layers of aluminum and double layer of parchment paper. Secure the parchment paper and aluminum foil with two steel wires.
8. Place the grinding jar on the mill and grind until the particle size is approved by QC.

Part II

1. Measure out ca. 20 L of item 5 into a container suitable for heating. Begin mixing with a suitable mixer. Heat the item 4 to 85°C to 90°C.
2. Measure out 15 L of heated item 5 into a 20-L container. Begin mixing using a propeller mixer.
3. Add item 6 slowly to the vortex. Avoid formation of excessive foam. Mix for at least 90 minutes until it is completely dissolved. (Mixing time is not less than 90 minutes.)
4. Add item 7, 10% solution, and mix well. Cool to room temperature.

Part III

1. Measure out ca. 37 L of item 8 into a mixing tank and begin mixing.
2. Add items 9, 10, 11, and 12, in order, allowing each to mix thoroughly or dissolve completely before adding the next.
3. Add part II to the mixing tank containing part III while mixing part III.
4. Use 3 to 4 L of item 8 to rinse the part II container. Add the rinsings to the mixing tank and mix thoroughly.

Part IV

1. Weigh out item 14 and carefully transfer it to a suitable flask.
2. Add 200 mL of item 13 and mix until item 14 is dissolved.
3. Add part IV to combined parts II and III and mix thoroughly.
4. Rinse the part IV flask with ca. 200 mL of item 15 and add the rinsings to the mixing tank.
5. Allow any foam to dissipate and QS the combined solution of parts II, III, and IV (product base) to 60 L with item 15. Mix thoroughly for at least 15 minutes. Sample.
6. Mix the product for at least 10 minutes before filtration.
7. Connect the sterilized filter and sterile filter with the aid of N_2 pressure (15–30 lb) into a sterilized 100-L stainless steel pressure vessel. Perform the bubble point test at NLT 40 psi and on a 0.22-μm inline gas filter at 18 psi. Sample.

Part V

1. Measure out and transfer item 17 into a suitable glass bottle. Seal the mouth of the bottle with two layers of aluminum foil and two layers of parchment paper and secure with two rubber bands.
2. Sterilize item 17 by autoclaving for at least 60 minutes at 121°C. Remove the bottle from the autoclave and allow it to cool to room temperature.

Mixing Procedure

1. Grind the steroid (part I) for at least 6 hours before mixing.
2. Aseptically receive 40 L of the sterile-filtered product base (combined parts II, III, and IV) into a sterilized glass bottle calibrated at 40 and 45 L.
3. Place the glass bottle containing the product base (combined parts II, III, and IV) on a magnetic mixing table. Place the bottle and magnetic mixer in front of a laminar air flow hood.
4. Aseptically add a sterilized magnetic stirring bar to the glass bottle containing the product base. Adjust the mixing speed such that a 0.5-in deep vortex is formed.
5. Aseptically pour the ground prednisolone acetate, part I, from the grinding jar through a sterilized funnel into the bottle containing the product base. Rinse the grinding jar and the funnel with the sterilized water purified (distilled; part V).
6. Add the rinsings to the bottle containing parts II, III, and IV. The volume of the suspension in the bottle should now be 45 L. Allow the product to mix with a 0.5-in deep vortex for at least 2 hours. Continue mixing at this setting.
7. Homogenize the product suspension with a sterilized homogenizer.
8. Allow the product to mix in the receiving bottle after completion of homogenization for at least 2 hours. Sample. If bulk assay results are acceptable, fill the product.
9. Aseptically fill sterile solution through P2 sintered glass into sterilized containers. Perform bubble point test on 0.22-μm inline gas filter before and after filtration at 18 psi.

Prednisolone Injection: Acetate/Phosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
80.00	mg	1	Prednisolone acetate, USP	80.00	g
20.00	mg	2	Prednisolone sodium phosphate, USP	20.00	g
25.00	mg	3	Niacinamide, USP	25.00	g
6.50	mg	4	Sodium chloride, USP	6.50	g
2.00	mg	5	Pectin, NF	2.00	g
1:10	M	6	Benzalkonium chloride, 50%, USP	1:10	M
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	mL	8	Glacial acetic acid for buffering		
QS	mL	9	Acetic acid for buffering; see item 8		

Acetate Suspension Injection (50 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Prednisolone acetate, USP	50.00	g
0.25	%	2	Pectin, NF	0.25	%
0.65	%	3	Sodium chloride, USP	0.65	%
0.01	%	4	Benzalkonium chloride, 50%, USP	0.01	%
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Glacial acetic acid for buffering		
QS	mL	7	Acetic acid for buffering; see item 6		

Acetate Suspension Injection (10 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Prednisolone acetate, USP	10.00	g
2.00	mg	2	Polysorbate 80, USP	2.00	g
1.00	mg	3	Carboxymethylcellulose sodium, USP	1.00	g
9.00	mg	4	Sodium chloride, USP	9.00	g
0.90	%	5	Benzyl alcohol, NF	0.90	%
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	mL	7	Glacial acetic acid for buffering		
QS	mL	8	Acetic acid for buffering; see item 7		

Prednisolone Acetate Suspension with Niacinamide Injection (20 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Prednisolone sodium phosphate, USP, equivalent to prednisolone phosphate	20.00	g
25.00	mg	2	Niacinamide, USP	25.00	g
1.00	mg	3	Sodium bisulfite, USP	1.00	g
5.00	mg	4	Liquefied phenol, USP	5.00	g
0.50	mg	5	Disodium edetate	0.50	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	mL	7	Sodium hydroxide for pH adjustment		

Prednisolone Ophthalmic Drops

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Qty	UOM
Part I					
		1	Borosilicate beads		
1.32	mg	2	Prednisolone acetate, USP, 10% overage	59.40	g
		3	Water purified (distilled), USP	221.70	mL
		4	Hydroxypropylmethyl cellulose micronizing diluent[a]	250.00	mL
0.000063	mL	5	Polysorbate 80, NF (use 10% solution)	28.30	mL
Part II					
		6	Water purified (distilled), USP	10.00	L
1.20[a]		7	Hydroxypropylmethyl cellulose F-4M	74.40	g
Part III					
		8	Water purified (distilled), USP	40.00	L
10.00		9	Boric acid, NF	635.30	g
3.00		10	Sodium citrate dihydrate, USP	190.60	g
0.548		11	Sodium metabisulfite	34.80	g
2.61[a]		12	Sodium chloride, USP	162.60	g
0.127		13	Disodium edetate, USP	8.07	g
0.04		14	Benzalkonium chloride, NF (use 10% solution)	25.40[b]	mL
		15	5 N hydrochloric acid, NF[c]	QS	mL
		16	1 N sodium hydroxide[c]	QS	mL
		17	Water purified (distilled), USP, QS add part II and part III	60.00	L
		18	Sterile filtrate, QS parts II and III	42.50	L
Part IV					
		19	Water purified (distilled), USP	2.00	L

[a] Includes amount contained in hydroxypropyl methylcellulose micronizing diluent. It contains 0.5% hydroxypropylmethyl cellulose F-4M and 0.9% sodium chloride.
[b] The amount of benzalkonium chloride, 10% solution, to be added must be calculated on the basis of the assay value of the raw material lot used according to the following formula: 25.4 mL × 10.0%/assay value (%) = mL benzalkonium chloride, 10% solution, required.
[c] For pH adjustment.

Manufacturing Directions

Part I

1. Weigh out and add item 2 to 1-L grinding jar containing ca. 50% to 55% glass beads.
2. Wrap the mouth of the grinding jar with two layers of aluminium foil and two layers of parchment paper, and secure them with two steel wires.
3. Sterilize the grinding jar by autoclaving for at least 3 hours at 121°C.
4. Remove the grinding jar from the autoclave and allow it to cool to room temperature.
5. Measure out and add items 3, 4, and 5 to a 1000-mL Erlenmeyer flask.
6. Wrap the mouth of the flask with two layers of aluminum foil and two layers of parchment paper and secure them with two steel wires. Sterilize the flask contents by autoclaving for at least 30 minutes at 121°C.
7. Remove the flask from the autoclave and allow it to cool to room temperature. Wrap a Teflon stopper that fits the mouth of the grinding jar with two layers of aluminum foil. Sterilize the Teflon stopper by autoclaving for at least 30 minutes at 121°C.
8. In the laminar flow hood, wearing sterile mask, gloves, and gown, aseptically transfer the sterilized solution of items 3, 4, and 5 into the grinding jar containing the sterilized item 2 and glass beads.
9. Aseptically seal the grinding jar with the sterilized Teflon stopper. Cover the Teflon stopper with two layers of aluminum foil and two layers of parchment paper and secure with two rubber bands.
10. Place the grinding jar on the mill and grind until the particle size is approved or for 7 days.

Part II

1. Measure out ca. 10 L of item 6 into a jacketed kettle for heating. Begin mixing with a suitable mixer. Heat it to 80°C to 90°C.
2. Measure out ca. 3 L of heated item 6 into a 6 L container. Begin mixing with a propeller mixer.
3. Add item 7 slowly to the vortex. Mix until it is thoroughly dispersed. Transfer the dispersion to a glass bottle and

rinse the container thoroughly with 2 to 3 L of hot item 6. Add the rinsings to the glass bottle.
4. Place the glass bottle into the water sink. Begin mixing with a suitable propeller mixer. Add item 6 to the bottle to bring the volume to 10 L.
5. Fill the water sink with cold industrial water. Cool the dispersion to less than 30°C. Cover the mouth of the bottle with two layers of aluminium foil. Place the bottle in the refrigerator.
6. Chill for at least 12 hours at 15°C or less until item 7 is completely hydrated.

Part III
1. Measure out ca. 40 L of item 8 into a mixing tank and begin mixing. Add items 9 to 14, in order, allowing each to mix thoroughly before adding the next. Avoid excess foam formation.
2. Add part II to the mixing tank containing part III while mixing part III. Rinse the pressure vessel from part II with 3 to 4 L of item 17. Add the rinsings to the mixing tank. Sample for pH (range 5.6–5.8). If necessary, adjust the pH with item 15 or 16.
3. Allow any foam to dissipate and QS the combined solution of parts II and III to 60 L with item 17. Mix combined parts II and III thoroughly for at least 15 minutes. Sample.
4. Sterile filter 42.5 L of combined parts II and III through a 0.2-μm filter. Discard any remaining combined parts II and III.

Part IV
1. Transfer item 18 into a suitable glass bottle. Seal the mouth of the bottle with two layers of aluminum foil paper and two layers of parchment paper and secure.
2. Sterilize it by autoclaving for at least 60 minutes at 121°C. Remove the bottle from the autoclave and allow it to cool to room temperature.

Sterile Filtration
Sterilize for 1 hour (range 45–60 minutes) at 121°C (–0, +5°C) in an autoclave at 15 psi the filter and 100-L stainless steel pressure vessel. Prior to this, perform the bubble point test at NLT 46 psi. Sample.

Mixing Procedure
1. Grind the steroid (part I) for at least 6 hours before mixing. Aseptically receive 42.5 L of sterile-filtered combined parts II and III into a sterilized glass bottle.
2. Place the pressure vessel containing the combined parts II and III on a magnetic mixing table. Place the magnetic mixer in front of a laminar air flow hood. Aseptically add a sterilized magnetic stirring bar to this pressure vessel. Adjust the mixing speed such that a 0.5-in deep vortex is formed.
3. Aseptically pour part I from the grinding jar through a sterilized polyethylene Buchner funnel into the bottle containing the combined parts II and III. Rinse with the sterilized water purified (part IV). Add the rinsings to the bottle containing parts I, II, and III. The volume of the suspension in the bottle should now be 45 L.
4. Allow the product to mix with a 0.5-in deep vortex for at least 2 hours.

Homogenization
Homogenize the suspension in a sterilized homogenizer. Filter and aseptically fill sterile solution through P2 sintered glass into sterilized containers.

Procaine Penicillin Injectable Suspension (300 mg/mL)

Formulation
1. Procaine penicillin G, 30.0 g.
2. Kollidon 17 PF [1], 0.4 g; carboxymethyl cellulose, 0.15 g; sodium citrate, 0.57 g; antioxidant QS; preservative, QS; water of injectables, add 100 mL.

Manufacturing Directions
1. Suspend procaine penicillin G in the well-stirred solution II.
2. To prevent of discoloration of the dissolved Kollidon during storage, 0.2% to 0.5% of cysteine could be added as antioxidant.

Procaine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Procaine HCl, USP	10.00	g
2.00	mg	2	Sodium bisulfite, USP	2.00	g
5.50	mg	3	Sodium chloride, USP	5.50	g
2.50	mg	4	Chlorobutanol anhydrous, USP	2.50	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Glacial acetic acid for buffering	QS	
QS	mL	7	Sodium acetate for buffering; see item 6	QS	

Note: For a 2% strength, reduce the quantity of sodium chloride (item 3) to 3.5 mg/mL

Prochlorperazine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Prochlorperazine as prochlorperazine edisylate equivalent	5.00	g
5.00	mg	2	Sodium biphosphate	5.00	g
12.00	mg	3	Sodium tartarate	12.00	g
0.90	mg	4	Sodium saccharin	0.75	g
7.50	mg	5	Benzyl alcohol	0.75	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Progesterone and Tocopheryl Acetate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
15.00	mg	1	Progesterone, 5% excess	15.73	g
30.00	mg	2	Tocopheryl acetate (vitamin E)	30.00	g
33.00	mg	3	Ethyl oleate	33.00	g
0.10	mg	4	Butylated hydroxy toluene	100.00	mg
QS		5	Arachis oil refined	QS to 1.00	L
QS		6	Nitrogen gas, NF	QS	

Manufacturing Directions

Note: All equipment must be thoroughly dried and free of any moisture.

1. Put 1 L of item 5 into a suitable container and heat to 150°C and maintain for 1 hour. Cool to 60°C to 70°C.
2. Dissolve item 1 in approximately 0.6 L of oil from step 1.
3. Dissolve item 2 in approximately 0.25 L of oil from step 1. Add to step 2 at room temperature.
4. Add item 4 to above solution. Make up volume with oil from step 1 at room temperature.
5. Filter through appropriate presterilized filter. Use only polyethylene tubing for filling assembly.
6. Fill 1.15 mL into type I amber ampoule under cover of item 6 dried by passing through calcium chloride and phenol traps.

Progesterone Injection Repository Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Progesterone, USP	50.00	g
120.00	mg	2	Ethyl alcohol, USP	120.00	g
150.00	mg	3	Benzyl alcohol, NF	150.00	g
QS	mg	4	Propylene glycol, USP	QS to 1.00	L

Promazine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Promazine HCl, USP	50.00	g
3.00	mg	2	Sodium chloride, USP	3.00	g
2.00	mg	3	Ascorbic acid, USP, ampoule grade	2.00	g
2.00	mg	4	Sodium metabisulfite, NF	2.00	g
QS	mL	5	Nitrogen gas, NF	QS	
QS		6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: This product requires N_2 gas and light protection during solution preparation. Store between 15°C and 30°C. Prepare solution in a clean glass-lined tank.

1. Preparation.
   a. Add water for injection to ca. 90% of the final volume into a glass-lined tank protected from light.
   b. Bubble filter N_2 gas into water for injection for 10 minutes.
   c. Add and dissolve sodium chloride, ascorbic acid, sodium metabisulfite, and promazine with mixing.
   d. Check and record pH (range 4.5–5.1). Adjust to 4.8 with 5 N sodium hydroxide solution. Record amount used.
   e. QS with water for injection to final volume.
   f. Sample for testing.
   g. Sterilize an approved 0.2- or 0.22-μm filter unit in a sterile, glass-lined holding container.
2. Preparation of ampoules. Use type I 1-mL sulfur-treated glass ampoules.
   a. Wash and dry ampoules and load into appropriate containers for sterilization.
   b. Sterilize using dry heat at 245°C for at least 3 hours and 25 minutes or an equivalent cycle.
   c. Deliver to the sterile filling area.
3. Filling.
   a. Connect bulk solution container by aseptic technique to the filling machines.
   b. Aseptically fill 1.2 mL (range 1.1–1.3 mL) into each clean, sterile ampoule.
   c. Flush the headspace of each ampoule with sterile-filtered N_2 gas.
   d. Immediately seal each ampoule.
4. Sterilization.
   a. Sterilize in an autoclave at 122°C for 12 minutes.
   b. Sample for testing.

Promethazine Hydrochloride Injection Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Promethazine hydrochloride	25.00	g
0.25	mg	2	Sodium metabisulfite	0.25	g
5.00	mg	3	Phenol liquefied	5.00	g
QS	mg	4	Acetic acid	QS	
QS	mg	5	Sodium acetate	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	ft^3	7	Nitrogen gas	QS	

Note: Adjust pH to 4.0 to 5.5 with item 4 or 5. Same composition for a 50 mg/mL dose. Light sensitive, process under cover. Provide item 7 cover throughout and fill with pre- and postflush of item 7.

Promethazine Hydrochloride Injection Cartridge Unit

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Promethazine hydrochloride	25.00	g
0.10	mg	2	Edetate sodium	0.10	g
5.00	mg	3	Phenol liquefied	5.00	g
5.00	mg	4	Monothioglycerol	5.00	g
0.04	mg	5	Calcium chloride	0.04	g
QS	mg	6	Acetic acid	QS	
QS	mg	7	Sodium acetate	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L
QS	ft^3	9	Nitrogen gas	QS	

Note: Adjust pH to 4.0 to 5.5 with item 4 or 5. Same composition for a 50 mg/mL dose. Light sensitive, process under cover. Provide item 9 cover throughout and fill with pre- and postflush of item 9.

Propanidid Injectable Solution (50 mg/mL)

Formulation

1. Propanidid, 5.0 g; Cremophor EL [1], 20.0 g.
2. Preservatives, QS; water for injectables, add 100 mL.

Manufacturing Directions

Mix propanidid with warm Cremophor EL (60°C) and add slowly the warm solution II. The sterilization can be done by filtration or heat.

Properties of the solution

A clear, colorless solution was obtained.

Remarks

- To reduce the viscosity and the side effects, Cremophor EL could be substituted by Solutol HS 15 [1].
- In Germany, Cremophor EL must be declared on the package of injectables.
- During the heat sterilization, a separation of two layers can be observed. Shaking of the ampoules during cooling gives homogeneous, clear solutions.

Propofol Emulsion Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Propofol	10.00	g
45.00	mg	2	Soybean oil refined	45.00	g
5.00	mg	3	Egg lecithin	5.00	g
22.50	mg	4	Glycerin	22.50	g
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	ft^3	7	Nitrogen gas NF	QS	

Manufacturing Directions

1. Put 0.9 L of item 6 into a jacketed stainless steel vessel and heat to 40°C. Maintain throughout manufacturing a blanket cover of item 7.
2. Add and dissolve items 3 and 4 and mix well until a uniform dispersion is obtained.
3. In a separate vessel, add item 2, heat to 40°C, and add and dissolve item 1 to complete solution.
4. Add step 3 into step 2 at 40°C. Mix well.
5. Check and adjust pH to 5.0 to 7.5 with item 5.
6. Homogenize emulsion in a homogenizer until globules are less than 1 μm.
7. Check and adjust pH again as in step 5.
8. Filter and fill under item 7 cover.

Pyridoxine and Thiamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Thiamine HCl, USP	100.00	g
100.00	mg	2	Pyridoxine HCl, USP	100.00	g
1.00	mg	3	Sodium formaldehyde sulfoxylate, NF	1.00	g
15.00	mg	4	Benzyl alcohol, NF	15.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Sodium hydroxide for pH adjustment	QS	

Pyridoxine Hydrochloride Injection (100 mg/mL, 30-mL vial)

Bill of Materials (Batch Size 30 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Pyridoxine HCl, USP, 10% excess	110.00	g
15.00	mg	2	Benzyl alcohol, NF	15.00	g
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Measure ca. one-third of the final volume of water for injection into an appropriate clean and identified mixing tank.
2. Add item 1 into the mixing tank and stir until a clear solution is obtained.
3. Add item 2 with constant stirring into the mixing tank.
4. Bring the final volume with item 5 and check pH.
5. Adjust pH between 2.0 and 3.8, if necessary.
6. Sample to test for pH and assay.
7. Filter through a sterile 0.45-μm prefilter and a 0.22-μm membrane filter. Check the integrity test of sterile filter and note results.
8. Aseptically fill sterile vials.
9. Autoclave at 121°C for 20 minutes.
10. Sample for full testing.

Pyridoxine Hydrochloride Injection (100 mg/mL, 1-mL Ampoule)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Pyridoxine HCl, USP, 10% excess	110.00	g
QS	mL	2	Sodium hydroxide for pH adjustment	QS	
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Preparation.
   a. Add water for injection to ca. 80% of the final volume into a glass-lined tank protected from light.
   b. Add and dissolve pyridoxine hydrochloride with mixing.
   c. Record and adjust pH to 3 (range 2.7–3.3) with 5 N sodium hydroxide solution.
   d. QS with water for injection to final volume.
   e. Sample for testing.
   f. Sterilize and approved 0.22-μm membrane filter with an approved prefilter.
   g. Filter the solution through the sterilized filter unit into a sterile, glass-lined holding container.
2. Preparation of ampoules.
   a. Wash and dry type 1 1-mL sulfur-treated ampoules and load into appropriate containers for sterilization.
   b. Sterilize by using dry heat at 245°C for at least 3 hours and 25 minutes or an equivalent cycle to assure sterile, pyrogen-free bottles.
   c. Deliver to the sterile filling area.
3. Filling.
   a. Connect bulk solution container by aseptic technique to the filling machines.
   b. Aseptically fill 1.2 mL (range 1.1–1.3 mL) into each clean, sterile ampoule.
   c. Immediately seal each ampoule.
4. Sterilization.
   a. Autoclave at 121°C for 20 minutes.
   b. Sample for testing.

Pyrilamine Maleate and Ephedrine Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Pyrilamine maleate, NF	25.00	g
10.00	mg	2	Ephedrine HCl, NF	10.00	g
3.00	mg	3	Chlorobutanol anhydrous, USP	3.00	g
QS		4	Water for injection	QS	

Quinidine Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
QS		1	Nitrogen gas, NF	QS	
877.13	mg	2	Propylene glycol, USP (QS to 1 L), ca.	877.13	g
190.00	mg	3	Quinidine sulfate, USP	190.00	g

Manufacturing Directions

Precaution: Prepare solution in a clean glass-lined tank. The product requires N_2 gas and light protection during solution preparation.

1. Preparation.
   a. Add propylene glycol into a glass-lined tank protected from light. Bubble N_2 gas into tank for 10 minutes.
   b. Add and dissolve quinidine sulfate with mixing.
   c. Check and record pH.
   d. QS with propylene glycol for injection to final volume.
   e. Sample.
   f. Sterilize an approved 0.2- or 0.22-μm membrane filter with an approved prefilter (0.45 μm).
   g. Filter the solution through the sterilized filter unit into a sterile, glass-lined holding container.
2. Preparation of ampoules. Use type 1 1-mL sulfur-treated ampoules.
   a. Wash and dry ampoule and load into appropriate containers for sterilization.
   b. Sterilize using dry heat at 245°C for at least 3 hours and 25 minutes (or equivalent cycle that ensures sterile, pyrogen-free bottles).
   c. Deliver to the sterile filling area.
3. Filling.
   a. Connect bulk solution container by aseptic technique to the filling machines.
   b. Aseptically fill 1.2 mL (range 1.1–1.3 mL) into each clean, sterile ampoule.
   c. Flush the headspace of each ampoule with sterile filtered N_2 gas. Immediately seal each ampoule.

Quinolone Lyophilized Injections

A variety of quinolone antibiotics can be prepared in a lyophilized form by a simple procedure wherein, as an example, 10 g of powdered antibiotic is dissolved in 50 mL of 1 M lactic acid, the pH adjusted to 4.5 with 1 N sodium hydroxide solution and diluted with distilled water for injection to 100 mL. This solution is filtered through a membrane filter (pore size 0.22 μm) and each 2 mL of the filtrate filled into clean and sterilized vials. These vials are cooled to –42°C and dried under vacuum. The temperature of the shelf is –20°C during the initial stage (up to 22 hours) of drying. Under vacuum, the temperature is elevated to 20°C and kept for 24 hours and further elevated to 40°C and kept for 6 hours to give a freeze-dried preparation.

Quinolone–Calcium Lactate Complex for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
30.00	mg	1	Quinolone antibiotic	30.00	g
12.00	mg	2	L-(+)-Lactic acid	12.00	g
1.90	mg	3	Calcium hydroxide	1.90	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: The complex is produced by dissolving the antibacterial compound in an aqueous lactic acid solution, preferably L-(+)-lactic acid solution, neutralizing the resulting solution with calcium hydroxide in a quantity that is selected so that any precipitation of the antibacterial compound from the solution is avoided and yet on IV injection, venous irritation by the neutralized solution is either absent or is minimized. Adjust the quantity of antibiotic according to amount of moisture in it.

Manufacturing Directions

1. Dissolve item 2 in ca. 0.9 L of item 4 in a suitable container and mix well.
2. Add item 1 with mixing until all the drug particles are dissolved.
3. Add item 3 with mixing.
4. Check pH (ca. 4.6–4.9); adjust pH with calcium hydroxide or lactic acid if necessary.
5. Sterilize the solution by filtering through a previously sterilized 0.22-μm membrane filter or equivalent using 5 for positive pressure.
6. Discard 100 mL of solution to flush the system. Aseptically fill 10.05 to 10.1 mL of the solution into previously sterilized and depyrogenated vials. Stopper loosely with slotted closures and lyophilize. Stopper and cap the lyophilized vials.

Ranitidine Injection Ampoule

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Ranitidine, use ranitidine HCl, 10% excess	27.50	g
2.40	mg	2	Sodium phosphate dibasic anhydrous, use as sodium phosphate dibasic.12 H_2O	2.40	g
0.96	mg	3	Potassium phosphate monobasic	0.96	g
5.00	mg	4	Liquefied phenol, NF	5.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Nitrogen gas, NF	QS	

Note: Quantity of ranitidine and sodium phosphate dibasic to be adjusted for assay on dry basis and to take into account moisture content.

Manufacturing Directions

1. Check item 5 that it does not have conductivity more than 1.0 μS/cm, pH range should be 5.0 to 7.0.
2. Put 0.9 L of item 5 into a suitable preparation vessel and bubble N_2 gas to expel dissolved oxygen. Monitor oxygen level.
3. Add and dissolve sodium phosphate dibasic, potassium phosphate monobasic, and phenol into solution in step 2. Mix well to make clear solution.
4. Add item 1 into the solution in step 3 and mix by stirring to make clear solution. Protect solution from light from this step on.
5. Check pH (range 6.87–7.2).
6. Make up volume and mix during bubbling N_2 gas until oxygen is undetectable.
7. Sample for testing.
8. Prepare filtration assembly and use silicone hoses and filter cartridges dedicated to product.
9. Transfer the solution from the preparation vessel to holding tank by passing through 0.45-μm cartridge.
10. Sterilize ampoules. Check integrity of final filtration filter of 0.22-μm filter.
11. Fill 2.1 to 2.2 mL into ampoules and seal. Perform leak test and optical check.
12. Sample for testing.

Ranitidine Injection Ampoule (50-mL Flexible Plastic Container)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Ranitidine hydrochloride	5.00	g
4.50	mg	2	Sodium chloride	4.50	g
0.30	mg	3	Citric acid	0.30	g
1.80	mg	4	Dibasic sodium phosphate	1.80	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill 50 mL into nonplasticized, thermoplastic copolyster (CR3) container; pH 6.7 to 7.3.

Reteplase Recombinant for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
18.10	mg	1	Reteplase	18.10	g
8.32	mg	2	Tranexamic acid	8.32	g
136.24	mg	3	Dipotassium hydrogen phosphate	136.24	g
51.27	mg	4	Phosphoric acid	51.27	g
364.00	mg	5	Sucrose	364.00	g
5.20	mg	6	Polysorbate 80	5.20	g

Note: Reconstitute lyophilized product with water for injection.

Retinol (Vitamin A) Injection

Bill of Materials (Batch Size 2 L)					
Scale/mL		Item	Material	Qty	UOM
5000	IU	1	Vitamin A (retinol in polysorbate 20)[a]	1000,000	IU
500.00	mg	2	Glycerin, USP	1000.00	g
150.00	mg	3	Polysorbate 20, NF[b]	300.00	g
QS	mL	4	Water for injection, USP	QS to 2.00	L
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS		6	Nitrogen gas, NF	QS	

[a]1000000 IU/(potency/g of raw material).
[b]This is the total amount of polysorbate 20 required for the batch. Because Vitamin A raw material used is provided in polysorbate 20, make adjustment for the contribution from the raw material.

Manufacturing Directions

1. Put item 3 into clean compounding tank of suitable size and place it on a hot plate. Heat it to approximately 40°C but do not exceed 60°C. Keep an N_2 blanket over the tank contents during all remaining compounding steps.
2. With constant stirring, add item 1 to the warm polysorbate 20 solution. Use a rubber policeman to transfer all item 1 to the tank. Keep stirring till a clear solution is obtained.
3. Stop heating the compounding tank. While agitating, add, in portions, glycerin to the compounding tank. Rinse the vessel containing item 1 raw material with glycerin and add the rinses to the compounding tank.
4. Add approximately 500 mL item 4 to the tank. Stir to a complete solution.
5. Check pH (6.0–7.0); adjust if necessary with 10% item 5. (Item 5 also contains 0.0027% butylated hydroxytoluene and 0.0006% butylated hydroxyanisole.)
6. Bring the final volume with item 4.
7. Sample for testing.
8. On approval of laboratory, filter through a 0.22-μm filter into a light-protected receiving container in the clean room. Keep N_2 blanket over the solution in the receiving container.
9. Fill with an N_2 postfill flush. Use type I amber vials and 1109 red with Y-40 coating stoppers.

Rh_o (D) Immune Globulin (Human) Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Rh_o (D) gamma globulin[a]	50.00	g
2.90	mg	2	Sodium chloride	2.90	g
0.10	mg	3	Polysorbate 80	0.10	g
15.00	mg	4	Glycine	15.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

[a] Small amounts of IgA, typically less than 15 μg per dose, are present. pH 6.20 to 6.55. Package in latex-free delivery system.

Ringer Lactate Solution Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.0024	mL	1	Lactic acid (min. assay 88%)	2.40	mL
1.16	mg	2	Sodium hydroxide, 8% excess	1.25	g
0.00063	mL	3	Hydrochloric acid dilute (10%)	0.70	mL
6.00	mg	4	Sodium chloride, 3% excess	6.20	g
0.40	mg	5	Potassium chloride, 5% excess	0.42	g
0.27	mg	6	Calcium chloride dihydrate, 8% excess	0.291	g
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Dissolve item 4 in 50 mL of item 7 and add item 1 with stirring.
2. Autoclave the solution in step 1 at 115°C for 60 minutes. Allow to cool and check pH.
3. Add item 3 slowly to reduce the pH to between 6.8 and 7.0. (Approximately full quantity of item 3 will be consumed.)
4. Dissolve items 4, 5, and 6 in 0.5 L of item 7 in a separate vessel with stirring at 60°C.
5. Add solution in step 4 to solution in step 3. Stir vigorously and make up the volume.
6. Check pH to between 5.0 and 7.0. Do not adjust pH.
7. Filter using at least a 0.45-μm filter before final filtration with a 0.22-μm filter and fill into 540-mL type I glass bottles.
8. Fill 540-mL while maintaining solution at 45°C to 50°C and seal immediately by using butyl gray rubber stoppers prewashed and sterilized at 116°C for 30 minutes; use triple aluminum seals and suitable plastic hangers.
9. Sterilize filled bottle by autoclaving at 121°C for 20 minutes.

Rituximab Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Rituximab	10.00	g
0.90	%	2	Sodium chloride, USP	0.90	%
7.35	mg	3	Sodium citrate dihydrate	7.35	g
0.70	mg	4	Polysorbate 80 (Tween®)	0.70	g
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	ft^3	8	Nitrogen gas, NF	QS	

Description

The rituximab antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is an IgG_1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. It has an approximate molecular weight of 145 kDa. Rituximab has a binding affinity for the CD20 antigen of ca. 8.0 nM. The chimeric anti-CD20 antibody is produced by mammalian cell (Chinese hamster ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. The anti-CD20 antibody is purified by affinity and ion exchange chromatography. The purification process includes specific viral inactivation and removal procedures.

Manufacturing Directions

1. Take 0.9 L of item 7 and purge with item 8 for 20 minutes.
2. Add items 2 and 3 and mix well.
3. Add item 4 gently to avoid frothing.
4. Add item 1 and mix well.
5. Check and adjust pH to 6.5 (range 6.3–6.6) with item 5 or 6.
6. Filter and aseptically fill either 10 mL (100 mg) or 50 mL (500 mg).

Rubella Virus Vaccine Live

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2000	TCID[a]	1	Rubella virus vaccine live wistar RA 27/3 strain	2000,000	TCID
29.00	mg	2	Sorbitol	29.00	g
3.80	mg	3	Sodium phosphate	3.80	g
3.80	mg	4	Sodium chloride	3.80	g
29.00	mg	5	Gelatin hydrolyzed	29.00	g
0.60	mg	6	Albumin (human)	0.60	g
50.00	mg	7	Neomycin	50.00	mg
QS	mL	8	Water for injection, USP	QS to 1.00	L

[a]Tissue culture infectious doses; dose = 0.5 mL; contains fetal bovine serum <1 ppm.

Salbutamol Aerosol for Inhalation

Bill of Materials (Batch Size 1000 U)					
Scale/mL		Item	Material	Qty	UOM
1.173	mg	1	Salbutamol, 10% manufacturing excess	26.40	g
0.1176	mg	2	Oleic acid, 10% manufacturing excess	2.64	g
277.61	mg	3	Trichloromonofluoromethane	5664.00	g
721.09	mg	4	Dichlorodifluoromethane	1470.00	g

Manufacturing Directions

Caution: Salbutamol is a low-dose bronchodilator. Operators should wear full protective clothing including suitable hat, face mask, and gloves during all stages of manufacture. It is a suspension-based aerosol and not a solution.

1. Preparation of suspension.
   a. Filter ca. 5 kg of trichloromonofluoromethane and oleic acid through a suitable 0.2-μm filter into a stainless steel concentrate container.
   b. Slowly add the salbutamol to the solution in step 1a and mix for approximately 15 minutes.
   c. Filter most of the remaining trichloromonofluoromethane through a suitable 0.2-μm filter into the suspension-holding tank.
   d. Add the slurry from step 1b to the holding tank. Rinse the concentrate container with filtered trichloromonofluoromethane and add the rinses to the holding tank. Make up the final mass of 5.693 kg with filtered trichloromonofluoromethane. Mix for further 5 minutes. Sample (to determine nonvolatile matter, range 0.49–0.53 w/w).
2. Filling. Packing commodity details

Valve, aerosol, 65 μL, Valois DF50 or valve, aerosol, 65 μL Bespak BK 356
Vial, aluminum, NS4, 12.5-mL fill, 20-mm opening
Mouthpiece adaptor
Cap for mouthpiece adaptor

   a. Fill 5.7 g of suspension into a clean aluminum vial and immediately crimp on the metering valve.
   b. Pressure-fill, through metering valve, sufficient dichlorodifluoromethane to produce a final fill weight of 20.4 g. Check-weigh each aerosol to ensure that the fill weight is in the range of 20 to 20.8 g. *Note*: At the start of the manufacture, fill three vials and apply non-metering valves. Pressure-test these vials with a special gauge adaptor to ensure that the correct propellant mix is being used. The internal pressure measured at 22°C should be 50 to 60 psi.
   c. Store the filled aerosols for a period of 2 weeks and again check-weigh as in step 2b. Test each aerosol by actuation to ensure correct operation.
   d. Pack the filled aerosol units into suitable cardboard cartons. Each carton should be filled with ca. 500 U. Sample.

Sisomicin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Sisomicin, use sisomicin sulfate	62.00	mg
3.00	mg	2	Sodium metabisulfite	3.00	g
3.60	mg	3	Sodium chloride	3.60	g
0.80	mg	4	Methyl paraben	0.80	g
0.10	mg	5	Propyl paraben	0.10	g
0.10	mg	6	Disodium edetate	0.10	g
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	ft^3	8	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Put ca. 0.7 L of item 7 into a suitable stainless steel-jacketed vessel and heat to approximately 70°C.
2. Charge the items 4 and 5 to the heated water and dissolve with agitation.
3. When completely dissolved, cool the contents of the tank to 25°C to 30°C.
4. Sparge the solution with item 8 and keep covered with item 8 cover during subsequent processing.
5. Charge and dissolve items 6, 3, 2, and 6.
6. Charge and dissolve item 1.
7. Bring the batch volume up to 51 L with item 7 and agitate until homogenous.
8. Check pH to 5.1 to 5.3; do not adjust.
9. Under sterile conditions, filter the solution through a suitable bacteria-retentive filter (0.22 μm) collecting the filtrate in a filling tank.
10. Fill the product aseptically into sterile, pyrogen-free, multiple-dose vials, ampoules, or syringes and seal.

Sobrerol Injectable Solution (75 mg/5 mL)

Formulation

Sobrerol, 1.5 g; Kollidon 17 PF [1], 6.0 g; water for injectables, 100.0 mL.

Manufacturing Directions

Dissolve sobrerol slowly in the well-stirred solution of Kollidon 17 PF. The sterilization can be done by filtration through a 0.2-μm filter.

Properties

Preservatives could be added if it is needed. To prevent of discoloration of Kollidon in the solution during storage, 0.1% to 0.5% of cysteine could be added as antioxidant.

Sodium Bicarbonate and Disodium Edetate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Sodium bicarbonate, USP	40.00	g
2.00	mg	2	Disodium edetate anhydrous, use disodium edetate, USP, dihydrate	2.214	g
QS		3	Nitrogen gas, NF	QS	
QS		4	Carbon dioxide gas technical	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: CO_2 gas is used to maintain the bicarbonate equilibrium in solution and to avoid the formation of carbonate. Do not fill solution below room temperature as this will form excessive internal pressure after filling and sealing. Prepare the solution in a glass-lined or 316 or higher temper-grade stainless steel tank, cleaned according to approved SOPs.

1. Preparation.
   a. Add water for injection to ca. 90% of the final volume into the tank.
   b. Bubble CO_2 gas into the water for injection and continue CO_2 gassing throughout the process.
   c. Add and dissolve the sodium bicarbonate and the disodium edetate with mixing.
   d. QS with water for injection to final volume and mix for not less than 15 minutes and until solution is uniform.
   e. Cool solution to 23°C (range 18–23°C).
   f. Filter solution through a previously rinsed filter press and recirculate for at least 30 minutes and until solution is clear.
   g. Filter solution through a previously rinsed filtration setup connected in series to the press, using an approved 0.45-μm or finer membrane. Collect solution in clean tank and protect with CO_2 gas by bubbling and flushing headspace.
   h. Check and record pH (range 7.7–7.9). If pH is more than 7.9, add more CO_2 gas until pH falls within the range. If pH is less than 7.9, add N_2 gas until the pH rises to within the range.
   i. Samples for testing.
   j. Store at room temperature if filled within 24 hours. If held longer, store in refrigerator.
   Note: Must allow to warm to room temperature before filling (range 18–23°C).
   k. Prepare for the filling line a sterile 0.22-μm membrane filtration setup.
2. Preparation of bottles. Use type I glass bottles.
   a. Wash and dry bottles and load into appropriate container for sterilization.
   b. Sterilize by using dry heat at 200°C (–0, +50°C) glass temperature for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for the duration of cycle.
   c. Deliver to the sterile filling area.
3. Preparation of stoppers. Use West or Faultless stoppers.
   a. Leach stoppers by boiling for 10 minutes in deionized water.
   b. Wash stoppers in a washer by using a rubber cycle (slow tumbling) with 10 mL of Triton X-100.
   c. Dry in a fast dryer at 55°C.
   d. Store in suitable containers until ready for use.
   e. Tray and inspect and rinse thoroughly. Wrap trays and identify properly.
   f. Sterilize in a steam autoclave at 121°C for 60 minutes.
   g. Deliver to the sterile filling area.
4. Filling. *Note*: Check pH frequently and keep in range of 7.7 to 7.9 by increasing or decreasing CO_2 flow.
   a. Aseptically connect tank, sterile filtration setup, and sterile surge bottle. Protect surge bottle headspace with filtered CO_2 gas.
   b. Aseptically fill specified amount into each clean, sterile bottle.
   c. Flush headspace with sterile CO_2 gas; apply closure and seal.
   d. Sample for testing.

Sodium Bicarbonate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
86.52	mg	1	Sodium bicarbonate, USP	86.62	g
QS	mL	2	Nitrogen gas, NF	QS	
QS	mL	3	Carbon dioxide gas technical	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: CO_2 gas is used to maintain the bicarbonate equilibrium in solution and to avoid the formation of carbonate. Do not fill solution below room temperature as this will form excessive internal pressure after filling and sealing. Prepare the solution in a glass-lined or a 316 or higher-temper-grade stainless steel tank cleaned according to approved SOPs.

1. Preparation.
   a. Add water for injection to ca. 90% of the final volume into the tank.
   b. Heat the water for injection to 35°C (30–38°C) and bubble CO_2 gas into the water for injection for 30 minutes.
   c. Add and dissolve the sodium bicarbonate with mixing.
   d. Cool solution to 25°C (range 20–30°C).
   e. QS with water for injection to final volume and mix for not less than 15 minutes and until solution is uniform.
   f. Check and record pH (range 7.7–7.9). If pH is more than 7.9, add more CO_2 gas until pH falls within the range. If pH is less than 7.9, add N_2 gas until the pH rises to within the range.
   g. Filter solution through a previously rinsed filtration setup connected in series to the press, using an approved 0.45-μm or finer membrane. Collect solution in clean tank and protect with CO_2 gas by bubbling and flushing headspace.
   h. Sample for testing.
   i. Prepare for the filling line a sterile 0.22-μm membrane filtration setup.
2. Preparation of bottles. Use type I 50-mL glass bottles.
   a. Wash and dry bottles and load into appropriate container for sterilization.
   b. Sterilize using dry heat at 200°C (–0, +50°C) glass temperature for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for the duration of cycle.
   c. Deliver to the sterile filling area.
3. Preparation of stoppers. Use West or Faultless stoppers, butyl rubber.
   a. Leach stoppers by boiling for 10 minutes in deionized water.
   b. Wash stoppers in a washer by using a rubber cycle (slow tumbling) with 10 mL of Triton X-100.
   c. Dry in a fast dryer at 55°C.
   d. Store in suitable containers until ready for use.
   e. Tray and inspect and rinse thoroughly. Wrap trays and identify properly.
   f. Sterilize in a steam autoclave at 121°C for 60 minutes.
   g. Deliver to the sterile filling area.
4. Filling. *Note*: Check pH frequently and keep in range of 7.7 to 7.9 by increasing or decreasing CO_2 flow.
   a. Aseptically connect tank, sterile filtration setup, and sterile surge bottle. Protect surge bottle headspace with filtered CO_2 gas.
   b. Aseptically fill 52.0 mL into each clean, sterile bottle.
   c. Flush headspace with sterile CO_2 gas, apply closure, and seal.
   d. Sample for testing.

Sodium Chloride Bacteriostatic Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
9.00	mg	1	Sodium chloride, USP	9.00	g
20.00	mg	2	Benzyl alcohol, NF	20.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Sodium Chloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
9.00	mg	1	Sodium chloride, NF, injectable grade, 4% overage	9.33	g
0.50	mg	2	Activated charcoal, NF	0.50	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Use freshly prepared item 3 stored for NMT 24 hours at 80°C. Add item 1 to item 3 at 60°C and mix for 15 minutes.
2. Add item 2 and mix vigorously for 15 minutes.
3. Filter the mixture in step 2 through a presterilized filter assembled suitable for retaining charcoal and to yield a clean solution.
4. Filter using at least a 0.45-μm filter before final filtration with a 0.22-μm filter and fill into 540-mL type I glass bottles (alkalinity-free test required to prevent precipitation on storage).
5. Fill 540 mL while maintaining solution at 45°C to 50°C and seal immediately by using butyl grey rubber stoppers prewashed and sterilized at 116°C for 30 minutes. Use triple aluminum seals and suitable plastic hangers.
6. Sterilized filled bottle by autoclaving at 121°C for 20 minutes. Do not exceed temperature by 3°C or time by 2 minutes either side of the limit.
7. Check pH of solution (range 4.0–4.3). Before autoclaving, pH is 5.5 to 6.5.

Sodium Ferric Gluconate Complex in Sucrose Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
12.50	mg	1	Elemental iron as sodium salt of a ferric ion carbohydrate complex-equivalent amount	12.50	mg
19.50	mg	2	Sucrose	195.00	g
9.00	mg	3	Benzyl alcohol	9.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Fill 5 mL per ampoule for 62.50 mg iron; adjust the amount of item 1 based on molecular weight and iron content; pH 7.7 to 9.7.

Sodium Hyaluronate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Sodium hyaluronate	10.00	g
8.50	mg	2	Sodium chloride	8.50	g
0.28	mg	3	Disodium hydrogen phosphate dihydrate	0.28	g
0.04	mg	4	Sodium dihydrogen phosphate hydrate	0.04	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill into syringe and terminally sterilize and aseptically package.

Sodium Lactate Compound (Hartmann's) Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.27	mg	1	Calcium chloride dihydrate	0.27	g
0.40	mg	2	Potassium chloride	0.40	g
6.00	mg	3	Sodium chloride	6.00	g
3.17	mg	4	Sodium lactate, use sodium lactate 60% solution	3.17	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Hydrochloric acid dilute	QS	mL

Manufacturing Directions

1. Add and dissolve 70% of items 5 (specific conductivity NMT 1.4 mS/cm), 3, 2, and 1 and 60% of item 4.
2. Make up volume and mix well until solution is uniform.
3. Check pH and adjust to 5.4 to 5.6, if necessary, with item 6.
4. Filter through a 0.45-μm membrane. Perform the bubble point test before and after filling.
5. Fill 545 or 1065 mL into 500- or 1-L blow-fill seal containers.
6. Sterilize the product by using recirculated hot water and air overpressure. Perform complete sterilization within 12 hours of addition of first ingredient.

Sodium Thiosulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
250.00	mg	1	Sodium thiosulfate pentahydrate, 10% excess	275.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Hydrochloric acid for pH adjustment	QS	

Manufacturing Directions

1. Boil item 2 in a clean, marked vessel.
2. Transfer 175 mL of item 2 into a clean, marked compounding vessel.
3. Add required quantity of item 1 into the compound vessel containing 175 mL of water. Stir thoroughly until a clear solution is obtained.
4. QS with item 2 and mix thoroughly. Sample for testing.
5. Sterile-filter through a 0.22-μm filter using a 0.45-μm prefilter and fill into type I 30-mL flint vials with 1888 gray Teflon-coated stoppers.

Somatropin (rDNA Origin) Injection (4- or 8-mg Vials, ca. 12 or 24 IU)

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
4.00	mg	1	Somatropin	4.00	g
8.80	mg	2	Glycine	8.00	g
1.30	mg	3	Disodium phosphate dihydrate	1.30	g
1.10	mg	4	Sodium dihydrogen phosphate dihydrate	1.10	g
44.00	mg	5	Mannitol	44.00	g

Note: Lyophilize in water for injection. Same formulation for 8-mg vial. Diluent is water for injection containing 1.5% benzyl alcohol.

Somatropin (rDNA Origin) Injection (5 mg/1.5 mL, 10 mg/1.5 mL, or 15 mg/1.5 mL Cartridge)

Bill of Materials (Batch Size 1.5 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Somatropin	5.00	g
1.00	mg	2	Histidine	1.00	g
4.50	mg	3	Poloxamer 188	4.50	g
4.50	mg	4	Phenol liquefied	4.50	g
60.00	mg	5	Mannitol	60.00	g
QS	mL	6	Hydrochloric acid for pH adjustment	QS	
QS	mL	7	Sodium hydroxide for pH adjustment	QS	
QS	mL	8	Water for injection, USP	QS to 1.50	L

Note: Same formulation for 10-mg dose; for 15-mg dose increase histidine to 1.7 mg and reduce mannitol to 58 mg. Each cartridge contains 1.5 mL.

Sterile Water for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
QS	mL	1	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Precaution: Freshly distill water for injection and do not use more than 24 hours after distillation. Store all bulk water in a refrigerator to minimize possibility of bacterial growth and in tightly closed containers to avoid absorption of CO_2 and other gases.

Note: Prepare the solution in a glass-lined or a 316 or higher temper-grade stainless steel.

1. Preparation.
   a. Add water for injection to final volume in tank.
   b. Filter solution through a previously rinsed filtration setup, using an approved 0.45-μm or finer membrane and an approved prefilter.
   c. Sample for testing.
2. Filling. Use type I 10-mL glass ampoules, USP.
   a. With a 0.22-μm membrane filtration setup, fill 10.5 mL of water for injection into each clean, dry ampoule.
   b. Seal.
3. Sterilization.
   a. Sterilize in a steam autoclave at 115°C and an F_0 range of 8 to 18. Use water spray cooling and terminal air overpressure if available.
   b. Inspect.
   c. Sample for testing.

Streptomycin Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
400.00	mg	1	Streptomycin sulfate	400.00	g
12.00	mg	2	Sodium citrate dihydrate	12.00	g
2.50	mg	3	Phenol liquefied	2.50	g
2.00	mg	4	Sodium metabisulfite	2.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: pH 5.0 to 8.0; fill 2.5 mL.

Succinylcholine Chloride Injection: Lyophilized

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Succinylcholine chloride, USP, anhydrous	44.00[a]	g
0.90	mg	2	Methyl paraben, NF	1.60[a]	g
0.10	mg	3	Propyl paraben, NF	0.20[a]	g
QS	mg	4	Sodium hydroxide, reagent-grade pellets, for pH adjustment	QS	
QS	mL	5	Hydrochloric acid, reagent-grade bottle, for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a]100% excess to satisfy label claim when 2.55 mL of solution is reconstituted into 5.10 mL/vial.

Manufacturing Directions

Precautions: Drug is extremely poisonous. Do not inhale powder or allow chemical or its solution to come in contact with skin. Wear a mask and goggles when handling powder. Persons with abrasions about hands or exposed portions of skin cannot work with this product. Operators are warned against rubbing the face around the eyes because of the solubility in eye fluid. Solution is sensitive to heat. Store the bulk solution prior to filling in a refrigerator at 2°C to 8°C. Prepare solution in a glass-lined or a 316 or higher temper-grade stainless steel tank cleaned according to approved plant BOPs.

1. Preparation.
   a. Dissolve items 2 and 3 in ca. 85% of the final volume. Heat to 95°C to 100°C.
   b. Cool solution to 25°C to 30°C. Add and dissolve the item 1.
   c. Check pH (range 4.2–4.5). If necessary, adjust pH upward with 1 N sodium hydroxide or downward with 1 N hydrochloric acid to pH 4.2. *Note*: Prepare a 1 N sodium hydroxide solution by dissolving 40 g of sodium hydroxide per liter of water for injection.
   d. Add water for injection to final volume and mix well.
   e. Filter solution through a previously rinsed filtration setup, using an approved 0.45-μm or finer membrane and an approved prefilter. Filter into clean glass bottles or a holding tank.
   f. Sample for testing.
   g. Store bulk solution in refrigerator at 2°C to 8°C until ready to fill.
   h. Prepare for the filling line a sterile 0.22-μm membrane filtration setup.
2. Preparation of bottles. Use type I or type II 5-mL glass bottles.
   a. Wash and dry bottles and load in appropriate containers for sterilization.
   b. Sterilize by using dry heat at 200°C (–0, +50°C) bottle temperature for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (+10°C) for the duration of the cycle.
   c. Deliver to the sterile filling area.
3. Preparation of stoppers. Use West or Faultless stoppers.
   a. Leach stoppers by boiling for 10 minutes in deionized water.
   b. Wash stoppers in washer.
   c. Dry in a fast dryer at 55°C.
   d. Store in a suitable container until ready for use.
   e. Tray and inspect and rinse thoroughly. Wrap trays and identify.
   f. Sterilize in a steam autoclave at 121°C for 60 minutes.
   g. Deliver to the sterile filling area.
4. Filling.
   a. Connect tank, sterile filtration setup, and sterile surge bottle by aseptic technique.
   b. Aseptically fill 2.55 mL of solution into each sterile bottle.
   c. Sample for testing.
   d. Place filled bottles into sterile metal trays and cover with sterile covers.
   e. Place trays in close cabinet truck until ready for freezing (must be frozen within 8 hours).
   f. Freeze at –50°C for 4.5 hours and lyophilize for 60 hours to less than 10% moisture. (Do not allow temperature to go more than 45°C.)
   g. On completion of lyophilization, immediately stopper aseptically.
   h. Sample for testing.
   i. Cap bottles with aluminum seals.
5. Finishing. Sample for final testing.

Succinylcholine Chloride Injection: Ampoule

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Succinylcholine chloride, USP	50.00	g
QS	mL	2	Sodium hydroxide for pH adjustment	QS	
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Caution: Extremely poisonous drug. Take all precautions against exposure. Solution sensitive to heat; keep bulk refrigerated. Prepare solution in a glass-lined or stainless steel tank.

1. Add 0.9 L of item 4 into tank. Add and dissolve item 1 with mixing. Mix well.
2. Make up volume with item 4.
3. Check and adjust pH 3.0 to 4.5; adjust with item 2 or 3, if necessary.
4. Circulate solution through a filter press precoated with activated carbon.
5. Check pH and adjust as in step 3, if necessary.
6. Filter solution by using a 0.45-μm prefilter and a 0.22-μm membrane filter into a sterile surge bottle.
7. Aseptically fill 10.2 mL (10-mL claim).
8. Sample for final testing.

Succinylcholine Chloride Injection: Veterinary Nonsterile

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20	mg	1	Succinylcholine chloride, USP	20.00	g
0.35	mg	2	Methyl paraben, USP	0.35	
0.175	mg	3	Propyl paraben, USP	0.175	mg
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Hydrochloric acid for pH adjustment	QS	

Sulfadimethoxine Veterinary Injectable Solution (2.5% = 250 mg/10 mL)

Formulation

I. Sulfadimethoxine, 5 g; ethanol 96%, 40 mL; propylene glycol [1], 40 mL.
II. Kollidon 12 PF [1], 70 g; antioxidant, QS; water for injectables, QS, add 200 mL.

Manufacturing Directions

Mix solution I slowly with solution II at 60°C and cool.

Sulfadoxine + Trimethoprim Veterinary Injectable Solution (1000 mg + 200 mg/10 mL)

Formulation

Sulfadoxine, 2.0 g; trimethoprim. 10.0 g; Soluphor P [1], 56.0 g; water for injectables, 29.0 g; sodium hydroxide, QS.

Manufacturing Directions

Dissolve sulfadoxine and trimethoprim in Soluphor P, add the water, and set to pH 8.5 with sodium hydroxide.

Sulfadoxine solution (2% = 20 mg/mL)

Formulation

I. Sulfadoxine, 2.0 g; Lutrol E 400 [1], 68.0 g.
II. Preservative, QS; water, 30.0 g.

Manufacturing Directions

Prepare solution I at 60°C. Heat the solution II to the same temperature and mix slowly with solution I.

Sulfamoxole + Trimethoprim Veterinary Injectable Solution (400 mg + 80 mg/10 mL)

Formulation

Sulfamoxole, 4.0 g; trimethoprim, 0.8 g; Kollidon 12 PF [1], 30.0 g; paraben, 0.2 g; sodium sulfite or cysteine, 0.4 g; propylene glycol [1], 10.0 g; water for injectables, 44.6 g; ethanol, 10.0 g.

Manufacturing Directions

Dissolve Kollidon, paraben, sodium sulfite (or cysteine) in the mixture of water und propylene glycol, heat, add the active ingredients and stir until they are dissolved. Add ethanol, cool, and sterilize.

Sulfathiazole veterinary injectable and oral solutions (0.8% = 8 mg/mL)

Formulations

Injectable oral solutions.

Manufacturing Directions

Dissolve Kollidon and sulfathiazole at 70°C in water and cool slowly to room temperature.

Sterilization of the injectable solution can be done by filtration through a 0.2-μm filter.

Sumatriptan Succinate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
12.00	mg	1	Sumatriptan base as succinate salt equivalent	16.75	g
7.00	mg	2	Sodium chloride	7.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: Fill 0.5 mL; pH 4.2 to 5.3.

Tenecteplase for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Tenecteplase, 5% excess	52.50	g
0.55	g	2	L-Arginine	0.55	kg
0.17	g	3	Phosphoric acid	0.17	kg
4.30	mg	4	Polysorbate 80	4.30	g

Note: Dissolve in water for injection and lyophilize appropriate volume. Product under partial vacuum.

Testosterone Suspension Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Testosterone, NF	25.00	g
1.00	mg	2	Carboxymethylcellulose sodium, USP	1.00	g
1.00	mg	3	Sodium phosphate, USP	1.00	g
9.00	mg	4	Sodium chloride, USP	9.00	g
1:10	M	5	Benzalkonium chloride 50%, USP	1:10	M
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Use different fill volumes for different strengths.

Testosterone Cypionate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Testosterone cypionate, USP	100.00	g
9.00	mg	2	Benzyl alcohol, NF	9.00	g
200.00	mg	3	Benzyl benzoate, USP	200.00	g
QS	mg	4	Cottonseed oil, USP	QS to 1.00	L

Note: Use different amounts of item 1 for different strengths.

Testosterone Enanthate–Estradiol Valerate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
90.00	mg	1	Testosterone enanthate, USP	90.00	g
4.00	mg	2	Estradiol valerate, USP	4.00	g
20.00	mg	3	Benzyl alcohol, NF	20.00	g
QS	mg	4	Sesame oil, USP	QS to 1.00	L

Note: Use same formulation for 180-mg dose.

Testosterone Enanthate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Testosterone enanthate	200.00	g
5.00	mg	2	Chlorobutanol	5.00	g
QS	mg	3	Sesame oil purified	QS to 1.00	L

Note: Fill 5 mL into each syringe; terminally sterilized.

Testosterone Repository Veterinary Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Testosterone propionate, USP	25.00	g
150.00	mg	2	Benzyl alcohol, NF	150.00	g
150.00	mg	3	Ethyl alcohol, USP	150.00	g
450.00	mg	4	Propylene glycol, USP	450.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Testosterone Propionate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Testosterone propionate, USP	25.00	g
20.00	mg	2	Benzyl alcohol, NF	20.00	g
QS	mg	3	Sesame oil, USP	QS to 1.00	L

Note: Fill 2 mL for 50-mg strength.

Testosterone Propionate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Testosterone propionate, USP	100.00	g
60.00	mg	2	Ethanol, USP	60.00	g
20.00	mg	3	Benzyl alcohol, NF	20.00	g
QS	mg	4	Sesame oil, USP	QS to 1.00	L

Tetrahydrozoline Ophthalmic Drops

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
17.20	mg	1	Boric acid	17.20	g
1.50	mg	2	Hydroxypropylmethylcellulose 2910, 4000 cps	1.50	g
0.40	mg	3	Borax (sodium borate) powder	1.00	g
0.50	mg	4	Tetrahydrozoline hydrochloride	0.50	g
0.585	mL	5	Benzalkonium chloride solution 17%, 7% excess	0.63	mL
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: Use thoroughly cleaned and rinsed steam-jacketed, glass-lined tank or stainless steel tank (No. 304 or better) equipped with a speed-controlled agitator; tank should have a cover. Foaming occurs because of benzalkonium chloride, which concentrates in foam. Processing and filling systems should be designed to minimize foaming and allow rapid dissipation of foaming.

1. Bulk solution.
   a. Charge 80% of final volume of water into mixing tank.
   b. If using methylcellulose, heat deionized water to 90°C. While agitating, add and disperse methylcellulose by slowly sprinkling onto the surface of solution. Mix to avoid excessive foaming. Allow 15 minutes for hydration of methylcellulose before discontinuing heating and allowing to cool to 40°C.
   c. While agitating, add and dissolve disodium edetate, benzalkonium chloride, boric acid, sodium borate, and tetrahydrozoline and continue cooling to 25°C. Discontinue agitation and QS to 1 L with deionized water. Sample.
2. Prefiltration. Methylcellulose solutions filter at a slow rate. Recirculate solution until clear and transfer to holding or sterilization.
3. Sterilization and filling. Use either heat sterilization or sterile filtration. In heat sterilization, sterilize at 112°C to 115°C for 60 minutes. Cool the solution to 25°C to 30°C and aseptically add the sterile naphazoline solution and mix well. Set up a previously sterilized filter and transfer line with a 10-μm stainless steel FulFlo filter or equivalent. Aseptically fill sterile solution into sterilized containers and apply sterile closure components. Sample. In sterile filtration, use appropriate Pall cartridge with Sartorius cartridge. Prepare and steam-sterilize the recommended filter units, aseptically fill the sterilize solution into each sterilized container, and apply sterile closure. Sample.

Theophylline Injectable Solution (4% = 200 mg/5 mL)

Formulation

Theophylline (Knoll), 2 g; Kollidon 12 PF [1], 15 g; propylene glycol [1], 10 g; preservative, QS; antioxidant, QS; water for injectables, add 50 g.

Manufacturing Directions

Dissolve Kollidon 12 PF and the preservative/antioxidant in water and add theophylline to the well-stirred solution.

Theophylline and Dextrose Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.40	mg	1	Theophylline powder, USP	0.40	g
50.00	mg	2	Dextrose monohydrate, USP	50.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS		4	Nitrogen gas, NF	QS	

Note: The amount of theophylline (item 1) to be changed for 0.8, 1.6, 2.0, and 4.0 mg/mL labeled quantity; the amount of item 2 does not change. The product is intended for IV infusion and packaged in containers of different sizes.

Manufacturing Directions

1. Add ca. 95% of the final volume of item 3 into a glass-lined or 316 or higher temper-grade stainless steel tank.
2. Bubble N_2 gas through the water and maintain N_2 gas protection throughout the remainder of the solution preparation.
3. Add and dissolve item 1 with mixing.
4. Add and dissolve item 2 with mixing.
5. QS with item 3 to the final volume and mix until the solution is uniform.
6. Filter solution with a prefilter.
7. Filter solution through a 0.45-μm or finer membrane filter.
8. Fill correct volume with 3% overage into each flexible container.
9. Seal, overwrap, and autoclave 121°C for 30 minutes.
10. Sample for final testing.

Thiamine Hydrochloride Injection: Unbuffered

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Thiamine hydrochloride, USP, 5% excess	105.00	g
5.00	mg	2	Chlorobutanol	5.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Measure ca. 0.7 L of the final volume of item 3 into an appropriate clean and identified tank.
2. Add item 1 into the mixing tank and mix until a clear solution is obtained.
3. Add item 2 into the mixing tank and mix until a clear solution is obtained.
4. Bring the final volume with item 3.
5. Check pH to 2.5 to 4.5.
6. Sample for testing.
7. Sterile-filter through a 0.22-μm membrane disc filter with a 0.45-μm prefilter into an appropriate container.
8. Sterilize 30-mL flint vials at 220°C for 240 minutes; use gray stoppers.

In the next four formulations, a 5% to 10% stability excess can be added.

Thiamine Hydrochloride Injection: with Citric Acid and Gelatin

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Thiamine HCl, USP	25.00	g
0.25	mg	2	Citric acid, USP	0.25	g
40.00	mg	3	Gelatin, USP	40.00	g
15.00	mg	4	Benzyl alcohol	15.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Sodium hydroxide for pH adjustment	QS	

Thiamine Hydrochloride Injection: Buffered

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Thiamine HCl, USP	25.00	g
52.50	mg	2	L-Glutamic acid (Buffer)	52.50	mg
5.00	mg	3	Chlorobutanol anhydrous, USP	5.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Sodium hydroxide for pH adjustment	QS	

Thiamine Hydrochloride Injection: with Sodium Formaldehyde Sulfoxylate

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Thiamine HCl, USP	100.00	g
1.00	mg	2	Sodium formaldehyde sulfoxylate, NF	1.00	g
15.00	mg	3	Benzyl alcohol, NF	15.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Sodium hydroxide for pH adjustment	QS	

Thiamine Hydrochloride Injection: Buffered and Gelatin

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Thiamine HCl	25.00	g
52.50	mg	2	L-Glutamic acid	52.50	mg
40.00	mg	3	Gelatin, USP	40.00	g
5.00	mg	4	Chlorobutanol anhydrous	5.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Thiopental Sodium for Injection

Bill of Materials (Batch Size 1000 Ampoules)					
Scale/mL		Item	Material	Qty	UOM
500.0	mg	1	Thiopental sodium, sodium carbonate mixture FMU sterilized	500.00	g
QS	mL	2	Nitrogen gas, NF	QS	

Manufacturing Directions

Caution: Use of CO_2 in place of N_2 may cause precipitation that may not be detectable; use of N_2 is thus preferred. Deliver item 1 in air-tight, sterile glass containers only. Pentothal sodium is sensitive to moisture and CO_2. This powder is sterile and must be handled aseptically in a dry, dust-free atmosphere. Minimize the time between filling and sealing the primary container. Relative humidity (RH) should preferably be less than 25% at 27°C; however, actual RH requirements will depend on the type of filling equipment and other process parameters. RH up to 45% at 25°C may be used. Avoid inhaling vapors. Protect bulk material from prolonged exposure to CO_2 and humidity. Aseptically flush exposed bulk containers with sterile N_2 gas and release.

1. Preparation.
   a. Record details of the drug used.
   b. Wipe outer surface of each bottle with 3A alcohol and deliver immediately to sterile area.
   c. Sample for testing.
2. Preparation of ampoules. Use type I, II, or III glass ampoules.
   a. Wash and dry ampoule and load into appropriate containers for sterilization.
   b. Sterilize by using dry heat at 200°C (–0, +50°C) ampoule temperature for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for the duration of the cycle. *Note*: This cycle or a cycle providing equivalent heat input may be used.
   c. Deliver to sterile filling area.
3. Filling.
   a. Sterile-fill 500 mg of powder into each clean, dry sterile ampoule. Seal ampoule. Remove from sterile area and pack into bulk containers, labeling each container with product lot number.
   b. Sample for testing.
   c. Sterile-fill powder equivalent to 0.5 g at a factor of 1.0 into each clean, dry sterile ampoule.
   d. Seal ampoule.

Thiotepa for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
15.00	mg	1	Thiotepa	15.00	g
0.03	mg	2	Sodium carbonate	2.00	g

Note: Dissolve in adequate amount of water for injection and lyophilize; reconstituted solution has pH of 6.5 to 8.1. Drug unstable in alkaline media.

Thiothixene Hydrochloride Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Thiothixene hydrochloride, 10% excess	5.50	g
59.60	mg	2	Mannitol	65.00	g
2.20	mL	3	Water for injection	2.20	mL

Note: Reconstitute with 2.2 mL of water for injection to give above concentration.

Thyrotropin-Alpha for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.10	mg	1	Thyrotropin alpha	1.10	g
36.00	mg	2	Mannitol	36.00	g
5.10	mg	3	Sodium phosphate	5.10	g
2.40	mg	4	Sodium chloride	2.40	g
1.20	mL	5	Water for injection, USP	QS to 1.20	L

Note: Reconstituted lyophilized solution has pH around 7.0 and concentration of item 1 is 0.90 mg/mL.

Timolol Ophthalmic Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.50	mg	1	Timolol as timolol hemihydrate	2.56	g
QS	mg	2	Monosodium phosphate dihydrate to adjust pH	QS	
QS	mg	3	Disodium phosphate dihydrate to adjust pH	QS	
0.10	mg	4	Benzalkonium chloride	0.10	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 6.5 to 7.5 with item 2 or 3. For 0.5% label use twice the amount of item 1.

Tinzaparin Sodium Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40,000	IU	1	Tinzaparin sodium	40 MM	IU
10.00	mg	2	Benzyl alcohol	10.00	g
3.10	mg	3	Sodium metabisulfite	3.10	g
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 5.0 to 7.5 with item 4.

Tirofiban Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.050	mg	1	Tirofiban as tirofiban hydrochloride monohydrate	56.18	mg
45.00	mg	2	Sodium chloride	45.00	g
0.54	mg	3	Sodium citrate dihydrate	0.54	g
0.16	mg	4	Citric acid anhydrous	0.16	g
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Fill 250 or 500 mL into plastic container; concentrate filled in 25-mL size with adjusted amounts; adjust pH to 5.5 to 6.5 with item 5 or 6.

Tobramycin Solution for Inhalation

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
60.00	mg	1	Tobramycin	60.00	g
2.25	mg	2	Sodium chloride	2.25	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	ft^3	5	Nitrogen gas	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Fill 5mL into a single-use ampoule; adjust pH to 6.0 with item 3 or 4. Provide item 5 cover throughout with pre- and postfill flush.

Tobramycin Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Tobramycin base, USP	10.00	g
2.92	mg	2	Sodium metabisulfite, NF	2.92	g
0.10	mg	3	Disodium edetate, USP, use disodium edetate, USP, dihydrate	0.11	g
20.98	mg	4	Sulfuric acid, reagent-grade bottle	20.98	g
QS		5	Sodium hydroxide, regent-grade bottle[a]	QS	
QS		6	Sulfuric acid, reagent-grade bottle[a]	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

[a]For pH adjustment, if necessary, to be used as 1 N sodium hydroxide solution, freshly prepared, by mixing 40 g of item 5 with sufficient water for injection to make 1000 mL. Use 10% sulfuric acid solution, freshly prepared, by adding 100 g or 57 mL of item 6 to sufficient water for injection to make 1000 mL.

Manufacturing Directions

1. Preparation of water.
   a. Obtain a sample from the water for injection source to be used for solution preparation and verify that it meets a conductivity limit of NMT 3 mS/cm and pH range of 5 to 7.
   b. Test the rinse draining from the tank for conductivity and oxidizable substances prior to batch preparation.
2. Preparation of solution.
   a. Add 1.1 L water for injection to a suitable tank. Sparge the water with filtered N_2 gas for not less than 30 minutes. Alternatively, heat the water to not less than 70°C and then cool to 25°C (range 20–30°C) while sparging with filtered N_2 gas.
   b. Transfer ca. 200 mL of this water for injection into another covered tank for use in step 2e. Protect the tank headspace with filtered N_2 gas.
   c. Continue N_2 sparging the bulk water for injection. While mixing with gentle agitation, add and dissolve disodium edetate, sodium metabisulfite, sulfuric acid, and tobramycin. Mix for not less than 20 minutes.
   d. Check and record pH. Adjust, if necessary, to pH 5.5 (range 5.5–6.0) with 10% sulfuric acid solution or 1 N sodium hydroxide solution. Mix thoroughly.
   e. Make up to 1 L with N_2-saturated water for injection cooled to ambient temperature from step 2b.
   f. Recheck and record pH. If necessary, readjust to pH 5.5 (range 5.3–6.0) as in step 2d.
   g. Sample for testing. Discontinue N_2 sparging and switch to N_2 gas protection of tank headspace. If the bulk solution does not meet the in-process specifications, make the necessary adjustment to the batch based on the results of testing.
   h. Prior to filtering the solution, flush the lines, filters, and the glass-lined or 316 or higher temper-grade stainless steel holding tank with filtered N_2 gas. Filter the solution through a previously rinsed filtration setup, using an approved 0.22-μm (or finer) membrane filter with an approved prefilter into the holding tank. Protect the headspace of the holding tank with filtered N_2 gas.
3. Filling. Use type I 2-mL glass ampoules.
   a. Fill specified amount into each clean, dry ampoule.
   b. Flush the headspace with filtered N_2 gas and seal the ampoule.
   c. Inspect.
   d. Sample for testing.
4. Sterilization. Steam-sterilize at 115°C and an F_0 of 8. Use product hold cycle, water spray cooling, and terminal overpressure.

Tobramycin Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Tobramycin base, USP	10.00	g
2.92	mg	2	Sodium metabisulfite, NF	2.92	g
0.10	mg	3	Disodium edetate, USP, use disodium edetate, USP, dihydrate	0.11	g
5.24	mg	4	Sulfuric acid	5.24	g
QS		5	Sodium hydroxide[a]	QS	
QS		6	Sulfuric acid[a]	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

[a]For pH adjustment, if necessary, to be used as 1 N sodium hydroxide solution, freshly prepared, by mixing 40 g of item 5 with sufficient water for injection to make 1000 mL. Use 10% sulfuric acid solution, freshly prepared, by adding 100 g or 57 mL of item 6 to sufficient water for injection to make 1000 mL.

Topotecan Hydrochloride for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.80	mg	1	Topotecan as topotecan hydrochloride	0.866	g
9.60	mg	2	Mannitol	9.60	g
4.00	mg	3	Tartaric acid	4.00	g
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 2.5 to 3.5 with item 4 or 5. Fill 5 mL and lyophilize.

Trace Element Concentrate Injection: (1- or 10-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.54	mg	1	Manganese sulfate monohydrate	1.54	g
3.93	mg	2	Copper sulfate pentahydrate	3.93	g
21.99	mg	3	Zinc sulfate heptahydrate	21.99	g
51.25	mg	4	Chromium chloride hexahydrate	51.25	mg
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Sulfuric acid for pH adjustment	QS	

Note: pH 1.5 to 2.5.

Trace Element Concentrate Injection (3- or 10-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.308	mg	1	Manganese sulfate monohydrate	0.308	g
1.57	mg	2	Copper sulfate pentahydrate	1.57	g
4.39	mg	3	Zinc sulfate heptahydrate	4.39	g
20.5	mg	4	Chromium chloride hexahydrate	20.50	mg
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Sulfuric acid for pH adjustment	QS	

Tranexamic Acid Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	g	1	Tranexamic acid	50.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	ft^3	3	Nitrogen gas, NF	QS	ft^3

Manufacturing Directions

1. Put approximately 0.9 L of item 2 into a stainless steel vessel, boil it for 10 minutes, and cool to room temperature.
2. Add item 1, stir to dissolve, and make up the volume.
3. Check pH (7.2–7.7)
4. Filter through previously sterilized filtration assembly by using a 0.22-μm membrane filter into a presterilized receiving vessel. Perform the bubble point test before and after filtration.
5. Sterile-fill into sterilized ampoules 5.3 mL of solution through sintered glass and seal.
6. Sample.
7. Sterilize in autoclave at 115°C for 30 minutes.
8. Sample for leak test, optical check, and complete specification testing.

Trastuzumab for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
44.00	mg	1	Trastuzumab	44.00	g
0.99	mg	2	L-Histidine hydrochloride	0.99	g
0.64	mg	3	L-Histidine	0.64	g
40.00	mg	4	Alpha, Alpha-trehalose dihydrate	40.00	g
11.00	mg	5	Benzyl alcohol	11.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Fill 10 mL per vial and lyophilize. Reconstitute with 20 mL water for injection for item 1 concentration of 21 mg/mL; pH ca. 6.0.

Triamcinolone Acetonide Suspension Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Triamcinolone acetonide, USP	40.00	g
0.40	mg	2	Polysorbate 80, USP	0.40	g
9.00	mg	3	Sodium chloride, USP	9.00	g
7.50	mg	4	Carboxymethylcellulose sodium, USP	7.50	g
9.00	mg	5	Benzyl alcohol, NF	9.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	mL	7	Sodium acetate for buffering	QS	
QS	mL	8	Glacial acetic acid for buffering; see item 7	QS	

Trifluprom azine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Trifluprom azine as hydrochloride salt and 5% excess	11.30	g
1.00	mg	2	Sodium acetate	1.00	g
0.0012	mL	3	Glacial acetic acid	1.20	mL
1.00	mg	4	Sodium metabisulfite	1.00	g
QS		5	Nitrogen gas, NF	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: The preparation is light sensitive. Protect and provide N_2 cover throughout.

1. In an appropriate 316 or higher temper-grade stainless steel vessel, take 1 L of freshly boiled item 6 and purge with item 5 for 20 minutes.
2. Add item 1 to ca. 0.9 L of item 6 as prepared in step 1.
3. Add items 2 and 3.
4. Check pH to 4.5 to 5.2; do not adjust.
5. Filter through a 0.45-μm prefilter and a 0.22-μm filter into a sterilized staging vessel.
6. Fill 1.1 mL into sterilized amber ampoule (200°C for 4 hours) with pre- and postflush of item 5.
7. Autoclave filled ampoules at 121°C for 30 minutes.
8. Sample for testing.

Trifluprомazine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Triflupromazine and hydrochloride	10.80	g
15.00	mg	2	Benzyl alcohol, NF	15.00	g
3.60	mg	3	Sodium chloride, NF	3.60	g
QS		4	Nitrogen gas, NF	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: The preparation is light sensitive. Protect and provide N_2 cover throughout.

1. Take 0.76 L of freshly distilled and boiled item 5 and flush with item 4 for 20 minutes.
2. Add item 3 to step 1 and stir to dissolve.
3. Add item 2 to step 2 and stir to dissolve.
4. Add item 1 to step 3 and stir to dissolve and make up volume.
5. Check pH to 4.1 to 4.3; do not adjust.
6. Filter through a 0.45-μm prefilter and a 0.22-μm filter into a sterilized staging vessel.
7. Fill 1.1 mL into a sterilized amber ampoule (200°C for 4 hours) with pre- and postflush of item 5.
8. Autoclave filled ampoules at 121°C for 30 minutes.
9. Sample for testing.

Trifluprомazine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Trifluperazine as trifluoperazine hydrochloride	1.085	g
4.75	mg	2	Sodium tartarate	4.75	g
11.60	mg	3	Sodium biphosphate	11.60	g
0.30	mg	4	Sodium saccharin	0.30	g
7.50	mg	5	Benzyl alcohol	7.50	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Fill 10-mL multidose vial.

Tripelennamine Hydrochloride Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Tripelennamine HCl, USP	20.00	g
5.00	mg	2	Chlorobutanol anhydrous USP	5.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Hydrochloric acid for pH adjustment	QS	

Tubocurarine Chloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
9.00	mg	1	Benzyl alcohol, NF	9.00	g
1.00	mg	2	Sodium metabisulfite, NF	1.00	g
3.00	mg	3	Tubocurarine chloride, USP	3.00	g
8.00	mg	4	Sodium chloride, USP	8.00	g
1.00	mg	5	Citric acid anhydrous powder, USP	1.00	g
0.30	mg	6	Sodium citrate dihydrate, USP	0.30	g
2.00	mg	7	Activated charcoal, USP[a]	2.00	g
QS		8	Nitrogen gas, NF	QS	
QS	mL	9	Water for injection, USP	QS to 1.00	L

Note: If necessary to remove color from solution.

Manufacturing Directions

1. Prepare the solution in a glass-lined or 316 stainless steel tank.
2. Add water for injection to ca. 90% of the final volume into the tank. Begin bubbling N_2 gas into water.
3. Add and dissolve, in order, benzyl alcohol, sodium metabisulfite, citric acid, sodium citrate, tubocurarine chloride, and sodium chloride with mixing.
4. QS to final volume with N_2-saturated water for injection and mix until all ingredients are dissolved and solution is uniform.
5. Check APHA color. The range should not exceed 15 APHA units. Use activated charcoal if necessary.
6. Check and record pH and adjust to 2.5 to 4.9 (final limit 2.5–5.0)
7. Aseptically filter the solution through a 0.22-μm or finer membrane.
8. Aseptically fill solution into type I glass vials with gray butyl rubber stoppers and flip-off cap.
9. Label and finish product.

Typhoid Vi Polysaccharide Vaccine

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Purified Vi polysaccharide	50.00	mg
4.15	mg	2	Sodium chloride	8.30	g
0.065	mg	3	Disodium phosphate dihydrate	0.130	g
0.023	mg	4	Monobasic sodium phosphate	0.046	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill in 0.5-mL syringe aseptically.

Uridine Triphosphate Injection

Prior to formulation, UTPNa_3dihydrate is kept frozen at –20°C. The UTP powder is allowed to warm to handling temperature for at least 1 hour prior to opening to minimize water absorption. The UTP raw material is dissolved in a sterile aqueous solution such as saline solution. An appropriate concentration of the saline solution is used to bring the osmolarity to ca. 300 mOsm, that is, an isotonic solution. Alternatively, UTP powder can be dissolved in sterile water and an appropriate amount of NaCl added to bring the osmolarity to ca. 300 mOsm. In either case, aqueous solution is added in sufficient volume to reach an optimum therapeutic UTP concentration level of 5 to 35 mg/mL. The pH of the liquid solution is adjusted to between 7.0 and 7.5. The resulting UTP solution is sterilized by filtration with an appropriate micrometer filter.

Urokinase for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50,000	IU	1	Urokinase concentrate[a]	438.62	mL
9.00	mg	2	Sodium chloride	9.00	g
5.00	mg	3	Mannitol (nonpyrogenic)	5.00	g
QS		4	Water for injection	QS to 1.00	L
QS		5	Sodium hydroxide, reagent grade, for pH adjustment	QS	
QS	mL	6	Hydrochloric acid, reagent grade, for pH adjustment	QS	

[a] Quantities of ingredients adjusted based on the potency and volume of urokinase concentrate. Urokinase concentrate contains not less than 110000 IU/mL and between 9 and 22 mg/mL sodium chloride. Dilutions are made such that the two values within the specification are maintained. Mannitol is used to adjust activity and sodium chloride is used to adjust its concentration. After assay, adjust accordingly.

Manufacturing Directions

1. Add and dissolve 20 g of item 5 in water for injection in a suitable vessel. Cool and keep.
2. Prepare item 6 solution in an exhausted hood or well-ventilated area. Wear gloves.
3. Under laminar flow hood and by aseptic techniques, transfer item 1 into a clean, sterile calibrated glass container. Sample. Keep refrigerated.
4. Check pH (range 6.5–7.2) and adjust with 2% item 5 solution or 2% item 6 solution. Add water for injection to QS volume.
5. Check pH and adjust again as in step 4.
6. Under aseptic conditions, filter by using a peristaltic pump through a 0.2-μm nylon membrane disc into a sterilized glass vessel. Sample.
7. Close the container and store refrigerated until ready for filling (NMT 5 days after the preparation).
8. Target fill to be with 17% excess, 292500 IU/vial, ca. 5.85 mL.
9. Lyophilize at –46°C to –55°C; break vacuum with filtered N_2 gas. Apply stoppers after removing vials aseptically; apply aluminum overseals. Sample.

Valproate Sodium Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Valproic acid as valproate sodium	115.25	g
0.40	mg	2	Disodium edetate	0.40	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill 5 mL per vial as single dose.

Valrubicin for Intravesical Instillation

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Valrubicin	40.00	g
0.50	mL	2	Cremaphor® EL (polyoxyethyleneglycol triricinoleate)	0.50	mL
0.50	mL	3	Dehydrated alcohol	QS to 1.00	L

Note: Dilute before administration.

Vancomycin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	g	1	Vancomycin HCl, USP	1.00[a]	g
QS	mL	2	Sodium hydroxide for pH adjustment	QS	
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Water for injection, USP	QS	
QS		5	Nitrogen gas, NF	QS	

[a] Use 0.5 g for 0.5-g strength.

Manufacturing Directions

1. Preparation of solution.
   a. Collect ca. 172 L (109 L for 0.5 g) of water for injection into a clean stainless steel tank. Cool.
   b. Add and dissolve item 1 with mixing.
   c. Check and record pH (3.0–4.0). Adjust with 10% hydrochloric acid solution or 2% sodium hydroxide solution, if necessary.
   d. QS with water for injection to bring volume to 217 L (137 L for 0.5 g). Mix slowly.
   e. Check and record pH; again adjust as in step 1c.
   f. Filter solution through a previously rinsed filter press and recirculate for approximately 30 minutes.
   g. Filter solution through a 0.2-μm filter into a clean stainless steel tank.
   h. Sample for testing.
   i. Store solution at 2°C to 8°C until ready for filling.
2. Sterile filtration and setup of initial stoppering.
   a. Connect portable tank to sterilized 0.2-mm nylon membrane disc filters. Connect the sterile lead-off hose to the outlet side of the sterile filter and the other end of the lead-off hose into the sterile bottle.
   b. Apply N_2 gas pressure to tank to provide adequate filtration rate.
   c. Transfer the sterile lead-off hose to the sterile surge bottle. Fill surge bottle with sterile-filtered solution.
   d. Sample for testing.
   e. Aseptically fill appropriate volume into each sterilized vial. Place lyophilization stoppers loosely on each vial. Place filled vials into sterilized stainless steel trays with stainless steel rings.
3. Drying/Final stoppering.
   a. Place filled vials into transport rack and transfer to lyophilizer. Start lyophilization cycle. Bring solution to 5°C. Reduce temperature to –40°C and keep at this temperature for 3.5 hours. Start vacuum and raise temperature to –20°C and keep at this temperature for 3 hours. Raise temperature to –15°C and keep at this temperature for 24 hours. Raise temperature to 15°C and keep at this temperature for 6 hours. Raise temperature to 35°C and hold for 6 hours.
   b. Stopper vials after lyophilization.
4. Oversealing and inspection.
   a. Apply aluminum overseals.
   b. Inspect each vial for defects.
   c. Sample for testing.

Varicella Virus Vaccine Live

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1350	PFU[a]	1	Varicella virus	2700,000	PFU
25.00	mg	2	Sucrose	50.00	g
12.50	mg	3	Hydrolyzed gelatin	25.00	g
3.20	mg	4	Sodium chloride	6.40	g
0.50	mg	5	Monosodium L-glutamate	1.00	g
0.45	mg	6	Sodium phosphate dibasic	0.90	g
0.08	mg	7	Potassium phosphate monobasic	0.16	g
0.08	mg	8	Potassium chloride	0.16	g
QS	mL	9	Water for injection, USP	QS to 1.00	L

[a]Plate forming units; may contain traces of EDTA, neomycin, and fetal bovine serum. Fill into 0.5-mL container. Above concentration achieved after reconstitution.

Vasopressin (8-Arginine Vasopressin) Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	U	1	Vasopressin (8-arginine vasopressin)	20,000	P Units
0.50	%	2	Chlorobutanol	5.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Glacial acetic acid for pH adjustment	QS	

Manufacturing Directions

1. Place 500 mL of water for injection into a clean compounding tank.
2. Add premeasured quantity of chlorobutanol to the compound tank and mix until a clear solution is obtained.
3. Add item 1 to the tank and mix thoroughly until a clear solution is obtained.
4. Bring the final volume QS with item 3.
5. Check the pH (2.5–4.5); adjust pH with item 4, if necessary.
6. Sample for testing.
7. After laboratory testing, sterile-filter through 0.22-μm filter membrane.
8. Fill into type I flint vials with gray stoppers without coating.

Vecuronium Bromide for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Vecuronium bromide	1.00	g
1.52	mg	2	Citric acid anhydrous	1.52	g
1.625	mg	3	Sodium phosphate dibasic	1.625	g
9.70	mg	4	Mannitol	9.70	g
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Phosphoric acid for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Fill 10 or 20 mL per vial and lyophilize; adjust to pH 4.0 with item 5 or 6. Use bacteriostatic water for injection for reconstitution (containing 0.9% benzyl alcohol); do not use bacteriostatic water for injection for newborns.

Verapamil Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.50	mg	1	Verapamil hydrochloride, USP	2.50	g
85.00	mg	2	Sodium chloride, USP	85.00	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	mL
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	cy	5	Nitrogen gas, NF	QS	cy

Manufacturing Directions

Note: Fill the product in sterile conditions under N_2 cover.

1. Collect 0.99 L of item 4 in a suitable stainless steel vessel. Purge item 5 throughout processing.
2. Add and dissolve items 1 and 2. Make up volume with item 4.
3. Check pH (4.5–5.0). Adjust with item 3, if necessary (approximate volume to be used, 0–6 mL).
4. Prepare pressurized vessel with N_2 for sterile filling. Sterilize filling unit, jars, and so on at 121°C for 1 hour. Sterilize type I glass ampoule at 210°C to 220°C for 2 hours.
5. Filter solution through a 0.22-μm membrane filter. Perform bubble point test before and after filtration.
6. Fill 2.15 mL into ampoules through inline sintered glass. Flush headspace with N_2.
7. Sterilize in autoclave at 121°C for 20 minutes.
8. Sample for leak test. Perform other testing.

Vinblastine Sulfate for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Vinblastine sulfate, USP[a]	2.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L

[a] Weight given is on anhydrous basis. Obtain water content from raw material specification and apply correction as follows: Mass required (g) = (10.60 × 100)/(100 – % water).

Manufacturing Directions

Caution: Vinblastine sulfate is a potent cytotoxic agent—handle with care.

1. Place approximately 900 mL of water for injection into a suitable stainless steel container.
2. Add item 1 to the tank stir until completely dissolved.
3. Check pH (3.5–5.0).
4. QS to volume with item 2.
5. Sample for testing.
6. After laboratory approval, filter through a 0.22-μm filter into a clean receiving vessel and proceed to fill into type I flint vials with 841 gray stoppers without coating.
7. Lyophilize the filled vials.
8. Transfer the filled vials in covered trays onto the shelves of lyophilizer.
9. Place thermocouples in representative vials.
10. Set the temperature controller to –40°C.
11. The thermocouples should register –40°C or less for at least 4 hours before starting the drying cycle.
12. Start condenser and let it cool to –50°C or less before pulling the vacuum.
13. Let the chamber achieve a level of 150 μm or less.
14. Set the temperature controller to +15°C and let it run for at least 18 hours.
15. Raise the shelf temperature to +25°C and run for approximately 10 hours till all the probes register +25°C (± 2°C) and hold for an additional 8 hours.
16. Bleed the chamber slowly with sterile dry N_2 gas.
17. Stopper vials using internal stoppering mechanism (or with depyrogenated cover in the laminar hood after withdrawing from the lyophilizer).
18. After withdrawal of the vials, clean and deice the lyophilizer.

Vincristine Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Vincristine sulfate, USP[a]	1.20	g
100.00	mg	2	Mannitol, USP	120.00	g
1.30	mg	3	Methyl paraben, NF	1.56	g
0.20	mg	4	Propyl paraben, NF	0.24	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Acetic acid 5% for pH adjustment	QS	
QS	mL	7	Sodium acetate 5% for pH adjustment	QS	

[a] Weight given is on anhydrous basis. Obtain water content from raw material specification and apply correction as follows:
Mass required (g) = (1.20 × 100)/(100 – % water)

Manufacturing Directions

Caution: Vincristine sulfate is a potent cytotoxic agent—handle with care. It is also light sensitive. All solutions should be protected from light as much as possible.

1. Place approximately 800 mL item 5 into a suitable mixing tank. Heat the water to approximately 65°C.
2. Add propyl paraben to the tank and stir vigorously. With constant stirring, maintain temperature till completely dissolved.
3. Add methyl paraben to the tank. Continue stirring until completely dissolved. Maintain temperature.
4. Allow the solution to cool to less than 50°C and then add item 2 with constant stirring until dissolved.
5. Allow the solution to cool down to room temperature (25°C) and then add item 1 and stir.
6. Check pH (4.0–5.0); adjust with either item 6 or 7.
7. Check final pH.
8. QS with item 5.
9. Sample for testing.
10. After laboratory approval, filter through a 0.22-μm filter and fill into type I amber vials with gray Teflon-coated stoppers.

Vincristine Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Vincristine sulfate	1.00	g
1.30	mg	2	Methyl paraben	1.30	g
0.20	mg	3	Propyl paraben	0.20	g
0.375	mg	4	Zinc sulfate heptahydrate	0.375	g
1.90	mg	5	Calcium gluconate monohydrate	1.90	g
50.00	mg	6	Ethanol USP, 95%	50.00	g
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take 0.4 L of item 7 into a suitable stainless steel vessel and dissolve item 1 with agitation.
2. Dissolve item 2 separately in 50 mL of item 7 and added to step 1.
3. Dissolve item 5 separately in 0.3 L of item 7 and add to step 2.
4. Dissolve items 2 and 3 separately in item 6 and add to step 2.
5. Make up volume with item 7.
6. Filter using a 0.22-μm membrane filter and fill aseptically into type I glass ampoules.

Water for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mL	1	Water for injection, USP	1.00	L

Manufacturing Directions

Precaution: Store all bulk water in a tightly closed container. Avoid absorption of CO_2 and other gases.

1. Preparation of water.
   a. Check the water for injection used for injection preparation and verify that it meets conductivity limit of NMT 1 μS/s and pH range of 5.0 to 7.0.
   b. Test the rinsings from the container that are used during solution preparation for conductivity (limit NMT 1.0 μS).
2. Preparation of water.
   a. Add water for injection to the final volume in the preparation tank and transfer to sterile mobile tank.
   b. Transfer the mobile tank from solution preparation area to solution room.
3. Preparation of ampoules. Use type I 10-mL clear glass ampoules, USP.
   a. Wash the ampoules according to operating procedures.
   b. Sterilize the ampoules by using a dry-heat tunnel.
   c. Set the temperature as per latest validation studies with revised cycle.
4. Sterilization. Sterilize the filtration assembly and ampoule-filling machine parts at 122°C for 30 minutes. Set parameters according to the current validated cycle.
5. Sterile filling.
   a. Aseptically connect the N_2 line through the sterile N_2 filter to the inlet of the mobile holding tank as per SOPs.
   b. Aseptically connect one end of the previously sterilized filtration assembly with a 0.22-μm pore-size filtration cartridge to the outlet of the mobile holding tank and the other end to the holding tank.
   c. Before starting the sterile filtration, check the integrity of filter cartridge according to SOPs.
   d. Operate the ampoule-filling machine according to SOPs. Bleed the dosing system as described in the operating procedures. Adjust the fill volume to 10.5 mL.
   e. Sterile-fill 10.5 mL sterile water for injection from the bulk into each sterile, dry clean ampoule and seal it.
6. Terminal sterilization. Sterilize the filled ampoules in a Finn Aqua autoclave at the current validated cycle. Set temperature at 121°C for 20 minutes.
7. Ampoule leak test. Perform the leak test according to SOPs and transfer to optical checking.
8. Optical checking. Inspect the ampoules under the optical checking machine and record and transfer to packaging.

Water for Injection, Bacteriostatic

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
15.00	mg	1	Benzyl alcohol, NF	15.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L

Zinc Sulfate Additive Injection (5-mL Vial)

Bill of Materials					
Scale/mL		Item	Material	Qty	UOM
21.95	mg	1	Zinc sulfate heptahydrate	21.95	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Sulfuric acid for pH adjustment	QS	

Zinc Sulfate Additive Injection (10-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
4.39	mg	1	Zinc sulfate heptahydrate	4.39	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Sulfuric acid for pH adjustment	QS	

Zinc Sulfate Additive Injection (30-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
4.39	mg	1	Zinc sulfate heptahydrate	4.39	g
0.90	%	2	Benzyl alcohol, NF	0.90	%
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Sulfuric acid for pH adjustment	QS	

Manufacturing Directions

1. Add approximately 850 mL of water for injection to a clean mixing tank.
2. Add accurately weighed zinc sulfate and mix until dissolved.
3. Check pH (2.0–4.0); adjust with 10% sulfuric acid (pH 4.0–7.0 used at different strengths).
4. QS to volume with water for injection.
5. Filter through a 0.22-μm filter into a clean receiving container.
6. Fill in type I glass vials with West gray stoppers and flip-off aluminum seals.

Zoledronic Acid for Injection

Bill of Materials (Batch Size 100 Vials)					
Scale/mL		Item	Material	Qty	UOM
4.00	mg	1	Zoledronic acid as zoledronic acid monohydrate	4.264	g
220.00	mg	2	Mannitol	220.00	g
24.00	mg	3	Sodium citrate	24.00	g

Note: Sterile powder for reconstitution for infusion.

COMMERCIAL PHARMACEUTICAL FORMULATIONS

- Abciximab, ReoPro®, is the Fab fragment of the chimeric human-murine monoclonal antibody 7E3. ReoPro is a clear, colorless, sterile, nonpyrogenic solution for IV use. Each single use vial contains 2 mg/mL of abciximab in a buffered solution (pH 7.2) of 0.01 M sodium phosphate, 0.15 M sodium chloride, and 0.001% polysorbate 80 in water for injection. No preservatives are added.
- AccuNeb® (albuterol sulfate) inhalation solution is a sterile, clear, colorless solution of the sulfate salt of racemic albuterol, albuterol sulfate. AccuNeb (albuterol sulfate) inhalation solution is supplied in two strengths in unit dose vials. Each unit dose vial contains either 0.75 mg of albuterol sulfate (equivalent to 0.63 mg of albuterol) or 1.50 mg of albuterol sulfate (equivalent to 1.25 mg of albuterol) with sodium chloride and sulfuric acid in a 3-mL isotonic, sterile aqueous solution. Sodium chloride is added to adjust isotonicity of the solution and sulfuric acid is added to adjust pH of the solution to 3.5.
- Actimmune® (interferon gamma-1b) is a highly purified sterile solution consisting of noncovalent dimers of two identical 16, 465 d monomers; with a specific activity of 20 million IU/mg (2×10^6 IU/0.5 mL) which is equivalent to 30 million U/mg. Actimmune is a sterile, clear colorless solution filled in a single-dose vial for subcutaneous (SC) injection. Each 0.5 mL of Actimmune contains 100 μg (2 million IU) of interferon gamma-1b formulated in 20 mg mannitol, 0.36 mg sodium succinate, 0.05 mg polysorbate 20, and sterile water for injection. Note that the above activity is expressed in international units (1 million IU/50 μg). This is equivalent to what was previously expressed as units (1.5 million U/50 μg).
- Activase (Alteplase) is a tissue plasminogen activator produced by recombinant DNA technology. It is a sterile, purified glycoprotein of 527 amino acids. Phosphoric acid and/or sodium hydroxide may be used prior to lyophilization for pH adjustment. Activase is a sterile, white to off-white, lyophilized powder for IV administration after reconstitution with sterile water for injection, USP. Quantitative composition of the lyophilized product—100-mg vial, 50-mg vial: alteplase, 100 mg (58 million IU), 50 mg (29 million IU); L-arginine, 3.5 g, 1.7 g; phosphoric acid, 1 g, 0.5 g; polysorbate 80, ≤ 11 mg, ≤ 4 mg; vacuum, no, yes.
- Adenocard® (adenosine injection) is a sterile, nonpyrogenic solution for rapid bolus IV injection. Each milliliter contains 3 mg adenosine and 9 mg sodium chloride in water for injection. The pH of the solution is between 4.5 and 7.5. The Ansyr® plastic syringe is molded from a specially formulated polypropylene. Water permeates from inside the container at an extremely slow rate, which will have an insignificant effect on solution concentration over the expected shelf life. Solutions in contact with the plastic container may leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the syringe material.
- Adenoscan (adenosine) vial contains a sterile, nonpyrogenic solution of adenosine 3 mg/mL and sodium chloride 9 mg/mL in water for injection, QS. The pH of the solution is between 4.5 and 7.5.
- Adriamycin (doxorubicin) is supplied in the hydrochloride form as a sterile red-orange lyophilized powder containing lactose and as a sterile, parenteral isotonic solution with sodium chloride for IV use only. Adriamycin (doxorubicin HCI) for injection, USP: each 10-mg lyophilized vial contains 10 mg of doxorubicin hydrochloride, USP, and 50 mg of lactose monohydrate, NF. Each 20-mg lyophilized vial contains 20 mg of doxorubicin hydrochloride, USP, and 100 mg of lactose monohydrate, NF. Each 50-mg lyophilized vial contains 50 mg of doxorubicin hydrochloride, USP, and 250 mg of lactose monohydrate, NF. Adriamycin (doxorubicin HCI) injection, USP: each 2 mg/mL, 5-mL (10-mg) vial contains 10 mg doxorubicin hydrochloride, USP; sodium chloride, 0.9% (to adjust tonicity) and water for injection, QS; pH adjusted to 3 using hydrochloric acid. Each 2 mg/mL, 10-mL (20-mg) vial contains 20 mg doxorubicin hydrochloride, USP; sodium chloride 0.9% (to adjust tonicity) and water for injection, QS; pH adjusted to 3 using hydrochloric acid. Each 2 mg/mL, 25-mL (50-mg) vial contains 50 mg doxorubicin hydrochloride, USP; sodium chloride 0.9% (to adjust tonicity) and water for injection, QS; pH adjusted to 3 using hydrochloric acid. Each 2 mg/mL, 100-mL (200-mg) multiple dose vial contains 200 mg doxorubicin hydrochloride, USP; sodium chloride 0.9% (to adjust tonicity) and water for injection QS; pH adjusted to 3 using hydrochloric acid.
- Aggrastat (tirofiban hydrochloride) injection premixed is supplied as a sterile solution in water for injection, for IV use only, in plastic containers of 100 or 250 mL. Each 100 mL of the premixed, isosmotic IV injection contains 5.618 mg tirofiban hydrochloride monohydrate equivalent to 5 mg tirofiban (50 μg/mL) and the following inactive ingredients: 0.9 mg sodium chloride, 54 mg sodium citrate dihydrate, and 3.2 mg citric acid anhydrous. Each 250 mL of the premixed, isosmotic IV injection contains 14.045 mg tirofiban hydrochloride monohydrate equivalent to 12.5 mg tirofiban (50 μg/mL) and the following inactive ingredients: 2.25 g sodium chloride, 135 mg sodium citrate dihydrate, and 8 mg citric acid anhydrous. Aggrastat injection is a sterile concentrated solution for IV infusion after dilution and is supplied in a 25- or a 50-mL vial. Each milliliter of the solution contains 0.281 mg of tirofiban hydrochloride monohydrate equivalent to 0.25 mg of tirofiban and the following inactive ingredients: 0.16 mg citric acid anhydrous, 2.7 mg sodium citrate dihydrate, 8 mg sodium chloride, and water for injection. The pH ranges from 5.5 to 6.5 and may have been adjusted with hydrochloric acid and/or sodium hydroxide.

- Alamast® (pemirolast potassium ophthalmic solution) is a sterile, aqueous ophthalmic solution with a pH of approximately 8 containing 0.1% of the mast cell stabilizer, pemirolast potassium, for topical administration to the eyes. Each milliliter contains the following: active ingredients: pemirolast potassium, 1 mg (0.1%); preservative—lauralkonium chloride, 0.005%. Inactives—glycerin, dibasic sodium phosphate, monobasic sodium phosphate, phosphoric acid and/or sodium hydroxide to adjust pH, and purified water. The osmolality of Alamast ophthalmic solution is approximately 240 mOsm/kg.
- Albumin (human) 25%, USP, (Plasbumin®-25) is a 25% sterile solution of albumin in an aqueous diluent. The preparation is stabilized with 0.02 M sodium caprylate and 0.02 M acetyltryptophan. The aluminum content of the product is NMT 200 μg/L. The approximate sodium content of the product is 145 mEq/L. It contains no preservative. Plasbumin-25 must be administered intravenously. Each vial of Plasbumin-25 is heat-treated at 60°C for 10 hours against the possibility of transmitting hepatitis viruses. Plasbumin-20 is a 20% sterile solution of albumin in an aqueous diluent. The preparation is stabilized with 0.016 M sodium caprylate and 0.016 M acetyltryptophan. The aluminum content of the product is NMT 200 μg/L. The approximate sodium content of the product is 145 mEq/L. It contains no preservative. Plasbumin-5 is a 5% sterile solution of albumin in an aqueous diluent. The preparation is stabilized with 0.004 M sodium caprylate and 0.004 M acetyltryptophan. The aluminum content of the product is NMT 200 μg/L. The approximate sodium content of the product is 145 mEq/L. It contains no preservative.
- Aldurazyme® (laronidase) is supplied as a sterile, nonpyrogenic, colorless to pale yellow, clear to slightly opalescent solution that must be diluted prior to administration in 0.9% sodium chloride injection, USP, containing 0.1% albumin (human). The solution in each vial contains a nominal laronidase concentration of 0.58 mg/mL and a pH of approximately 5.5. The extractable volume of 5.0 mL from each vial provides 2.9 mg laronidase, 43.9 mg sodium chloride, 63.5 mg sodium phosphate monobasic monohydrate, 10.7 mg sodium phosphate dibasic heptahydrate, and 0.05 mg polysorbate 80. Aldurazyme does not contain preservatives. Vials are for single use only.
- Alferon N Injection® [interferon alpha-n3 (human leukocyte derived)] is a sterile aqueous formulation of purified, natural, human interferon-alpha proteins for use by injection. Each milliliter contains 5 million IU of interferon alpha-n3 in phosphate-buffered saline (8.0 mg sodium chloride, 1.74 mg sodium phosphate dibasic, 0.20 mg potassium phosphate monobasic, and 0.20 mg potassium chloride) containing 3.3 mg phenol as a preservative and 1 mg albumin (human) as a stabilizer.
- Alimta® pemetrexed for injection is supplied as a sterile lyophilized powder for IV infusion available in single-dose vials. The product is a white to either light yellow or green-yellow lyophilized solid. Each 500-mg vial of Alimta contains pemetrexed disodium equivalent to 500 mg pemetrexed and 500 mg of mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.
- Alkeran (melphalan) single-use vial contains melphalan hydrochloride equivalent to 50 mg melphalan and 20 mg povidone. Alkeran for injection is reconstituted using the sterile diluent provided. Each vial of sterile diluent contains sodium citrate 0.2 g, propylene glycol 6.0 mL, ethanol (96%) 0.52 mL, and water for injection to a total of 10 mL. Alkeran for injection is administered intravenously.
- Aloprim (allopurinol sodium) for injection is a sterile solution for IV infusion only. It is available in vials as the sterile lyophilized sodium salt of allopurinol equivalent to 500 mg of allopurinol. Aloprim (allopurinol sodium) for injection contains no preservatives.
- Aloxi 1 (palonosetron hydrochloride) injection is a sterile, clear, colorless, nonpyrogenic, isotonic, buffered solution for IV administration. Each 5-mL vial of Aloxi injection contains 0.25 mg palonosetron base as hydrochloride, 207.5 mg mannitol, disodium edetate, and citrate buffer in water for IV administration. The pH of the solution is 4.5 to 5.5.
- Aralast™, alpha-1 proteinase inhibitor (human), is a sterile, stable lyophilized preparation of purified human alpha-1 proteinase inhibitor [(alpha) 1-PI], also known as alpha-1—antitrypsin. Each vial of Aralast is labeled with the amount of functionally active (alpha) 1-PI expressed in milligram per vial. The formulation contains no preservative. The pH of the solution ranges from 7.2 to 7.8. Product must only be administered intravenously.
- AmBisome for injection is a sterile, nonpyrogenic lyophilized product for IV infusion. Each vial contains 50 mg of amphotericin B, USP, intercalated into a liposomal membrane consisting of approximately 213 mg hydrogenated soy phosphatidylcholine; 52 mg cholesterol, NF; 84 mg distearoylphosphatidylglycerol; 0.64 mg alpha-tocopherol, USP; together with 900 mg sucrose, NF; and 27 mg disodium succinate hexahydrate as buffer. Following reconstitution with sterile water for injection, USP, the resulting pH of the suspension is between 5 and 6. AmBisome is a true single bilayer liposomal drug delivery system.
- Amevive® (alefacept) is supplied as a sterile, white to off-white, preservative-free, lyophilized powder for parenteral administration. After reconstitution with 0.6 mL of the supplied sterile water for injection, USP, the solution of Amevive is clear, with a pH of approximately 6.9. Amevive is available in two formulations. Amevive for IM injection contains 15 mg alefacept per 0.5 mL of reconstituted solution. Amevive for IV injection contains 7.5 mg alefacept per 0.5 mL of reconstituted solution. Both formulations also contain 12.5 mg sucrose, 5.0 mg glycine, 3.6 mg sodium citrate dihydrate, and 0.06 mg citric acid monohydrate per 0.5 mL.
- Aminohippurate sodium is provided as a sterile, nonpreserved 20% aqueous solution for injection, with a pH of 6.7 to 7.6. Each 10 mL contains aminohippurate sodium, 2 g. Inactive ingredients: sodium hydroxide to adjust pH, water for injection, QS.
- Ammonul® (sodium phenylacetate and sodium benzoate) injection 10%/10% is a sterile, concentrated aqueous solution of sodium phenylacetate and sodium benzoate. The pH of the solution is between 6 and 8. Each milliliter of Ammonul contains 100 mg of sodium phenylacetate and 100 mg of sodium benzoate and water for injection. Sodium hydroxide and/or hydrochloric acid may have been used for pH adjustment.
- Antihemophilic Factor (human), Koate®-DVI, is a sterile, stable, purified, dried concentrate of human antihemophilic factor (AHF, factor VIII, AHG) which has been treated with tri-*n*-butyl phosphate (TNBP) and polysorbate 80 and heated in lyophilized form in the final container at 80°C for 72 hours. Koate-DVI is intended for use in therapy of classical hemophilia (hemophilia A).

- Antivenin (*Latrodectus mactans*) is a sterile, nonpyrogenic preparation derived by drying a frozen solution of specific venom-neutralizing globulins obtained from the blood serum of healthy horses immunized against venom of black widow spiders (*L. mactans*). Each vial contains not less than 6000 antivenin units. One unit of antivenin will neutralize one average mouse lethal dose of black widow spider venom when the antivenin and the venom are injected simultaneously in mice under suitable conditions.
- Antivenin (*Micrurus fulvius*) is a refined, concentrated, and lyophilized preparation of serum globulins obtained by fractionating blood from healthy horses that have been immunized with eastern coral snake (*M. fulvius fulvius*) venom. Prior to lyophilization, the product contains 0.25% phenol and 0.005% thimerosal (mercury derivative).
- Apokyn™ (apomorphine hydrochloride, USP) 10 mg/mL is a clear, colorless sterile solution for SC injection and is available in 2-mL ampoules and 3-mL cartridges. Each milliliter of solution contains 10 mg of apomorphine hydrochloride, USP, as apomorphine hydrochloride hemihydrate and 1 mg of sodium metabisulfite, NF, in water for injection, USP. In addition, each milliliter of solution may contain sodium hydroxide, NF, and/or hydrochloric acid, NF, to adjust the pH of the solution. In addition, the cartridges contain 5 mg/mL of benzyl alcohol.
- Aquacel® Ag with Hydrofiber® (Aquacel Ag) silver impregnated antimicrobial dressing is a soft, sterile nonwoven pad or ribbon dressing composed of sodium carboxymethylcellulose and 1.2% ionic silver which allows for a maximum of 12 mg of silver for 4 in × 4 in dressing.
- AquaMEPHYTON phytonadione is a vitamin which is a clear, yellow to amber, viscous, odorless or nearly odorless liquid. AquaMEPHYTON injection is a yellow, sterile, aqueous colloidal solution of vitamin K1, with a pH of 5.0 to 7.0, available for injection by IV, IM, and SC routes. Each milliliter contains phytonadione, 2 or 10 mg. Inactive ingredients: polyoxyethylated fatty acid derivative, 70 mg; dextrose, 37.5 mg; water for injection, QS, 1 mL; added as preservative—benzyl alcohol, 0.9%.
- Aramine, metaraminol bitartrate, contains metaraminol bitartrate equivalent to metaraminol 10 mg. Inactive ingredients: sodium chloride, 4.4 mg; water for injection, QS, add 1 mL; methyl paraben, 0.15%; propyl paraben, 0.02%; and sodium bisulfite, 0.2%, added as preservatives.
- Aranesp® is formulated as a sterile, colorless, preservative-free protein solution for IV or SC administration. Single-dose vials are available containing 25, 40, 60, 100, 150, 200, 300, or 500 μg of Aranesp. Single-dose prefilled syringes are available containing 25, 40, 60, 100, 150, 200, 300, or 500 μg of Aranesp. Single-dose vials and prefilled syringes are available in two formulations that contain excipients as follows: polysorbate solution, each milliliter contains 0.05 mg polysorbate 80, and is formulated at pH 6.2±0.2 with 2.12 mg sodium phosphate monobasic monohydrate, 0.66 mg sodium phosphate dibasic anhydrous, and 8.18 mg sodium chloride in water for injection, USP (to 1 mL); albumin solution, each milliliter contains 2.5 mg albumin (human) and is formulated at pH 6.0±0.3 with 2.23 mg sodium phosphate monobasic monohydrate, 0.53 mg sodium phosphate dibasic anhydrous, and 8.18 mg sodium chloride in water for injection, USP (to 1 mL).
- Attenuvax (measles virus vaccine live) is a live virus vaccine for vaccination against measles (rubeola). The reconstituted vaccine is for SC administration. Each 0.5-mL dose contains not less than 1000 tissue culture infectious doses (TCID) of measles virus. Each dose of the vaccine is calculated to contain sorbitol (14.5 mg), sodium phosphate, sucrose (1.9 mg), sodium chloride, hydrolyzed gelatin (14.5 mg), human albumin (0.3 mg), fetal bovine serum (<1 ppm), other buffer and media ingredients, and approximately 25 μg of neomycin. The product contains no preservative. Before reconstitution, the lyophilized vaccine is a light yellow compact crystalline plug. Attenuvax, when reconstituted as directed, is clear yellow.
- Avastin™ (Bevacizumab) is a recombinant humanized monoclonal IgG1 antibody. Avastin is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for IV infusion. Avastin is supplied in 100- and 400-mg preservative-free, single-use vials to deliver 4 or 16 mL of Avastin (25 mg/mL). The 100-mg product is formulated in 240 mg (alpha), (alpha)-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and water for injection, USP. The 400 mg product is formulated in 960 mg (alpha), (alpha)-trehalose dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and water for injection, USP.
- Avonex® (interferon beta-1a) is formulated as a sterile, white to off-white lyophilized powder for IM injection after reconstitution with supplied diluent (sterile water for injection, USP). Each vial of reconstituted Avonex contains 30 μg of interferon beta-1a; 15 mg albumin (human), USP; 5.8 mg sodium chloride, USP; 5.7 mg dibasic sodium phosphate, USP; and 1.2 mg monobasic sodium phosphate, USP, in 1 mL at a pH of approximately 7.3. A prefilled syringe of Avonex is formulated as a sterile liquid for IM injection. Each 0.5-mL (30-μg) dose of Avonex in a prefilled glass syringe contains 30 μg of interferon beta-1a; 0.79 mg sodium acetate trihydrate, USP; 0.25 mg glacial acetic acid, USP; 15.8 mg arginine hydrochloride, USP; and 0.025 mg polysorbate 20 in water for injection, USP, at a pH of approximately 4.8.
- Azopt® (brinzolamide ophthalmic suspension), 1%, is supplied as a sterile, aqueous suspension of brinzolamide which has been formulated to be readily suspended and slow settling, following shaking. It has a pH of approximately 7.5 and an osmolality of 300 mOsm/kg. Each milliliter of Azopt (brinzolamide ophthalmic suspension), 1%, contains 10 mg brinzolamide. Inactive ingredients are mannitol, carbomer 974P, tyloxapol, edetate disodium, sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH), and purified water. Benzalkonium chloride, 0.01%, is added as a preservative.
- BeneFIX®, coagulation factor IX (recombinant), is available in single-use vials containing the labeled amount of factor IX activity, expressed in international units. Each vial contains nominally 250, 500 or 1000 IU of coagulation factor IX (recombinant). After reconstitution of the lyophilized drug product, the concentrations of excipients in the 500- and 1000-IU dosage strengths are 10 mM L-histidine, 1% sucrose, 260 mM glycine, 0.005% polysorbate 80. The concentrations after reconstitution in the 250-IU dosage strength are half those of the other two dosage strengths. The 500- and 1000-IU dosage strengths are isotonic after reconstitution and the 250 IU dosage strength has half the tonicity of the other two dosage strengths after reconstitution.

All dosage strengths yield a clear, colorless solution upon reconstitution.

- Betadine®, povidone-iodine is a broad-spectrum microbicide. Betadine, 5%, sterile ophthalmic prep solution contains 5% povidone-iodine (0.5% available iodine) as a sterile dark brown solution stabilized by glycerin. Inactive ingredients: citric acid, glycerin, nonoxynol-9, sodium chloride, sodium hydroxide, and dibasic sodium phosphate.
- Betaseron® (interferon beta-lb) vial contains 0.3 mg of interferon beta-lb. Mannitol, USP, and albumin (human), USP (15 mg/vial), are added as stabilizers. Lyophilized Betaseron is a sterile, white to off-white powder for SC injection after reconstitution with the diluent supplied (sodium chloride, 0.54% solution).
- Betimol® (timolol ophthalmic solution), 0.25% and 0.5%, is a clear, colorless, isotonic, sterile microbiologically preserved phosphate buffered aqueous solution. It is supplied in two dosage strengths, 0.25% and 0.5%. Each milliliter of Betimol, 0.25%, contains 2.56 mg of timolol hemihydrate equivalent to 2.5 mg timolol. Each milliliter of Betimol, 0.5%, contains 5.12 mg of timolol hemihydrate equivalent to 5.0 mg timolol. Inactive ingredients: monosodium and disodium phosphate dihydrate to adjust pH (6.5–7.5) and water for injection, benzalkonium chloride, 0.01%, added as preservative. The osmolality of Betimol is 260 to 320 mOsm/kg.
- Betoptic S® ophthalmic suspension, 0.25%, contains the following in each milliliter: active—betaxolol HCl, 2.8 mg, equivalent to 2.5 mg of betaxolol base; preservative—benzalkonium chloride 0.01%; inactive—mannitol, poly(styrene-divinyl benzene) sulfonic acid, carbomer 934P, edetate disodium, hydrochloric acid or sodium hydroxide (to adjust pH), and purified water.
- Boostrix® (tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed) (Tdap) is a noninfectious, sterile vaccine adsorbed onto aluminum hydroxide. Both toxins are detoxified with formaldehyde; concentrated by ultrafiltration; and purified by precipitation, dialysis, and sterile filtration. Each antigen is individually adsorbed onto aluminum hydroxide. All antigens are then diluted and combined to produce the final formulated vaccine. Each 0.5-mL dose is formulated to contain 2.5 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, 2.5 μg of pertactin, 8 μg of FHA, and 8 μg of inactivated PT. Each 0.5-mL dose also contains 4.5 mg of NaCl, aluminum adjuvant (NMT 0.39 mg aluminum by assay), ≤100 μg of residual formaldehyde, and ≤100 μg of polysorbate 80 (Tween 80). This vaccine does not contain a preservative.
- Buminate, 25%, albumin (human), 25% solution is a sterile, nonpyrogenic preparation of albumin in a single-dosage form for IV administration. Each 100 mL contains 25 g of albumin and is prepared from human venous plasma using the Cohn cold ethanol fractionation process. It has been adjusted to physiological pH with sodium bicarbonate and/or sodium hydroxide and stabilized with sodium acetyltryptophanate and sodium caprylate. The sodium content is 145±15 mEq/L. This solution contains no preservative and none of the coagulation factors found in fresh whole blood or plasma. Buminate 25%, albumin (human), 25% solution is a transparent or slightly opalescent solution which may have a greenish tint or may vary from a pale straw to an amber color. Buminate 5%, albumin (human), 5% solution, is a sterile, nonpyrogenic preparation of albumin in a single-dosage form for IV administration. Buminate 5%, albumin (human), 5% solution, contains no blood group isoagglutinins thereby permitting its administration without regard to the recipient's blood group. Each 100 mL contains 5 g of albumin and was prepared from human venous plasma using the Cohn cold ethanol fractionation process. Source material for fractionation may be obtained from another U.S. licensed manufacturer. It has been adjusted to physiological pH with sodium bicarbonate and/or sodium hydroxide and has been stabilized with sodium acetyltryptophanate and sodium caprylate. The sodium content is 145±15 mEq/L. The solution contains no preservative and none of the coagulation factors found in fresh whole blood or plasma. Buminate 5%, albumin (human), 5% solution, is a transparent or slightly opalescent solution which may have a greenish tint or may vary from a pale straw to an amber color.
- Byetta™ (exenatide) injection is supplied for SC injection as a sterile, preserved isotonic solution in a glass cartridge that has been assembled in a pen injector (pen). Each milliliter contains 250 μg synthetic exenatide, 2.2 mg metacresol as an antimicrobial preservative, mannitol as a tonicity-adjusting agent, and glacial acetic acid and sodium acetate trihydrate in water for injection as a buffering solution at pH 4.5. Two prefilled pens are available to deliver unit doses of 5 or 10 μg. Each prefilled pen will deliver 60 doses to provide 30 days of twice daily administration (BID).
- Calcijex® (calcitriol injection). Each milliliter contains calcitriol, 1 μg; polysorbate 20, 4 mg; sodium ascorbate, 2.5 mg added. May contain hydrochloric acid and/or sodium hydroxide for pH adjustment; pH is 6.5 (5.9–7.0). Contains no more than 1 μg/mL of aluminum.
- Calcium disodium versenate (edetate calcium disodium injection, USP) is a sterile, injectable chelating agent in concentrated solution for IV infusion or IM injection. Each 5-mL ampoule contains 1000 mg of edetate calcium disodium (equivalent to 200 mg/mL) in water for injection.
- Campath® (Alemtuzumab) single-use vial of Campath contains 30 mg alemtuzumab, 8.0 mg sodium chloride, 1.44 mg dibasic sodium phosphate, 0.2 mg potassium chloride, 0.2 mg monobasic potassium phosphate, 0.1 mg polysorbate 80, and.0187 mg disodium edetate dihydrate. No preservatives are added.
- Cancidas is a sterile, lyophilized product for IV infusion that contains a semisynthetic lipopeptide (echinocandin) compound synthesized from a fermentation product of *Glarea lozoyensis*. Cancidas, 50 mg, also contains 39 mg sucrose, 26 mg mannitol, glacial acetic acid, and sodium hydroxide. Cancidas, 70 mg, also contains 54 mg sucrose, 36 mg mannitol, glacial acetic acid, and sodium hydroxide.
- Carnitor® (levocarnitine) injection is a sterile aqueous solution containing 1 g of levocarnitine per 5 mL vial. The pH is adjusted to 6.0 to 6.5 with hydrochloric acid or sodium hydroxide.
- Cathflo® Activase® (alteplase) is a tissue plasminogen activator (t-PA) produced by recombinant DNA technology. It is a sterile, purified glycoprotein of 527 amino acids. Cathflo Activase is a sterile, white to pale yellow, lyophilized powder for intracatheter instillation for restoration of function to central venous access devices following reconstitution with sterile water for injection, USP. Each vial of Cathflo Activase contains 2.2 mg of alteplase (which includes a 10% overfill), 77 mg of L-arginine, 0.2 mg of polysorbate 80, and phosphoric acid for pH adjustment. Each reconstituted vial will deliver 2 mg of Cathflo Activase, at a pH of approximately 7.3.

- Cefoxitin sodium contains approximately 53.8 mg (2.3 mEq) of sodium per gram of cefoxitin activity. Premixed IV solution Mefoxin (cefoxitin sodium injection) is supplied as a sterile, nonpyrogenic, frozen isosmotic solution of cefoxitin sodium. Each 50 mL contains cefoxitin sodium equivalent to either 1 or 2 g of cefoxitin. Dextrose hydrous USP has been added to the above dosages to adjust osmolality (approximately 2 g and 1.1- to 1- and 2-g dosages, respectively). The pH is adjusted with sodium bicarbonate and may have been adjusted with hydrochloric acid. The pH is approximately 6.5. After thawing, the solution is intended for IV use only. Solutions of Mefoxin range from colorless to light amber.
- Cerubidine (daunorubicin hydrochloride) is the hydrochloride salt of an anthracycline cytotoxic antibiotic produced by a strain of *Streptomyces coeruleorubidus*. It is provided as a sterile, reddish lyophilized powder in vials for IV administration only. Each vial contains 21.4 mg daunorubicin hydrochloride (equivalent to 20 mg of daunorubicin) and 100 mg mannitol. It is soluble in water when adequately agitated and produces a reddish solution.
- Ciloxan® (ciprofloxacin hydrochloride ophthalmic ointment) contains the following: active—ciprofloxacin HCl, 3.33 mg, equivalent to 3-mg base; inactives—mineral oil, white petrolatum.
- Cipro IV ciprofloxacin solution is available as a sterile 1.0% aqueous concentrate, which is intended for dilution prior to administration. Ciprofloxacin solution contains lactic acid as a solubilizing agent and hydrochloric acid for pH adjustment. The pH range for the 1.0% aqueous concentrate is 3.3 to 3.9.
- Ciprodex® (ciprofloxacin, 0.3%, and dexamethasone, 0.1%) sterile otic contains ciprofloxacin hydrochloride (equivalent to 3 mg ciprofloxacin base), 1 mg dexamethasone, and 0.1 mg benzalkonium chloride as a preservative. The inactive ingredients are boric acid, sodium chloride, hydroxyethyl cellulose, tyloxapol, acetic acid, sodium acetate, edetate disodium, and purified water. Sodium hydroxide or hydrochloric acid may be added for adjustment of pH.
- Cogentin (benztropine mesylate) is supplied as a sterile injection for IV and IM use. Benztropine mesylate is a synthetic compound containing structural features found in atropine and diphenhydramine. Each milliliter of the injection contains benztropine mesylate, 1 mg; sodium chloride, 9 mg; water for injection, QS, 1 mL.
- Comvax [Haemophilus B conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine] is a sterile bivalent vaccine made of the antigenic components used in producing PedvaxHIB [Haemophilus B conjugate vaccine (meningococcal protein conjugate)] and Recombivax HB [hepatitis B vaccine (recombinant)]. The individual PRP-OMPC and HBsAg adjuvanted bulks are combined to produce Comvax. Each 0.5-mL dose of Comvax is formulated to contain 7.5 μg PRP conjugated to approximately 125 μg OMPC, 5 μg HBsAg, approximately 225 μg aluminum as amorphous aluminum hydroxyphosphate sulfate, and 35 μg sodium borate (decahydrate) as a pH stabilizer, in 0.9% sodium chloride. The vaccine contains NMT 0.0004% (w/v) residual formaldehyde. The product contains no preservative. Comvax is a sterile suspension for IM injection.
- Copaxone® (glatiramer acetate) consists of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with an average molar fraction of 0.141, 0.427, 0.095, and 0.338, respectively. The average molecular weight of glatiramer acetate is 5 000 to 9 000 Da. Glatiramer acetate is identified by specific antibodies. Chemically, glatiramer acetate is designated L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt). Copaxone injection is a clear, colorless to slightly yellow, sterile nonpyrogenic solution for SC injection. Each 1 mL of solution contains 20 mg of glatiramer acetate and 40 mg of mannitol, USP. The pH range of the solution is approximately 5.5 to 7.0
- Cosmegen dactinomycin is a sterile, yellow lyophilized powder for injection by the IV route or by regional perfusion after reconstitution. Each vial contains 0.5 mg (500 μg) of dactinomycin and 20.0 mg of mannitol.
- Cosopt (dorzolamide hydrochloride-timolol maleate ophthalmic solution) is supplied as a sterile, isotonic, buffered, slightly viscous aqueous solution. The pH of the solution is approximately 5.65 and the osmolarity is 242 to 323 mOsm. Each milliliter of Cosopt contains 20 mg dorzolamide (22.26 mg of dorzolamide hydrochloride) and 5 mg timolol (6.83 mg timolol maleate). Inactive ingredients are sodium citrate, hydroxyethyl cellulose, sodium hydroxide, mannitol, and water for injection. Benzalkonium chloride (0.0075%) is added as a preservative.
- Cubicin is supplied as a sterile, preservative-free, pale yellow to light brown lyophilized cake containing approximately 900 mg/g of daptomycin for IV use following reconstitution with 0.9% sodium chloride injection. The only inactive ingredient is sodium hydroxide which is used in minimal quantities for pH adjustment. Freshly reconstituted solutions of cubicin range in color from pale yellow to light brown.
- Curosurf® (poractant alpha) intratracheal suspension is a sterile, nonpyrogenic pulmonary surfactant intended for intratracheal use only. It is suspended in 0.9% sodium chloride solution. The pH is adjusted as required with sodium bicarbonate to a pH of 6.2 (5.5–6.5). Curosurf contains no preservatives. Curosurf is a white to creamy white suspension of poractant alpha. Each milliliter of surfactant mixture contains 80 mg of surfactant (extract) that includes 76 mg of phospholipids and 1 mg of protein of which 0.2 mg is SP-B. The amount of phospholipids is calculated from the content of phosphorus and contains 55 mg of phosphatidylcholine of which 30 mg is dipalmitoylphosphatidylcholine.
- CytoGam®, cytomegalovirus immune globulin intravenous (human) (CMV-IGIV), is an immunoglobulin G (IgG) containing a standardized amount of antibody to CMV. CMV-IGIV is formulated in final vial as a sterile liquid. The globulin is stabilized with 5% sucrose and 1% albumin (human). CytoGam contains no preservative. Each milliliter contains 50±10 mg of immunoglobulin, primarily IgG, and trace amounts of IgA and IgM; 50 mg of sucrose; 10 mg of albumin (human). The sodium content is 20 to 30 mEq/L, that is, 0.4 to 0.6 mEq/20 mL or 1.0 to 1.5 mEq/50 mL. The solution should appear colorless and translucent.
- Dantrium intravenous is a sterile, nonpyrogenic lyophilized formulation of dantrolene sodium for injection. Dantrium intravenous is supplied in 70-mL vials containing 20 mg dantrolene sodium, 3000 mg mannitol, and sufficient sodium hydroxide to yield a pH of approximately 9.5 when reconstituted with 60 mL sterile water for injection USP (without a bacteriostatic agent).

- Decadron dexamethasone sodium phosphate injection is a sterile solution (pH 7.0–8.5) of dexamethasone sodium phosphate, sealed under nitrogen, and is supplied in two concentrations: 4 mg/mL and 24 mg/mL. Each milliliter of Decadron phosphate injection, 4 mg/mL, contains dexamethasone sodium phosphate equivalent to 4 mg dexamethasone phosphate or 3.33 mg dexamethasone. Inactive ingredients per milliliter: 8 mg creatinine, 10 mg sodium citrate, sodium hydroxide to adjust pH, and water for injection, QS, with 1 mg sodium bisulfite, 1.5 mg methyl paraben, and 0.2 mg propyl paraben added as preservatives. Each milliliter of Decadron phosphate injection, 24 mg/mL, contains dexamethasone sodium phosphate equivalent to 24 mg dexamethasone phosphate or 20 mg dexamethasone. Inactive ingredients per milliliter: 8 mg creatinine, 10 mg sodium citrate, 0.5 mg disodium edetate, sodium hydroxide to adjust pH, and water for injection, QS, with 1 mg sodium bisulfite, 1.5 mg methylparaben, and 0.2 mg propylparaben added as preservatives.
- DepoDur (morphine sulfate extended-release liposome injection) is a sterile, nonpyrogenic, white to off-white, preservative-free suspension of multivesicular lipid-based particles containing morphine sulfate, USP. The median diameter of the liposome particles is in the range of 17 to 23 μm. The liposomes are suspended in a 0.9% sodium chloride solution. Each vial contains morphine sulfate (expressed as the pentahydrate) at a nominal concentration of 10 mg/mL. Inactive ingredients and their approximate concentrations are 1, 2-dioleoyl- sn-glycero-3-phosphocholine (DOPC), 4.2 mg/mL; cholesterol, 3.3 mg/mL; 1, 2-dipalmitoyl- sn -glycero-3-phospho-rac-(1-glycerol) (DPPG), 0.9 mg/mL; tricaprylin, 0.3 mg/mL; and triolein, 0.1 mg/mL. The pH of DepoDur is in the range of 5.0 to 8.0.
- Depo-Medrol sterile aqueous suspension contains methylprednisolone acetate. Depo-Medrol is an anti-inflammatory glucocorticoid for IM, intrasynovial, soft tissue, or intralesional injection. It is available as single-dose vials in two strengths: 40 and 80 mg/mL. Each mL of these preparations contains methylprednisolone acetate, 40 or 80 mg; polyethylene glycol 3350, 29 or 28 mg; myristyl-gamma-picolinium chloride, 0.195 or 0.189 mg. Sodium chloride was added to adjust tonicity. When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid. The pH of the finished product remains within the USP specified range, that is, 3.5 to 7.0. Also available as 20 mg/mL.
- Depo-Provera contraceptive injection (CI) contains medroxyprogesterone acetate. Depo-Provera CI for IM injection is available in vials and prefilled syringes, each containing 1 mL of medroxyprogesterone acetate sterile aqueous suspension 150 mg/mL. Each milliliter contains medroxyprogesterone acetate,150 mg; polyethylene glycol 3350, 28.9 mg; polysorbate 80, 2.41 mg; sodium chloride, 8.68 mg; methyl paraben, 1.37 mg; propyl paraben, 0.150 mg; water for injection, QS. When necessary, pH is adjusted with sodium hydroxide or hydrochloric acid, or both.
- Depo-subQ provera 104 contains medroxyprogesterone acetate (MPA). Depo-subQ provera 104 for SC injection is available in prefilled syringes (160 mg/mL), each containing 0.65 mL (104 mg) of medroxyprogesterone acetate sterile aqueous suspension. Each 0.65 mL contains medroxyprogesterone acetate, 104 mg; methyl paraben, 1.040 mg; propyl paraben, 0.098 mg; sodium chloride, 5.200 mg; polyethylene glycol, 18.688 mg; polysorbate 80, 1.950 mg; monobasic sodium phosphate.H_2O, 0.451 mg; dibasic sodium phosphate.$12H_2O$, 0.382 mg; methionine, 0.975 mg; povidone, 3.250 mg; water for injection, QS. When necessary, the pH is adjusted with sodium hydroxide or hydrochloric acid, or both.
- Desferal, deferoxamine mesylate USP, is available in vials for IM, SC, and IV administration. Desferal is supplied as vials containing 500 mg and 2 g of deferoxamine mesylate USP, in sterile, lyophilized form.
- Digibind, digoxin immune Fab (ovine), is a sterile lyophilized powder of antigen-binding fragments (Fab) derived from specific antidigoxin antibodies raised in sheep. Each vial, which will bind approximately 0.5 mg of digoxin (or digitoxin), contains 38 mg of digoxin-specific Fab fragments derived from sheep plus 75 mg of sorbitol as a stabilizer and 28 mg of sodium chloride. The vial contains no preservatives. Digibind is administered by IV injection after reconstitution with sterile water for injection (4 mL/vial).
- Dilaudid (hydromorphone hydrochloride), each 1 mL of sterile solution contains 10 mg hydromorphone hydrochloride with 0.2% sodium citrate and 0.2% citric acid solution. It is also available as lyophilized Dilaudid for IV, SC, or IM administration. Each single-dose vial contains 250 mg sterile, lyophilized hydromorphone HCl to be reconstituted with 25 mL of sterile water for injection USP to provide a solution containing 10 mg/mL. Ampoules (for parenteral administration) containing 1, 2, and 4 mg hydromorphone hydrochloride per milliliter with 0.2% sodium citrate, 0.2% citric acid solution. Dilaudid ampoules are sterile. Multiple-dose vials (for parenteral administration) containing 20 mL of solution. Each milliliter contains 2 mg hydromorphone hydrochloride and 0.5 mg edetate disodium with 1.8 mg methyl paraben and 0.2 mg propyl paraben as preservatives. Sodium hydroxide or hydrochloric acid is used for pH adjustment. Dilaudid multiple-dose vials are sterile.
- Diprivan® (propofol) injectable emulsion in addition to the active component, propofol, the formulation also contains soybean oil (100 mg/mL), glycerol (22.5 mg/mL), egg lecithin (12 mg/mL), and disodium edetate (0.005%), with sodium hydroxide to adjust pH. Diprivan injectable emulsion is isotonic and has a pH of 7.0 to 8.5.
- Diuril (chlorothiazide sodium), IV sodium Diuril, is a sterile lyophilized white powder and is supplied in a vial containing chlorothiazide sodium equivalent to chlorothiazide, 0.5 g; inactive ingredients—mannitol, 0.25 g; sodium hydroxide to adjust pH.
- Doxil® (doxorubicin HCl liposome injection) is doxorubicin hydrochloride (HCl) encapsulated in Stealth® liposomes for IV administration. Doxil is provided as a sterile, translucent red liposomal dispersion in 10- or 30-mL glass single-use vials. Each vial contains 20 or 50 mg doxorubicin HCl at a concentration of 2 mg/mL and a pH of 6.5. The Stealth liposome carriers are composed of *N*-(carbonyl-methoxypolyethylene glycol 2000)-1, 2-distearoyl- sn -glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and cholesterol, 3.19 mg/mL. Each milliliter also contains ammonium sulfate, approximately 2 mg; histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control; and sucrose to maintain isotonicity. More than 90% of the drug is encapsulated in the Stealth liposomes.
- DuoNeb® contains albuterol sulfate and ipratropium bromide. Each 3-mL vial of DuoNeb contains 3.0 mg (0.1%)

of albuterol sulfate [equivalent to 2.5 mg (0.083%) of albuterol base] and 0.5 mg (0.017%) of ipratropium bromide in an isotonic, sterile aqueous solution containing sodium chloride, hydrochloric acid to adjust to pH 4, and edetate disodium, USP (a chelating agent).

- Edex® (alprostadil for injection) is a sterile, pyrogen-free powder containing alprostadil in an alfadex [(alpha)-cyclodextrin] inclusion complex. Edex is supplied in single-dose, dual-chamber cartridges. Edex is lyophilized in single-dose, dual-chamber cartridges intended for use with the reusable Edex injection device. One chamber of the cartridge contains alprostadil, alfadex, and lactose as a sterile pyrogen-free powder. The other chamber contains 1.075 mL of sterile 0.9% sodium chloride. The Edex cartridges are supplied in three strengths: 10-μg cartridge [10.75 μg alprostadil, 347.55 μg (alpha)-cyclodextrin, 51.06 mg lactose]; 20-μg cartridge [21.5 μg alprostadil, 695.2 μg (alpha)-cyclodextrin, 51.06 mg lactose]; 40-μg cartridge [43.0 μg alprostadil, 1, 390.3 μg (alpha)-cyclodextrin, 51.06 mg lactose]. The Edex injection device is used to reconstitute the sterile powder in one chamber with the sterile 0.9% sodium chloride in the other chamber. After reconstitution, the Edex injection device is used to administer the intracavernous injection of alprostadil. After reconstitution, the active ingredient, alprostadil, immediately dissociates from the (alpha)-cyclodextrin inclusion complex. The reconstituted solution is clear and colorless and has a pH between 4 and 8. When the single-dose, dual-chamber cartridge containing either 10.75, 21.5 or 43.0 μg of alprostadil is placed into the Edex injection device and reconstituted, the deliverable amount of alprostadil in each milliliter is 10, 20 or 40 μg, respectively.
- Elestat® (epinastine HCl ophthalmic solution), 0.05%, each milliliter contains the following: active—epinastine HCl, 0.05% (0.5 mg/mL), equivalent to epinastine 0.044% (0.44 mg/mL); preservative—benzalkonium chloride, 0.01%; inactives—edetate disodium; purified water; sodium chloride; sodium phosphate, monobasic; and sodium hydroxide and/or hydrochloric acid (to adjust the pH). Elestat has a pH of approximately 7 and an osmolality range of 250 to 310 mOsm/kg.
- Elspar (Asparaginase), the specific activity of ELSPAR is at least 225 IU/mg of protein and each vial contains 10,000 IU of asparaginase and 80 mg of mannitol, an inactive ingredient, as a sterile, white lyophilized plug or powder for IV or IM injection after reconstitution.
- Enbrel® (etanercept) is supplied in a single-use prefilled 1-mL syringe as a sterile, preservative-free solution for SC injection. The solution of Enbrel is clear and colorless and is formulated at pH 6.3±0.2. Each Enbrel single-use prefilled syringe contains 0.98 mL of a 50 mg/mL solution of etanercept with 10 mg/mL sucrose, 5.8 mg/mL sodium chloride, 5.3 mg/mL L-arginine hydrochloride, 2.6 mg/mL sodium phosphate monobasic monohydrate, and 0.9 mg/mL sodium phosphate dibasic, anhydrous. Administration of one 50 mg/mL prefilled syringe of Enbrel provides a dose equivalent to two 25-mg vials of lyophilized Enbrel, when vials are reconstituted and administered as recommended. Enbrel multiple-use vials contain sterile, white, preservative-free, lyophilized powder. Reconstitution with 1 mL of the supplied sterile bacteriostatic water for injection (BWFI), USP (containing 0.9% benzyl alcohol) yields a multiple-use, clear, and colorless solution with a pH of 7.4±0.3 containing 25 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine.
- Engerix-B [hepatitis B vaccine (recombinant)] is a noninfectious recombinant DNA hepatitis B vaccine supplied as a sterile suspension for IM administration. The vaccine is ready for use without reconstitution; it must be shaken before administration since a fine white deposit with a clear, colorless supernatant may form on storage. Pediatric/Adolescent: Each 0.5-mL dose contains 10 μg of hepatitis B surface antigen adsorbed on 0.25 mg aluminum as aluminum hydroxide. The pediatric/adolescent vaccine is formulated without preservatives. The pediatric formulation contains a trace amount of thimerosal (<0.5 μg mercury) from the manufacturing process, sodium chloride (9 mg/mL), and phosphate buffers (disodium phosphate dihydrate, 0.98 mg/mL; sodium dihydrogen phosphate dihydrate, 0.71 mg/mL). Adult: Each 1-mL adult dose contains 20 μg of hepatitis B surface antigen adsorbed on 0.5 mg aluminum as aluminum hydroxide. The adult vaccine is formulated without preservatives. The adult formulation contains a trace amount of thimerosal (<1.0 μg mercury) from the manufacturing process, sodium chloride (9 mg/mL), and phosphate buffers (disodium phosphate dihydrate, 0.98 mg/mL; sodium dihydrogen phosphate dihydrate, 0.71 mg/mL).
- EpiPen® and EpiPen Jr® autoinjectors contain 2 mL epinephrine injection for emergency IM use. Each EpiPen autoinjector delivers a single dose of 0.3 mg epinephrine from epinephrine injection, USP, 1:1000 (0.3 mL) in a sterile solution. Each EpiPen Jr autoinjector delivers a single dose of 0.15 mg epinephrine from epinephrine injection, USP, 1:2000 (0.3 mL) in a sterile solution. For stability purposes, approximately 1.7 mL remains in the autoinjector after activation and cannot be used. Each 0.3 mL in EpiPen contains 0.3 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0. Each 0.3 mL in EpiPen Jr contains 0.15 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0.
- Epogen (erythropoietin), single-dose, preservative-free vial: Each 1 mL of solution contains 2000, 3000, 4000 or 10,000 U of epoetin alpha, 2.5 mg albumin (human), 5.8 mg sodium citrate, 5.8 mg sodium chloride, and 0.06 mg citric acid in water for injection, USP (pH 6.9±0.3). This formulation contains no preservative. Single-dose, preservative-free vial: 1 mL (40,000 U/mL). Each milliliter of solution contains 40,000 U of epoetin alpha, 2.5 mg albumin (human), 1.2 mg sodium phosphate monobasic monohydrate, 1.8 mg sodium phosphate dibasic anhydrate, 0.7 mg sodium citrate, 5.8 mg sodium chloride, and 6.8 μg citric acid in water for injection, USP (pH 6.9±0.3). This formulation contains no preservative. Multidose preserved vial: 2 mL (20,000 U; 10,000 U/mL). Each 1 mL of solution contains 10,000 U of epoetin alpha, 2.5 mg albumin (human), 1.3 mg sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in water for injection, USP (pH 6.1±0.3). Multidose preserved vial: 1 mL (20,000 U/mL). Each 1 mL of solution contains 20,000 U of epoetin alpha, 2.5 mg albumin (human), 1.3 mg sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in water for injection, USP (pH 6.1±0.3).
- Eraxis for injection is a sterile, lyophilized product for IV infusion that contains anidulafungin. Eraxis for injection contains the following inactive ingredients: fructose (50 mg), mannitol (250 mg), polysorbate 80 (125 mg), tartaric acid

(5.6 mg), and sodium hydroxide and/or hydrochloric acid for pH adjustment.

- Ethyol® (amifostine) is the trihydrate form of amifostine and is supplied as a sterile lyophilized powder requiring reconstitution for IV infusion. Each single-use 10-mL vial contains 500 mg of amifostine on the anhydrous basis.
- Euflexxa™ is a viscoelastic, sterile solution of highly purified, high molecular weight (2.4–3.6 million Da) hyaluronan (also known as sodium hyaluronate) in phosphate-buffered saline. Euflexxa is a highly purified product extracted from bacterial cells. Each milliliter of Euflexxa contains sodium hyaluronate, 10 mg; sodium chloride, 8.5 mg; disodium hydrogen phosphate dodecahydrate, 0.56 mg; sodium dihydrogen phosphate dihydrate, 0.05 mg; water for injection, QS.
- Faslodex® (fulvestrant) injection contains as inactive ingredients—alcohol USP, benzyl alcohol NF, and benzyl benzoate USP, as cosolvents, and castor oil, USP, as a cosolvent and release rate modifier. Faslodex is supplied in sterile single patient prefilled syringes containing 50 mg/mL fulvestrant either as a single 5-mL or two concurrent 2.5-mL injections to deliver the required monthly dose. Faslodex is administered as an IM injection of 250 mg once monthly.
- Feiba VH anti-inhibitor coagulant complex, vapor heated (AICC) is a freeze-dried sterile human plasma fraction with factor VIII inhibitor bypassing activity. Reconstituted FEIBA VH AICC contains 4 mg of trisodium citrate and 8 mg/mL of sodium chloride.
- Flolan (epoprostenol sodium) for injection is a sterile sodium salt formulated for IV administration. Each vial of Flolan contains epoprostenol sodium equivalent to either 0.5 mg (500,000 ng) or 1.5 mg (1,500,000 ng) epoprostenol, 3.76 mg glycine, 2.93 mg sodium chloride, and 50 mg mannitol. Sodium hydroxide may have been added to adjust pH. Epoprostenol (PGI 2, PGX, prostacyclin), a metabolite of arachidonic acid, is a naturally occurring prostaglandin with potent vasodilatory activity and inhibitory activity of platelet aggregation. Flolan is a white to off-white powder that must be reconstituted with sterile diluent for Flolan. Sterile diluent for Flolan is supplied in glass vials containing 50 mL of 94 mg glycine, 73.3 mg sodium chloride, sodium hydroxide (added to adjust pH), and water for injection, USP. The reconstituted solution of Flolan has a pH of 10.2 to 10.8 and is increasingly unstable at a lower pH.
- Floxin® otic (ofloxacin otic) solution, 0.3%, is a sterile aqueous anti-infective (antibacterial) solution for otic use. Floxin otic contains 0.3% (3 mg/mL) ofloxacin with benzalkonium chloride (0.0025%), sodium chloride (0.9%), and water for injection. Hydrochloric acid and sodium hydroxide are added to adjust the pH to 6.5±0.5.
- Floxin otic Singles™ (ofloxacin otic) solution, 0.3%, is a sterile aqueous antiinfective (antibacterial) solution for otic use. Floxin otic Singles contains 0.3% (3 mg/mL) ofloxacin with benzalkonium chloride (0.0025%), sodium chloride (0.9%), and water for injection. Hydrochloric acid and sodium hydroxide are added to adjust the pH to 6.5±0.5.
- Fluarix™, influenza virus vaccine for IM use, is a sterile suspension prepared from influenza viruses propagated in embryonated chicken eggs. Each 0.5-mL dose also contains octoxynol-10 (Triton® X-100), ≤0.085 mg; alpha-tocopheryl hydrogen succinate, ≤0.1 mg; and polysorbate 80 (Tween 80), ≤0.415 mg. The vaccine is formulated without preservatives. Thimerosal is used at the early stages of manufacture and is removed by subsequent purification steps to <1.25 μg mercury per dose. Each dose may also contain residual amounts of hydrocortisone, ≤0.0016 μg; gentamicin sulfate, ≤0.15 μg; ovalbumin, ≤1 μg; formaldehyde, ≤50 μg; and sodium deoxycholate, ≤50 μg, from the manufacturing process. Fluarix is supplied as a 0.5-mL dose in a prefilled syringe. Fluarix, after shaking well, is colorless to slightly opalescent.
- Flumist influenza virus vaccine live, intranasal (FluMist®) is a live trivalent nasally administered vaccine. FluMist does not contain any preservatives. Each prefilled FluMist sprayer contains a single 0.5-mL dose.
- Fluorescite injection is a sterile aqueous solution in two strengths for use intravenously as a diagnostic aid. The solution contains fluorescein sodium (equivalent to fluorescein 10% or 25%), sodium hydroxide and/or hydrochloric acid (to adjust pH), and water for injection.
- Fortaz in sterile crystalline form is supplied in vials equivalent to 500 mg, 1 g, 2 g, or 6 g of anhydrous ceftazidime and in ADD-Vantage® vials equivalent to 1 or 2 g of anhydrous ceftazidime. Solutions of Fortaz range in color from light yellow to amber, depending on the diluent and volume used. The pH of freshly constituted solutions usually ranges from 5 to 8. Fortaz is available as a frozen, isosmotic, sterile, nonpyrogenic solution with 1 or 2 g of ceftazidime as ceftazidime sodium premixed with approximately 2.2 or 1.6 g, respectively, of dextrose hydrous, USP. Dextrose has been added to adjust the osmolality. Sodium hydroxide is used to adjust pH and neutralize ceftazidime pentahydrate free acid to the sodium salt. The pH may have been adjusted with hydrochloric acid. Solutions of premixed Fortaz range in color from light yellow to amber. The solution is intended for IV use after thawing to room temperature. The osmolality of the solution is approximately 300 mOsm/kg and the pH of thawed solutions ranges from 5.0 to 7.5. The plastic container for the frozen solution is fabricated from a specially designed multilayer plastic, PL 2040.
- Forteo® is supplied as a sterile, colorless, clear isotonic solution in a glass cartridge which is preassembled into a disposable pen device for SC injection. Each prefilled delivery device is filled with 3.3 mL to deliver 3 mL. Each milliliter contains 250 μg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.10 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3.0 mg metacresol, and water for injection. In addition, hydrochloric acid solution (10%) and/or sodium hydroxide solution (10%) may have been added to adjust the product to pH 4. Each cartridge preassembled into a pen device delivers 20 μg of teriparatide per dose each day for up to 28 days.
- Fortical® calcitonin-salmon (rDNA origin) nasal spray delivers 200 IU calcitonin-salmon in a volume of 0.09 mL. Active ingredient: calcitonin-salmon 2200 IU/mL, corresponding to 200 IU per actuation (0.09 mL). Inactive ingredients: sodium chloride, USP; citric acid, USP; phenylethyl alcohol, USP; benzyl alcohol, NF; polysorbate 80, NF; hydrochloric acid, NF, or sodium hydroxide, NF (added as necessary to adjust pH); and purified water USP.
- Gama STAN™ S/D, Immune globulin (human)—Gama STAN S/D contains no preservative. Gama STAN S/D is prepared by cold ethanol fractionation from human plasma. The immune globulin is isolated from solubilized Cohn fraction II. The fraction II solution is adjusted to a final concentration of 0.3% tri-*n*-butyl phosphate (TNBP) and 0.2% sodium cholate. After the addition of solvent

(TNBP) and detergent (sodium cholate), the solution is heated to 30°C and maintained at that temperature for not less than 6 hours. After the viral inactivation step, the reactants are removed by precipitation, filtration, and finally ultrafiltration and diafiltration. Gama STAN S/D is formulated as a 15% to 18% protein solution at a pH of 6.4 to 7.2 in 0.21 to 0.32 M glycine. Gama STAN S/D is then incubated in the final container for 21 to 28 days at 20°C to 27°C.

- Gammagard S/D, immune globulin intravenous (human, IGIV) when reconstituted with the total volume of diluent (sterile water for injection, USP) supplied. This preparation contains approximately 50 mg/mL of protein (5%), of which at least 90% is gamma-globulin. The product, reconstituted to 5%, contains a physiological concentration of sodium chloride (approximately 8.5 mg/mL) and has a pH of 6.8±0.4. Stabilizing agents and additional components are present in the following maximum amounts for a 5% solution: 3 mg/mL albumin (human), 22.5 mg/mL glycine, 20 mg/mL glucose, 2 mg/mL polyethylene glycol (PEG), 1 μg/mL tri-*n*-butyl phosphate, 1 μg/mL octoxynol 9, and 100 μg/mL polysorbate 80. Gammagard S/D, immune globulin intravenous (human) contains no preservative. Gammagard liquid immune globulin intravenous (human), 10%, is a ready-for-use sterile liquid preparation of highly purified and concentrated immunoglobulin G (IgG) antibodies.
- Gamunex® is made from large pools of human plasma by a combination of cold ethanol fractionation, caprylate precipitation and filtration, and anion-exchange chromatography. The protein is stabilized during the process by adjusting the pH of the solution to 4.0 to 4.5. Isotonicity is achieved by the addition of glycine. Gamunex is incubated in the final container (at the low pH of 4.0–4.3), for a minimum of 21 days at 23°C to 27°C.
- Garamycin (gentamicin sulfate) injectable is a sterile aqueous solution for parenteral administration. Each milliliter contains gentamicin sulfate, USP, equivalent to 40 mg gentamicin base; 1.8 mg methyl paraben and 0.2 mg propyl paraben as preservatives; 3.2 mg sodium bisulfite; and 0.1 mg edetate disodium.
- Gardasil is a noninfectious recombinant, quadrivalent vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV types 6, 11, 16, and 18. The quadrivalent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum containing adjuvant and the final purification buffer. Gardasil is a sterile preparation for IM administration. Each 0.5-mL dose contains approximately 20 μg of HPV 6 L1 protein, 40 μg of HPV 11 L1 protein, 40 μg of HPV 16 L1 protein, and 20 μg of HPV 18 L1 protein. Each 0.5-mL dose of the vaccine contains approximately 225 μg of aluminum (as amorphous aluminum hydroxyphosphate sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 μg of polysorbate 80, 35 μg of sodium borate, and water for injection. The product does not contain a preservative or antibiotics.
- Gemzar® (gemcitabine HCl) vial contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.
- Geodon for injection contains a lyophilized form of ziprasidone mesylate trihydrate. Geodon for injection is available in a single-dose vial as ziprasidone mesylate (20 mg ziprasidone/mL when reconstituted. Each millimeter of ziprasidone mesylate for injection (when reconstituted) contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether (beta)-cyclodextrin sodium (SBECD).
- GlucaGen® [glucagon (rDNA origin) for injection], 1 mg (1 IU), is supplied as a sterile, lyophilized white powder in a 2-mL vial alone, or accompanied by sterile water for reconstitution (1 mL) also in a 2-mL vial. Glucagon, as supplied at pH 2.5 to 3.5, is soluble in water. Active ingredient in each vial—glucagon as hydrochloride, 1 mg (corresponding to 1 IU). Other ingredients—lactose monohydrate (107 mg). When the glucagon powder is reconstituted with sterile water for reconstitution, it forms a solution of 1 mg (1 IU)/mL glucagon for SC, IM, or IV injection.
- Glucagon for injection (rDNA origin) is a polypeptide hormone identical to human glucagon that increases blood glucose and relaxes smooth muscle of the gastrointestinal tract. Glucagon is available for use intravenously, intramuscularly, or subcutaneously in a kit that contains a vial of sterile glucagon and a syringe of sterile diluent. The vial contains 1 mg (1 U) of glucagon and 49 mg of lactose. Hydrochloric acid may have been added during manufacture to adjust the pH of the glucagon; 1 IU of glucagon is equivalent to 1 mg of glucagon. The diluent syringe contains 12 mg/mL of glycerin, water for injection, and hydrochloric acid.
- Havrix (hepatitis A vaccine, inactivated) is a noninfectious hepatitis A vaccine supplied as a sterile suspension for IM administration. Each 1-mL adult dose of vaccine consists of 1440 ELU of viral antigen, adsorbed on 0.5 mg of aluminum as aluminum hydroxide. Each 0.5-mL pediatric dose of vaccine consists of 720 ELU of viral antigen, adsorbed onto 0.25 mg of aluminum as aluminum hydroxide. The vaccine preparations also contain 0.5% (w/v) of 2-phenoxyethanol as a preservative. Other excipients are amino acid supplement (0.3% w/v) in a phosphate-buffered saline solution and polysorbate 20 (0.05 mg/mL). Residual MRC-5 cellular proteins (NMT5 μg/mL) and traces of formalin (NMT0.1 mg/mL) are present. Neomycin sulfate, an aminoglycoside antibiotic, is included in the cell growth media; only trace amounts (≤40 ng/mL) remain, following purification.
- Hemofil M, antihemophilic factor (human, AHF), method M, monoclonal purified, is a sterile, nonpyrogenic, dried preparation of antihemophilic factor (factor VIII, factor VIII:C, AHF) in concentrated form with a specific activity range of 2 to 20 AHF IU/mg of total protein. Hemofil M contains a maximum of 12.5 mg/mL albumin, and per AHF IU, 0.07 mg polyethylene glycol (3350), 0.39 mg histidine, 0.1 mg glycine as stabilizing agents, not more than 0.1 ng mouse protein, 18 ng organic solvent (tri-*n*-butyl phosphate) and 50 ng detergent (octoxynol 9). In the absence of the added albumin (human), the specific activity is approximately 2 000 AHF IU/mg of protein.
- Hepatitis B immune globulin (human), hyper Hep B™ S/D treated with solvent/detergent, is a sterile solution of hepatitis B hyperimmune immune globulin for IM administration; it contains no preservative. Hyper Hep B S/D is formulated as a 15% to 18% protein solution at a pH of 6.4 to 7.2 in 0.21 to 0.32 M glycine. Hyper Hep B S/D is then incubated in the final container for 21 to 28 days at 20°C to

27°C. Each vial contains anti-HBs antibody equivalent to 220 IU/mL.

- Herceptin (Trastuzumab) is a recombinant DNA-derived humanized monoclonal. Herceptin is a sterile, white to pale yellow, preservative-free lyophilized powder for IV administration. The nominal content of each Herceptin vial is 440 mg trastuzumab, 400 mg (alpha), (alpha)-trehalose dihydrate, 9.9 mg L-histidine HCl, 6.4 mg L-histidine, and 1.8 mg polysorbate 20, USP. Reconstitution with 20 mL of the supplied bacteriostatic water for injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative, yields a multidose solution containing 21 mg/mL trastuzumab, at a pH of approximately 6.
- HibTITER. Haemophilus B conjugate vaccine (diphtheria CRM 197 protein conjugate) HibTITER is a sterile solution of a conjugate of oligosaccharides of the capsular antigen of *Haemophilus influenzae* type B (Haemophilus B) and diphtheria CRM 197 protein (CRM 197) dissolved in 0.9% sodium chloride. The conjugate is purified to remove unreacted protein, oligosaccharides, and reagents; sterilized by filtration; and filled into vials. HibTITER is intended for IM use. The vaccine is a clear, colorless solution. Each single dose of 0.5 mL is formulated to contain 10 μg of purified Haemophilus B saccharide and approximately 25 μg of CRM 197 protein. The potency of HibTITER is determined by chemical assay for polyribosylribitol.
- Humatrope® (somatropin, rDNA origin, for injection) is a sterile, white lyophilized powder intended for SC or IM administration after reconstitution. Phosphoric acid and/or sodium hydroxide may have been added to adjust the pH. Reconstituted solutions have a pH of approximately 7.5. This product is oxygen sensitive. Vial—Each vial of Humatrope contains 5 mg somatropin (15 IU or 225 nmol), 25 mg mannitol, 5 mg glycine, and 1.13 mg dibasic sodium phosphate. Each vial is supplied in a combination package with an accompanying 5-mL vial of diluting solution. The diluent contains water for injection with 0.3% metacresol as a preservative and 1.7% glycerin. Cartridge—The cartridges of somatropin contain either 6 mg (18 IU), 12 mg (36 IU), or 24 mg (72 IU) of somatropin. The 6-, 12-, and 24-mg cartridges contain respectively, mannitol 18, 36, and 72 mg; glycine 6, 12, and 24 mg; dibasic sodium phosphate 1.36, 2.72, and 5.43 mg. Each cartridge is supplied in a combination package with an accompanying syringe containing approximately 3 mL of diluting solution. The diluent contains water for injection; 0.3% metacresol as a preservative; and 1.7%, 0.29%, and 0.29% glycerin in the 6-, 12-, and 24-mg cartridges, respectively.
- Humira (adalimumab) is supplied in single-use 1 mL prefilled glass syringes as a sterile, preservative-free solution for SC administration. The solution of Humira is clear and colorless, with a pH of approximately 5.2. Each syringe delivers 0.8 mL (40 mg) of drug product. Each 0.8 mL of Humira contains 40 mg adalimumab, 4.93 mg sodium chloride, 0.69 mg monobasic sodium phosphate dihydrate, 1.22 mg dibasic sodium phosphate dihydrate, 0.24 mg sodium citrate, 1.04 mg citric acid monohydrate, 9.6 mg mannitol, 0.8 mg polysorbate 80, and water for injection, USP. Sodium hydroxide added as necessary to adjust pH.
- Hycamtin (topotecan hydrochloride) for injection is supplied as a sterile, lyophilized, buffered, light yellow to greenish powder available in single-dose vials. Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan as free base. The reconstituted solution ranges in color from yellow to yellow-green and is intended for administration by IV infusion. Inactive ingredients are mannitol, 48 mg, and tartaric acid, 20 mg. Hydrochloric acid and sodium hydroxide may be used to adjust the pH. The solution pH ranges from 2.5 to 3.5.
- Hyper Hep B™ S/D, hepatitis B immune globulin (human)—each vial contains anti-HBs antibody equivalent to or exceeding the potency of anti-HBs in a U.S. reference hepatitis B immune globulin (Center for Biologics Evaluation and Research, FDA).
- Hyper RAB™ S/D, rabies immune globulin (human)—hyper RAB™ S/D treated with solvent/detergent is a sterile solution of antirabies immune globulin for IM administration; it contains no preservative.
- Hyper RHO S/D, Rho (D) immune globulin (human)—hyper RHO™ S/D full dose is formulated as a 15% to 18% protein solution at a pH of 6.4 to 7.2 in 0.21 to 0.32 M glycine. Hyper RHO S/D full dose is then incubated in the final container for 21 to 28 days at 20°C to 27°C. The potency is equal to or more than 1500 IU. Each single-dose vial or syringe contains sufficient anti-Rho (D) to effectively suppress the immunizing potential of 15 mL of Rho (D) positive red blood cells.
- Hyper RHO™ S/D mini dose, Rho (D) immune globulin (human), is formulated as a 15% to 18% protein solution at a pH of 6.4 to 7.2 in 0.21 to 0.32 M glycine. One dose of Hyper RHO S/D mini dose contains not less than one-sixth the quantity of Rho (D) antibody contained in one standard dose of Rho (D) immune globulin (human) and it will suppress the immunizing potential of 2.5 mL of Rho (D) positive packed red blood cells or the equivalent of whole blood (5 mL). The quantity of Rho (D) antibody in hyper RHO S/D mini dose is not less than 250 IU.
- Hyper TET™ S/D, tetanus immune globulin (human) is formulated as a 15% to 18% protein solution at a pH of 6.4 to 7.2 in 0.21 to 0.32 M glycine. Hyper TET S/D is then incubated in the final container for 21 to 28 days at 20°C to 27°C.
- Hyperstat IV injection—each ampoule (20 mL) contains 300 mg diazoxide, USP, in a clear, sterile colorless aqueous solution; the pH is adjusted to approximately 11.6 with sodium hydroxide.
- Imitrex (sumatriptan succinate) injection is a clear, colorless to pale yellow, sterile, nonpyrogenic solution for SC injection. Each 0.5 mL of Imitrex injection (8 mg/mL solution) contains 4 mg of sumatriptan (base) as the succinate salt and 3.8 mg of sodium chloride, USP, in water for injection, USP. Each 0.5 mL of Imitrex injection (12 mg/mL solution) contains 6 mg of sumatriptan (base) as the succinate salt and 3.5 mg of sodium chloride, USP, in water for injection, USP. The pH range of both solutions is approximately 4.2 to 5.3. The osmolality of both injections is 291 mOsm.
- Immune globulin (human)—Gama STAN S/D treated with solvent/detergent is a sterile solution of immune globulin for IM administration; it contains no preservative. Gama STAN S/D is formulated as a 15% to 18% protein solution at a pH of 6.4 to 7.2 in 0.21 to 0.32 M glycine. Gama STAN S/D is then incubated in the final container for 21 to 28 days at 20°C to 27°C.
- Immune globulin intravenous (human) (IGIV), Carimune® NF, nanofiltered, is a sterile, highly purified polyvalent antibody product containing in concentrated form all the IgG antibodies which regularly occur in the donor population. The manufacturing process by which Carimune® NF is prepared from plasma consists of frac-

tionation and purification steps that comprise filtrations in the presence of filter aids. Final container lyophilized units are prepared so as to contain 1, 3, 6, or 12 g protein with 1.67 g sucrose and less than 20 mg NaCl/g of protein. The lyophilized preparation contains no preservative and may be reconstituted with sterile water, 5% dextrose or 0.9% saline to a solution with protein concentrations ranging from 3% to 12%.

- Immune globulin intravenous (human), 10% caprylate/chromatography purified (Gamunex), is a ready-to-use sterile solution of human immune globulin protein for IV administration. Gamunex consists of 9% to 11% protein in 0.16 to 0.24 M glycine. Not less than 98% of the protein has the electrophoretic mobility of gamma-globulin. Gamunex contains trace levels of fragments, IgA (average 0.046 mg/mL), and IgM. The distribution of IgG subclasses is similar to that found in normal serum. The measured buffer capacity is 35 mEq/L and the osmolality is 258 mOsm/kg solvent, which is close to physiological osmolality (285–295 mOsm/kg). The pH of Gamunex is 4.0 to 4.5. Gamunex contains no preservative.
- Increlex™ [mecasermin (rDNA origin) injection] is a sterile, aqueous, clear, and colorless solution intended for SC injection. Each multidose vial of Increlex contains 10 mg/mL mecasermin, 9 mg/mL benzyl alcohol, 5.84 mg/mL sodium chloride, 2 mg/mL polysorbate 20, and 0.05 M acetate at a pH of approximately 5.4.
- Indocin IV (indomethacin for injection) for IV administration is lyophilized indomethacin for injection. Each vial contains indomethacin for injection equivalent to 1 mg indomethacin as a white to yellow lyophilized powder or plug. Variations in the size of the lyophilized plug and the intensity of color have no relationship to the quality or amount of indomethacin present in the vial.
- Infanrix (diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed) is a noninfectious, sterile combination of diphtheria and tetanus toxoids and three pertussis antigens [inactivated pertussis toxin (PT), filamentous hemagglutinin (FHA), and pertactin (69 kDa outer membrane protein)] adsorbed onto aluminum hydroxide. Infanrix is intended for IM injection only. Each antigen is individually adsorbed onto aluminum hydroxide. Each 0.5-mL dose is formulated to contain 25 Lf of diphtheria toxoid, 10 Lf of tetanus toxoid, 25 μg of inactivated PT, 25 μg of FHA, and 8 μg of pertactin. Each 0.5-mL dose also contains 2.5 mg of 2-phenoxyethanol as a preservative, 4.5 mg of NaCl, and aluminum adjuvant (≤0.625 mg aluminum by assay). Each dose also contains ≤100 μg of residual formaldehyde and ≤100 μg of polysorbate 80 (Tween 80). Infanrix does not contain thimerosal.
- INFeD (iron dextran injection, USP) is a dark brown, slightly viscous sterile liquid complex of ferric hydroxide and dextran for IV or IM use. Each milliliter contains the equivalent of 50 mg of elemental iron (as an iron dextran complex), approximately 0.9% sodium chloride, in water for injection. Sodium hydroxide and/or hydrochloric acid may have been used to adjust pH. The pH of the solution is between 5.2 and 6.5.
- Insulin Lispro mixture. Humalog® Mix75/25™ [75% insulin lispro protamine suspension and 25% insulin lispro injection (rDNA origin)] is a mixture of insulin lispro solution, a rapid-acting blood glucose-lowering agent and insulin lispro protamine suspension, an intermediate-acting blood glucose-lowering agent. Humalog Mix75/25 disposable insulin delivery devices contain a sterile suspension of insulin lispro protamine suspension mixed with soluble insulin lispro for use as an injection. Each milliliter of Humalog Mix75/25 injection contains insulin lispro 100 U, 0.28 mg protamine sulfate, 16 mg glycerin, 3.78 mg dibasic sodium phosphate, 1.76 mg metacresol, zinc oxide content adjusted to provide 0.025 mg zinc ion, 0.715 mg phenol, and water for injection. Humalog Mix75/25 has a pH of 7.0 to 7.8. Hydrochloric acid, 10%, and/or sodium hydroxide, 10%, may have been added to adjust pH.
- Insulin Lispro—Humalog® (insulin lispro, rDNA origin) is a human insulin analog that is a rapid-acting parenteral blood glucose-lowering agent. The vials, cartridges, and pens contain a sterile solution of Humalog for use as an injection. Humalog injection consists of zinc-insulin lispro crystals dissolved in a clear aqueous fluid. Each milliliter of Humalog injection contains insulin lispro 100 U, 16 mg glycerin, 1.88 mg dibasic sodium phosphate, 3.15 mg metacresol, zinc oxide content adjusted to provide 0.0197 mg zinc ion, trace amounts of phenol, and water for injection. Insulin lispro has a pH of 7.0 to 7.8. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.
- Insulin. Humulin R (U-500) consists of zinc-insulin crystals dissolved in a clear fluid. Humulin R (U-500) is a sterile solution and is for SC injection. The concentration of Humulin R (U-500) is 500 U/mL. Each milliliter contains 500 U of biosynthetic human insulin, 16 mg glycerin, 2.5 mg *m*-cresol as a preservative, and zinc-oxide calculated to supplement endogenous zinc to obtain total zinc content of 0.017 mg/100 U. Sodium hydroxide and/or hydrochloric acid may be added during manufacture to adjust the pH. Humulin is available in six formulations—Regular (R), NPH (N), Lente (L), Ultralente® (U), 50% human insulin isophane suspension (NPH)/50% human insulin injection (buffered regular, 50/50), and 70% human insulin isophane suspension (NPH)/30% human insulin injection (buffered regular, 70/30). Humulin R (U-500) is the only human insulin manufactured by Eli Lilly and Company that has a concentration of 500 U/mL. The concentration of Humulin N in Humulin N Pen is 100 U/mL (U-100).
- Integrilin (eptifibatide) injection is a clear, colorless, sterile, nonpyrogenic solution for IV use. Each 10-mL vial contains 2 mg/mL of eptifibatide and each 100-mL vial contains either 0.75 mg/mL of eptifibatide or 2 mg/mL of eptifibatide. Each vial of either size also contains 5.25 mg/mL citric acid and sodium hydroxide to adjust the pH to 5.35.
- Interleukin eleven is a thrombopoietic growth factor that directly stimulates the proliferation of hematopoietic stem cells and megakaryocyte progenitor cells and induces megakaryocyte maturation resulting in increased platelet production.
- Intron® A injection is a clear, colorless solution. The 3 million IU vial of Intron A injection contains 3 million IU of interferon alpha-2b, recombinant per 0.5 mL. The 18 million IU multidose vial of Intron A injection contains a total of 22.8 million IU of interferon alpha-2b, recombinant per 3.8 mL (3 million IU/0.5 mL) to provide the delivery of six 0.5-mL doses, each containing 3 million IU of Intron A (for a label strength of 18 million IU). The 18 million IU Intron A injection multidose pen contains a total of 22.5 million IU of interferon alpha-2b, recombinant per 1.5 mL (3 million IU/0.2 mL) to provide the delivery of six 0.2-mL doses, each containing 3 million IU of Intron A (for a label strength of 18 million IU). Each milliliter also

contains 7.5 mg sodium chloride, 1.8 mg sodium phosphate dibasic, 1.3 mg sodium phosphate monobasic, 0.1 mg edetate disodium, 0.1 mg polysorbate 80, and 1.5 mg *m*-cresol as a preservative. Based on the specific activity of approximately 2.6×10^8 IU/mg protein as measured by HPLC assay, the corresponding quantities of interferon alpha-2b, recombinant in the vials and pen described above are approximately 0.012, 0.088, and 0.087 mg protein, respectively.

- Invanz (ertapenem for injection) is supplied as sterile lyophilized powder for IV infusion after reconstitution with appropriate diluent and transfer to 50 mL 0.9% sodium chloride injection or for IM injection following reconstitution with 1% lidocaine hydrochloride. Each vial contains 1.046 g ertapenem sodium, equivalent to 1 g ertapenem. The sodium content is approximately 137 mg (approximately 6 mEq). Each vial of Invanz contains the following inactive ingredients: 175 mg sodium bicarbonate and sodium hydroxide to adjust pH to 7.5.
- Iveegam EN, immune globulin intravenous (human) (IGIV), is a sterile freeze-dried concentrate of immunoglobulin G (IgG). Reconstitution of the freeze-dried powder with the accompanying quantity of sterile water for injection, USP, gives a 5% protein solution suitable for IV administration. This final solution contains, per milliliter, 50±5 mg of IgG, 50 mg of glucose as a stabilizer, and 3 mg of sodium chloride. Trace amounts of IgM and IgA are also present. The reconstituted solution is clear, colorless, and free of detectable aggregates. It contains no preservative.
- Kepivance™ (palifermin) is supplied as a sterile, white, preservative-free, lyophilized powder for IV injection after reconstitution with 1.2 mL of sterile water for injection, USP. Reconstitution yields a clear, colorless solution of Kepivance (5 mg/mL) with a pH of 6.5. Each single-use vial of Kepivance contains 6.25 mg palifermin, 50 mg mannitol, 25 mg sucrose, 1.94 mg L-histidine, and 0.13 mg polysorbate 20 (0.01% w/v).
- Kineret® (anakinra) is supplied in single-use prefilled glass syringes with 27 gauge needles as a sterile, clear, colorless to white, preservative-free solution for daily SC administration. Each prefilled glass syringe contains 0.67 mL (100 mg) of anakinra in a solution (pH 6.5) containing sodium citrate (1.29 mg), sodium chloride (5.48 mg), disodium EDTA (0.12 mg), and polysorbate 80 (0.70 mg) in water for injection, USP.
- Koate-DVI contains purified and concentrated factor VIII. When reconstituted as directed, Koate-DVI contains approximately 50 to 150 times as much factor VIII as an equal volume of fresh plasma. The specific activity, after addition of albumin (human), is in the range of 9 to 22 IU/mg protein. Koate-DVI must be administered by the IV route. The final product when reconstituted as directed contains NMT 1500 μg/mL polyethylene glycol (PEG), NMT 0.05 M glycine, NMT 25 μg/mL polysorbate 80, NMT 5 μg/g tri-*n*-butyl phosphate (TNBP), NMT 3 mM calcium, NMT 1 μg/mL aluminum, NMT 0.06 M histidine, and NMT 10 mg/mL albumin (human).
- Koate-DVI, antihemophilic factor (human), is a sterile, stable, purified, dried concentrate of human antihemophilic factor (AHF, factor VIII, AHG). The specific activity, after addition of albumin (human), is in the range of 9 to 22 IU/mg protein. The final product when reconstituted as directed contains NMT 1500 μg/mL polyethylene glycol (PEG), NMT 0.05 M glycine, NMT 25 μg/mL polysorbate 80, NMT 5 μg/g tri-*n*-butyl phosphate (TNBP), NMT 3 mM calcium, NMT 1 μg/mL aluminum, NMT 0.06 M histidine, and NMT 10 mg/mL albumin (human).
- Kogenate® FS antihemophilic factor (recombinant) is a sterile, stable, purified, nonpyrogenic, dried concentrate formulated with sucrose (0.9–1.3%), glycine (21–25 mg/mL), and histidine (18–23 mM) as stabilizers in the final container in place of albumin (human) as used in Kogenate, and is then lyophilized. The final product also contains calcium chloride (2–3 mM), sodium (27–36 mEq/L), chloride (32–40 mEq/L), polysorbate 80 (NMT 96 μg/mL), imidazole (NMT 20 μg/1000 IU), tri-*n*-butyl phosphate (NMT 5 μg/1000 IU), and copper (NMT 0.6 μg/1000 IU). The product contains no preservatives. The amount of sucrose in each vial is 28 mg. Intravenous administration of sucrose contained in Kogenate FS will not affect blood glucose levels. Each vial of Kogenate FS contains the labeled amount of recombinant FVIII in international units. One IU, as defined by the World Health Organization standard for blood coagulation FVIII, human, is approximately equal to the level of FVIII activity found in 1 mL of fresh pooled human plasma. Kogenate FS must be administered by the IV route.
- Lacrisert (hydroxypropyl cellulose ophthalmic insert) is a sterile, translucent, rod-shaped, water-soluble, ophthalmic insert made of hydroxypropyl cellulose, for administration into the inferior cul-de-sac of the eye. Each Lacrisert is 5 mg of hydroxypropyl cellulose. Lacrisert contains no preservatives or other ingredients. It is approximately 1.27 mm in diameter by approximately 3.5 mm long.
- Lanoxin (digoxin), injection pediatric, is a sterile solution of digoxin for IV or IM injection. The vehicle contains 40% propylene glycol and 10% alcohol. The injection is buffered to a pH of 6.8 to 7.2 with 0.17% sodium phosphate and 0.08% anhydrous citric acid. Each 1-mL ampoule contains 100 μg (0.1 mg) digoxin. Dilution is not required. Lanoxin injection is a sterile solution of digoxin for IV or IM injection. The vehicle contains 40% propylene glycol and 10% alcohol. The injection is buffered to a pH of 6.8 to 7.2 with 0.17% dibasic sodium phosphate and 0.08% anhydrous citric acid. Each 2-mL ampoule contains 500 μg (0.5 mg) digoxin [250 μg (0.25 mg]/mL)]. Dilution is not required.
- Lantus® [insulin glargine (rDNA origin) injection] is a sterile solution of insulin glargine for use as an injection. Each milliliter of Lantus (insulin glargine injection) contains 100 IU (3.6378 mg) insulin glargine, 30 μg zinc, 2.7 mg *m*-cresol, 20 mg glycerol 85%, and water for injection. The pH is adjusted by addition of aqueous solutions of hydrochloric acid and sodium hydroxide. Lantus has a pH of approximately 4.
- Leukine® (sargramostim) liquid is formulated as a sterile, preserved (1.1% benzyl alcohol), injectable solution (500 μg/mL) in a vial. Lyophilized Leukine is a sterile, white, preservative-free powder (250 μg) that requires reconstitution with 1 mL sterile water for injection, USP, or 1 mL bacteriostatic water for injection, USP. Liquid Leukine and reconstituted lyophilized Leukine are clear, colorless liquids suitable for SC injection or IV infusion. Liquid Leukine contains 500 μg (2.8×10^6 IU/mL) sargramostim, 1.9 mg/mL edetate disodium, and 1.1% benzyl alcohol in a 1-mL solution. The vial of lyophilized Leukine contains 250 μg (1.4×10 6 IU/vial) sargramostim. The liquid Leukine vial and reconstituted lyophilized Leukine vial also contain 40 mg/mL mannitol, USP; 10 mg/mL

sucrose, NF, and 1.2 mg/mL tromethamine, USP, as excipients.

- Lovenox injection is available in two concentrations: (1) 100 mg/mL; prefilled syringes: 30 mg/0.3 mL, 40 mg/0.4 mL; graduated prefilled syringes: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/1 mL; multiple-dose vials: 300 mg/3.0 mL; Lovenox injection (100 mg/mL): concentration contains 10 mg enoxaparin sodium (approximate antifactor Xa activity of 1000 IU/0.1 mL water for injection; (2) 150 mg/mL; graduated prefilled syringes: 120 mg/0.8 mL, 150 mg/1 mL; Lovenox injection (150 mg/mL): concentration contains 15 mg enoxaparin sodium (approximate antifactor Xa activity of 1500 IU/0.1 mL water for injection. The Lovenox prefilled syringes and graduated prefilled syringes are preservative-free and intended for use only as a single-dose injection. The multiple-dose vial contains 15 mg/1.0 mL benzyl alcohol as a preservative. The pH of the injection is 5.5 to 7.5.
- LPVirazole®, a brand name for ribavirin for inhalation solution, is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100 mL glass vial contains 6 g of ribavirin, and when reconstituted to the recommended volume of 300 mL with sterile water for injection or sterile water for inhalation (no preservatives added), will contain 20 mg/mL of ribavirin, pH approximately 5.5. Aerosolization is to be carried out in a small particle aerosol generator (SPAG-2) nebulizer only.
- Lupron Depot-PED, leuprolide acetate, is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, become a suspension intended as a single IM injection. The front chamber of Lupron Depot-PED 7.5 mg, 11.25 mg, and 15 mg prefilled dual-chamber syringe contains leuprolide acetate (7.5/11.25/15 mg), purified gelatin (1.3/1.95/2.6 mg), D-lactic and glycolic acids copolymer (66.2/99.3/132.4 mg), and D-mannitol (13.2/19.8/26.4 mg). The second chamber of diluent contains carboxymethylcellulose sodium (5 mg), D-mannitol (50 mg), polysorbate 80 (1 mg), water for injection, USP, and glacial acetic acid, USP, to control pH. During the manufacture of Lupron Depot-PED, acetic acid is lost, leaving the peptide.
- Maxipime (cefepime hydrochloride, USP) for injection is supplied for IM or IV administration in strengths equivalent to 500 mg, 1 g, and 2 g of cefepime. Maxipime is a sterile, dry mixture of cefepime hydrochloride and L-arginine. It contains the equivalent of not less than 90% and not more than 115% of the labeled amount of cefepime. The L-arginine, at an approximate concentration of 725 mg/g of cefepime, is added to control the pH of the constituted solution at 4 to 6. Freshly constituted solutions of Maxipime will range in color from colorless to amber.
- Mefoxin (cefoxitin for injection) contains approximately 53.8 mg (2.3 mEq) of sodium per gram of cefoxitin activity. Solutions of Mefoxin range from colorless to light amber in color. The pH of freshly constituted solutions usually ranges from 4.2 to 7.0.
- Merrem® IV (meropenem for injection) is a sterile, pyrogen-free, synthetic, broad-spectrum carbapenem antibiotic for IV administration. When constituted as instructed (see Dosage and Administration; Preparation of Solution), each 1-g Merrem IV vial will deliver 1 g of meropenem and 90.2 mg of sodium as sodium carbonate (3.92 mEq). Each 500-mg Merrem IV vial will deliver 500 mg meropenem and 45.1 mg of sodium as sodium carbonate (1.96 mEq).
- Meruvax II is a sterile lyophilized preparation of the Wistar Institute RA 27/3 strain of live attenuated rubella virus. Each dose of the vaccine is calculated to contain sorbitol (14.5 mg), sodium phosphate, sucrose (1.9 mg), sodium chloride, hydrolyzed gelatin (14.5 mg), human albumin (0.3 mg), fetal bovine serum (<1 ppm), other buffer and media ingredients, and approximately 25 μg of neomycin. The product contains no preservative. Before reconstitution, the lyophilized vaccine is a light yellow compact crystalline plug. Meruvax II, when reconstituted as directed, is clear yellow.
- Miacalcin® (calcitonin-salmon) injection is provided in sterile solution for IM injection. Each milliliter contains calcitonin-salmon 200 IU; acetic acid, USP, 2.25 mg; phenol, USP, 5.0 mg; sodium acetate trihydrate, USP, 2.0 mg; sodium chloride, USP, 7.5 mg; water for injection, USP, QS to 1.0 mL.
- Mirena® (levonorgestrel-releasing intrauterine system) consists of a T-shaped polyethylene frame (T-body) with a steroid reservoir (hormone elastomer core) around the vertical stem. The reservoir consists of a cylinder, made of a mixture of levonorgestrel and silicone (polydimethylsiloxane), containing a total of 52 mg levonorgestrel. The reservoir is covered by a silicone (polydimethylsiloxane) membrane. The T-body is 32 mm in both the horizontal and vertical directions. The polyethylene of the T-body is compounded with barium sulfate, which makes it radiopaque. A monofilament brown polyethylene removal thread is attached to a loop at the end of the vertical stem of the T-body. Mirena is packaged sterile within an inserter. The inserter, which is used for insertion of Mirena into the uterine cavity, consists of a symmetric two-sided body and slider that are integrated with flange, lock, prebent insertion tube, and plunger. Once Mirena is in place, the inserter is discarded.
- Mivacron (mivacurium chloride) is a sterile, nonpyrogenic solution (pH 3.5–5.0) containing mivacurium chloride equivalent to 2 mg/mL mivacurium in water for injection. Hydrochloric acid may have been added to adjust pH. Multiple-dose vials contain 0.9% w/v benzyl alcohol.
- M-M-R II (measles, mumps, and rubella virus vaccine live) is a live virus vaccine for vaccination against measles (rubella), mumps and rubella (German measles). M-M-R II is a sterile lyophilized preparation of (1) Attenuvax (measles virus vaccine live), (2) Mumpsvax (mumps virus vaccine live), and (3) Meruvax II (rubella virus vaccine live). The reconstituted vaccine is for SC administration. Each 0.5-mL dose contains not less than 1000 TCID 50 (tissue culture infectious doses) of measles virus; 20,000 TCID 50 of mumps virus; and 1000 TCID 50 of rubella virus. Each dose of the vaccine is calculated to contain sorbitol (14.5 mg), sodium phosphate, sucrose (1.9 mg), sodium chloride, hydrolyzed gelatin (14.5 mg), human albumin (0.3 mg), fetal bovine serum (<1 ppm), other buffer and media ingredients, and approximately 25 μg of neomycin. The product contains no preservative. Before reconstitution, the lyophilized vaccine is a light yellow compact crystalline plug. M-M-R II, when reconstituted as directed, is clear yellow.
- Mycamine is a sterile, lyophilized product for IV infusion that contains micafungin sodium. Each single-use vial contains 50 mg micafungin sodium, 200 mg lactose, with citric acid, and/or sodium hydroxide (used for pH adjustment). Mycamine must be diluted with 0.9% sodium chloride injection, USP, or 5% dextrose injection, USP. Following re-

constitution with 0.9% sodium chloride injection, USP, the resulting pH of the solution is between 5 and 7.

- Mylotarg® (gemtuzumab ozogamicin for injection) is a sterile, white, preservative-free lyophilized powder containing 5 mg of drug conjugate (protein equivalent) in an amber vial. The drug product is light sensitive and must be protected from direct and indirect sunlight and unshielded fluorescent light during the preparation and administration of the infusion. The inactive ingredients are dextran 40, sucrose, sodium chloride, monobasic and dibasic sodium phosphate.
- Nabi-HB hepatitis B immune globulin (human) is a sterile solution of immunoglobulin (5±1% protein) containing antibodies to hepatitis B surface antigen (anti-HBs). Nabi-HB is formulated in 0.075 M sodium chloride, 0.15 M glycine, and 0.01% polysorbate 80, at pH 6.2. The product is supplied as a nonturbid sterile liquid in single-dose vials and appears as clear to opalescent. It contains no preservative and is intended for single use by the IM route only.
- Naropin® injection contains ropivacaine HCl is preservative-free and is available in single-dose containers in 2.0 (0.2%), 5.0 (0.5%), 7.5 (0.75%) and 10.0 mg/mL (1.0%) concentrations. The specific gravity of Naropin injection solutions ranges from 1.002 to 1.005 at 25°C.
- Natrecor® (nesiritide) is a sterile, purified preparation of human B-type natriuretic peptide (hBNP) and is manufactured from *Escherichia coli* using recombinant DNA technology. Natrecor is formulated as the citrate salt of rhBNP and is provided in a sterile, single-use vial. Each 1.5-mg vial contains a white to off-white lyophilized powder for IV administration after reconstitution. The quantitative composition of the lyophilized drug per vial is the following: nesiritide, 1.58 mg; mannitol, 20.0 mg; citric acid monohydrate, 2.1 mg; and sodium citrate dihydrate, 2.94 mg.
- Navelbine (vinorelbine tartrate) injection is for IV administration. Each vial contains vinorelbine tartrate equivalent to 10 mg (1-mL vial) or 50 mg (5-mL vial) vinorelbine in water for injection. No preservatives or other additives are present. The aqueous solution is sterile and nonpyrogenic. The aqueous solubility is >1000 mg/mL in distilled water. The pH of Navelbine injection is approximately 3.5.
- Neulasta® (pegfilgrastim) supplied in 0.6-mL prefilled syringes for SC injection. Each syringe contains 6 mg pegfilgrastim (based on protein weight), in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), sorbitol (30.0 mg), polysorbate 20 (0.02 mg), and sodium (0.02 mg) in water for injection, USP.
- Neumega. Oprelvekin, the active ingredient in Neumega, is produced in *E. coli* by recombinant DNA technology. Neumega is formulated in single-use vials containing 5 mg of oprelvekin (specific activity approximately 8×10^6 U/mg) as a sterile, lyophilized powder with 23 mg glycine, USP, 1.6 mg dibasic sodium phosphate heptahydrate, USP, and 0.55 mg monobasic sodium phosphate monohydrate, USP. When reconstituted with 1 mL of sterile water for injection, USP, the resulting solution has a pH of 7.0 and a concentration of 5 mg/mL.
- Neupogen® Filgrastim is a sterile, clear, colorless, preservative-free liquid for parenteral administration containing Filgrastim at a specific activity of $1.0 \pm 0.6 \times 10^8$ U/mg (as measured by a cell mitogenesis assay). The product is available in single-use vials and prefilled syringes. The single-use vials contain either 300 or 480 μg filgrastim at a fill volume of 1.0 or 1.6 mL, respectively. The single-use prefilled syringes contain either 300 or 480 μg filgrastim at a fill volume of 0.5 or 0.8 mL, respectively. It contains acetate, 0.59/mg; sorbitol, 50 mg/mL; sodium, 0.035/mL; and Tween 80, 0.004%.
- Nexium® IV (esomeprazole sodium) for injection is supplied as a sterile, freeze-dried, white to off-white, porous cake or powder in a 5-mL vial, intended for IV administration after reconstitution with 0.9% sodium chloride injection, USP; lactated Ringer's injection, USP, or 5% dextrose injection, USP. Nexium IV for injection contains esomeprazole sodium, 21.3 or 42.5 mg; equivalent to esomeprazole, 20 or 40 mg; edetate disodium, 1.5 mg; and sodium hydroxide, QS for pH adjustment. The pH of reconstituted solution of Nexium IV for injection depends on the reconstitution volume and is in the pH range of 9 to 11. The stability of esomeprazole sodium in aqueous solution is strongly pH dependent. The rate of degradation increases with decreasing pH.
- Infasurf® (calfactant) intratracheal suspension is a sterile, nonpyrogenic lung surfactant intended for intratracheal instillation only. It is an extract of natural surfactant from calf lungs which includes phospholipids, neutral lipids, and hydrophobic surfactant-associated proteins B and C (SP-B and SP-C). It contains no preservatives. Infasurf is an off-white suspension of calfactant in 0.9% aqueous sodium chloride solution. It has a pH of 5.0 to 6.2 (target pH 5.7). Each milliliter of Infasurf contains 35 mg total phospholipids (including 26 mg phosphatidylcholine of which 16 mg is disaturated phosphatidylcholine) and 0.65 mg proteins including 0.26 mg of SP-B.
- Nimbex (cisatracurium besylate) injection is a sterile, nonpyrogenic aqueous solution provided in 5-, 10-, and 20-mL vials. The pH is adjusted to 3.25 to 3.65 with benzenesulfonic acid. The 5- and 10-mL vials each contain cisatracurium besylate, equivalent to 2 mg/mL cisatracurium. The 20-mL vial, intended for ICU use only, contains cisatracurium besylate, equivalent to 10 mg/mL cisatracurium. The 10-mL vial, intended for multiple-dose use, contains 0.9% benzyl alcohol as a preservative. The 5- and 20-mL vials are single-use vials and do not contain benzyl alcohol. Cisatracurium besylate slowly loses potency with time at a rate of approximately 5% per year under refrigeration (5°C).
- Nipent® (pentostatin for injection) is supplied as a sterile, apyrogenic, lyophilized powder in single-dose vials for IV administration. Each vial contains 10 mg of pentostain and 50 mg of mannitol, USP. The pH of the final product is maintained between 7.0 and 8.5 by addition of sodium hydroxide or hydrochloric acid.
- Norditropin® is the Novo Nordisk A/S registered trademark for somatropin, a polypeptide hormone of recombinant DNA origin. Norditropin cartridges are supplied as solutions in ready-to-administer cartridges or prefilled pens with a volume of 1.5 mL. Each Norditropin cartridge contains the following: somatropin, 5 mg/1.5 mL, 10 mg/1.5 mL, 15 mg/1.5 mL; histidine, 1, 1.7 mg; poloxamer 188, 4.5 mg; phenol, 4.5 mg; mannitol, 60 mg, 58 mg; HCl/NaOH, QS; water for injection, add 1.5 mL.
- Norflex. Orphenadrine citrate injection contains 60 mg of orphenadrine citrate in aqueous solution in each ampoule. Norflex injection also contains sodium bisulfite NF, 2.0 mg; sodium chloride, USP, 5.8 mg; sodium hydroxide, to adjust pH; and water for injection USP, QS to 2 mL.
- NovoLog® [insulin aspart (rDNA origin) injection] is a human insulin analog that is a rapid-acting parenteral blood glucose-lowering agent. NovoLog is a sterile, aqueous, clear, and colorless solution that contains insulin aspart (B28 asp regular human insulin analog), 100 U/mL;

glycerin, 16 mg/mL; phenol, 1.50 mg/mL; metacresol, 1.72 mg/mL; zinc, 19.6 μg/mL; disodium hydrogen phosphate dihydrate, 1.25 mg/mL; and sodium chloride, 0.58 mg/mL. NovoLog has a pH of 7.2 to 7.6. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.

- NovoLog Mix 70/30 [70% insulin aspart protamine suspension and 30% insulin aspart injection, (rDNA origin)] is a human insulin analog suspension containing 70% insulin aspart protamine crystals and 30% soluble insulin aspart. NovoLog Mix 70/30 is a uniform, white, sterile suspension that contains insulin aspart (B28 asp regular human insulin analog), 100 U/mL; mannitol, 36.4 mg/mL; phenol, 1.50 mg/mL; metacresol, 1.72 mg/mL; zinc, 19.6 μg/mL; disodium hydrogen phosphate dihydrate, 1.25 mg/mL; sodium chloride, 0.58 mg/mL; and protamine sulfate, 0.33 mg/mL. NovoLog Mix 70/30 has a pH of 7.20 to 7.44. Hydrochloric acid or sodium hydroxide may be added to adjust pH.
- NovoSeven® is recombinant human coagulation factor VIIa (rFVIIa). NovoSeven is supplied as a sterile, white lyophilized powder of rFVIIa in single-use vials. Each vial of lyophilized drug contains the following: 1.2 mg (60 KIU), 2.4 mg (120 KIU), 4.8 mg (240 KIU) corresponding to rFVIIa, 1200 μg, 2400 μg, 4800 μg respectively; sodium chloride—5.84 mg, 11.68 mg, 23.36 mg respectively; calcium chloride dehydrate—2.94 mg, 5.88 mg, 11.76 mg respectively; glycylglycine—2.64 mg, 5.28 mg, 10.56 mg respectively; polysorbate 80—0.14 mg, 0.28 mg, 0.56 mg respectively; and mannitol—60.0 mg, 120.0 mg, 240.0 mg respectively. After reconstitution with the appropriate volume of sterile water for injection, each vial contains approximately 0.6 mg/mL NovoSeven (corresponding to 600 μg/mL). The reconstituted vials have a pH of approximately 5.5 in sodium chloride (3 mg/mL), calcium chloride dihydrate (1.5 mg/mL), glycylglycine (1.3 mg/mL), polysorbate 80 (0.1 mg/mL), and mannitol (30 mg/mL). The reconstituted product is a clear, colorless solution which contains no preservatives.
- Nutropin (hGh) is a sterile, white, lyophilized powder intended for SC administration after reconstitution with bacteriostatic water for injection, USP (benzyl alcohol preserved). The reconstituted product is nearly isotonic at a concentration of 5 mg/mL growth hormone (GH) and has a pH of approximately 7.4. Each 5-mg Nutropin vial contains 5 mg (approximately 15 IU) somatropin, lyophilized with 45 mg mannitol, 1.7 mg sodium phosphates (0.4 mg sodium phosphate monobasic and 1.3 mg sodium phosphate dibasic), and 1.7 mg glycine. Each 10-mg Nutropin vial contains 10 mg (approximately 30 IU) somatropin, lyophilized with 90 mg mannitol, 3.4 mg sodium phosphates (0.8 mg sodium phosphate monobasic and 2.6 mg sodium phosphate dibasic), and 3.4 mg glycine. Bacteriostatic water for injection, USP, is sterile water containing 0.9% benzyl alcohol per milliliter as an antimicrobial preservative packaged in a multidose vial. The diluent pH is 4.5 to 7.0.
- Nutropin AQ is a human growth hormone (hGH) produced by recombinant DNA technology. Nutropin AQ is a sterile liquid intended for SC administration. The product is nearly isotonic at a concentration of 5 mg of GH/mL and has a pH of approximately 6. The Nutropin AQ, 2-mL vial, contains 10 mg (approximately 30 IU) somatropin, formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate 20, and 10 mM sodium citrate. The Nutropin AQ 2-mL pen cartridge contains 10 mg (approximately 30 IU) somatropin, formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate 20, and 10 mM sodium citrate.
- Ontak® (denileukin diftitox) is supplied in single use vials as a sterile, frozen solution intended for IV administration. Each 2-mL vial of Ontak contains 300 μg of recombinant denileukin diftitox in a sterile solution of citric acid (20 mM), EDTA (0.05 mM), and polysorbate 20 (<1%) in water for injection, USP. The solution has a pH of 6.9 to 7.2.
- Optipranolol® (metipranolol ophthalmic solution), 0.3%, contains metipranolol. Each milliliter of Optipranolol contains 3 mg metipranolol. Inactives: povidone, glycerin, hydrochloric acid, sodium chloride, edetate disodium, and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. Preservative: Benzalkonium chloride, 0.004%.
- Optivar® (azelastine hydrochloride ophthalmic solution), 0.05%, is a sterile ophthalmic solution containing azelastine hydrochloride. Each milliliter of Optivar contains the following: active—0.5 mg azelastine hydrochloride, equivalent to 0.457 mg of azelastine base; preservative—0.125 mg benzalkonium chloride; inactives—disodium edetate dihydrate, hydroxypropylmethylcellulose, sorbitol solution, sodium hydroxide, and water for injection. It has a pH of approximately 5.0 to 6.5 and an osmolality of approximately 271 to 312 mOsm/L.
- Orthovisc® is a sterile, nonpyrogenic, clear, viscoelastic solution of hyaluronan contained in a single-use syringe. Orthovisc consists of high molecular weight (1.0–2.9 million Da), ultrapure natural hyaluronan dissolved in physiological saline. Hyaluronan is a natural complex sugar of the glycosaminoglycan family. The hyaluronan is extracted from chicken combs.
- Panhematin (hemin for injection) is a sterile, lyophilized powder suitable for IV administration after reconstitution. Each dispensing vial of Panhematin contains the equivalent of 313 mg hemin, 215 mg sodium carbonate, and 300 mg of sorbitol. The pH may have been adjusted with hydrochloric acid; the product contains no preservatives. When mixed as directed with sterile water for injection, USP, each 43 mL provides the equivalent of approximately 301 mg hematin (7 mg/mL).
- Patanol (olopatadine hydrochloride ophthalmic solution), 0.1%, is a sterile ophthalmic solution containing olopatadine. Each milliliter of Patanol contains active: 1.11 mg olopatadine hydrochloride equivalent to 1 mg olopatadine; preservative: benzalkonium chloride 0.01%; inactives: dibasic sodium phosphate, sodium chloride, hydrochloric acid/sodium hydroxide (adjust pH), and purified water. It has a pH of approximately 7 and an osmolality of approximately 300 mOsm/kg.
- Pediarix® [diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant) and inactivated poliovirus vaccine combined] is a noninfectious, sterile, multivalent vaccine. Each 0.5-mL dose also contains 2.5 mg of 2-phenoxyethanol as a preservative, 4.5 mg of NaCl, and aluminum adjuvant (not more than 0.85 mg aluminum by assay). Each dose also contains ≤100 μg of residual formaldehyde and ≤100 μg of polysorbate 80 (Tween 80). Thimerosal is used at the early stages of manufacture and is removed by subsequent purification steps to below the analytical limit of detection (<25 ng of mercury/20 μg HBsAg) which upon calculation is <12.5 ng mercury/dose. Neomycin sulfate and polymyxin B are used in the polio vaccine manufacturing process and may be present in the final vaccine at ≤0.05 ng neomycin and ≤0.01 ng polymyxin B/dose. The procedures used to manufacture

the HBsAg antigen result in a product that contains ≤5% yeast protein.

- PEG-Intron®, peginterferon alpha-2b, powder for injection is a covalent conjugate of recombinant alpha-2b interferon with monomethoxy polyethylene glycol (PEG). PEG-Intron is supplied in both vial and the Redipen® for SC use. Vials: Each vial contains either 74, 118.4, 177.6, or 222 μg of PEG-Intron as a white to off-white tablet-like solid, that is whole/in pieces or as a loose powder, and 1.11 mg dibasic sodium phosphate anhydrous, 1.11 mg monobasic sodium phosphate dihydrate, 59.2 mg sucrose, and 0.074 mg polysorbate 80. Following reconstitution with 0.7 mL of the supplied sterile water for injection, USP, each vial contains PEG-Intron at strengths of either 50 μg/0.5 mL, 80 μg/0.5 mL, 120 μg/0.5 mL, or 150 μg/0.5 mL.
- Redipen is a dual-chamber glass cartridge containing lyophilized PEG-Intron as a white to off-white tablet or powder that is whole or in pieces in the sterile active chamber and a second chamber containing sterile water for injection, USP. Each PEG-Intron Redipen contains either 67.5, 108, 162, or 202.5 μg of PEG-Intron, and 1.013 mg dibasic sodium phosphate anhydrous, 1.013 mg monobasic sodium phosphate dihydrate, 54 mg sucrose, and 0.0675 mg polysorbate 80. Each cartridge is reconstituted to allow for the administration of up to 0.5 mL of solution. Following reconstitution, each Redipen contains PEG-Intron at strengths of either 50 μg/0.5 mL, 80 μg/0.5 mL, 120 μg/0.5 mL, or 150 μg/0.5 mL for single use. Because a small volume of reconstituted solution is lost during preparation of PEG-Intron, each Redipen contains an excess amount of PEG-Intron powder and diluent to ensure delivery of the labeled dose.
- Plasbumin-25, albumin (human) 25%, USP (Plasbumin-25), is a 25% sterile solution of albumin in an aqueous diluent. The preparation is stabilized with 0.02 M sodium caprylate and 0.02 M acetyltryptophan. The aluminum content of the product is not more than 200 μg/L. The approximate sodium content of the product is 145 mEq/L. It contains no preservative. Plasbumin-25 must be administered intravenously. Each vial of Plasbumin-25 is heat-treated at 60°C for 10 hours against the possibility of transmitting the hepatitis viruses. Albumin (human) 5%, USP (Plasbumin®-5) is a 5% sterile solution of albumin in an aqueous diluent. The preparation is stabilized with 0.004 M sodium caprylate and 0.004 M acetyltryptophan. The aluminum content of the product is not more than 200 μg/L. The approximate sodium content of the product is 145 mEq/L. It contains no preservative. Plasbumin-5 must be administered intravenously. Each vial of Plasbumin-5 is heat-treated at 60°C for 10 hours against the possibility of transmitting the hepatitis viruses.
- Plasmanate. Each 100 mL of plasma protein fraction (human) 5%, USP–Plasmanate® contains 5 g selected plasma proteins buffered with sodium carbonate and stabilized with 0.004 M sodium caprylate and 0.004 M acetyltryptophan. The plasma proteins consist of approximately 88% normal human albumin, 12% alpha- and beta-globulins and not more than 1% gamma-globulin as determined by electrophoresis. The concentration of these proteins is such that this solution is isooncotic with normal human plasma and is isotonic. The approximate concentrations of the significant electrolytes in Plasmanate are sodium, 145 mEq/L; potassium, 0.25 mEq/L; and chloride, 100 mEq/L. Plasmanate must be administered intravenously. This product is designed to bring to the medical profession a preparation derived from human blood and similar to human plasma. Each vial of Plasmanate is sterile and heat-treated at 60°C for 10 hours against the possibility of transmitting the hepatitis viruses.
- Premarin® intravenous (conjugated estrogens, USP) for injection contains a mixture of conjugated estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of materials derived from pregnant mares' urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains as concomitant components, as sodium sulfate conjugates, 17-alpha-dihydroequilin, 17-alpha-estradiol, and 17-beta-dihydroequilin. Each Secule® vial contains 25 mg of conjugated estrogens, USP, in a sterile lyophilized cake which also contains lactose, 200 mg; sodium citrate, 12.2 mg; and simethicone, 0.2 mg. The pH is adjusted with sodium hydroxide or hydrochloric acid. A sterile diluent (5 mL) containing 2% benzyl alcohol in sterile water is provided for reconstitution. The reconstituted solution is suitable for IV or IM injection.
- Prevnar®, pneumococcal 7-valent conjugate vaccine (diphtheria CRM 197 protein), is manufactured as a liquid preparation. Each 0.5-mL dose is formulated to contain 2 μg of each saccharide for serotypes 4, 9V, 14, 18C, 19F, and 23F, and 4 μg of serotype 6B per dose (16 μg total saccharide); approximately 20 μg of CRM 197 carrier protein; and 0.125 mg of aluminum/0.5-mL dose as aluminum phosphate adjuvant.
- Prograf (tacrolimus injection) containing the equivalent of 5 mg anhydrous tacrolimus in 1 mL contains polyoxyl 60 hydrogenated castor oil, 200 mg, and dehydrated alcohol, USP, 80.0% v/v. Prograf injection must be diluted with 0.9% sodium chloride injection or 5% dextrose injection before use.
- Prolastin®, alpha-1 proteinase inhibitor (human), is a sterile, stable, lyophilized preparation of purified human alpha-1 proteinase inhibitor (alpha-1 PI). When reconstituted, Prolastin has a pH of 6.6 to 7.4, a sodium content of 100 to 210 mEq/L, a chloride content of 60 to 180 mEq/L, a sodium phosphate content of 0.015 to 0.025 M, a polyethylene glycol content of not more than (NMT) 5 ppm, and NMT 0.1% sucrose.
- Prolastin, each vial of Prolastin contains the labeled amount of functionally active alpha-1–PI in milligrams per vial (mg/vial). Prolastin contains no preservative and must be administered by the IV route. The specific activity of Prolastin is ≥0.35 mg functional alpha-1–PI/mg protein and when reconstituted as directed, the concentration of alpha-1–PI is ≥20 mg/mL. When reconstituted, Prolastin has a pH of 6.6 to 7.4, a sodium content of 100 to 210 mEq/L, a chloride content of 60 to 180 mEq/L, a sodium phosphate content of 0.015 to 0.025 M, a polyethylene glycol content of NMT 5 ppm, and NMT 0.1% sucrose. Prolastin contains small amounts of other plasma proteins including alpha-2 plasmin inhibitor, alpha-1 antichymotrypsin, C 1-esterase inhibitor, haptoglobin, antithrombin III, alpha-1 lipoprotein, albumin, and IgA.
- Proleukin® (aldesleukin) for injection is a sterile, white to off-white, lyophilized cake in single-use vials intended for IV administration. When reconstituted with 1.2 mL sterile water for injection, USP, each milliliter contains 18 million IU (1.1 mg) Proleukin, 50 mg mannitol, and 0.18 mg sodium dodecyl sulfate, buffered with approximately 0.17 mg monobasic and 0.89 mg dibasic sodium phosphate to a pH of 7.5 (range 7.2–7.8). The manufacturing process for Proleukin involves fermentation in a defined medium con-

taining tetracycline hydrochloride. The presence of the antibiotic is not detectable in the final product. Proleukin contains no preservatives in the final product.

- Pulmicort Respules sterile suspension for inhalation via jet nebulizer and contains the active ingredient budesonide (micronized) and the inactive ingredients disodium edetate, sodium chloride, sodium citrate, citric acid, polysorbate 80, and water for injection. Two dose strengths are available in single-dose ampoules (Respules™ ampoules): 0.25 mg and 0.5 mg/2 mL Respule ampoule.
- Pulmozyme® (dornase alpha) inhalation solution is a sterile, clear, colorless, highly purified solution of recombinant human deoxyribonuclease I (rhDNase), an enzyme which selectively cleaves DNA. Each Pulmozyme single-use ampoule will deliver 2.5 mL of the solution to the nebulizer bowl. The aqueous solution contains 1.0 mg/mL dornase alpha, 0.15 mg/mL calcium chloride dihydrate and 8.77 mg/mL sodium chloride. The solution contains no preservative. The nominal pH of the solution is 6.3.
- Quixin® (levofloxacin ophthalmic solution) ,0.5%, is a sterile topical ophthalmic solution. Each milliliter of Quixin contains 5.12 mg of levofloxacin hemihydrate equivalent to 5 mg levofloxacin. Active: levofloxacin, 0.5% (5 mg/mL); preservative: benzalkonium chloride, 0.005%; inactives: sodium chloride and water. May also contain hydrochloric acid and/or sodium hydroxide to adjust pH. Quixin solution is isotonic and formulated at pH 6.5 with an osmolality of approximately 300 mOsm/kg. Levofloxacin is a fluorinated 4-quinolone containing a six-member (pyridobenzoxazine) ring from positions 1 to 8 of the basic ring structure.
- RabAvert® rabies vaccine is a sterile freeze-dried vaccine obtained by growing the fixed-virus strain flury LEP in primary cultures of chicken fibroblasts. The vaccine is lyophilized after addition of a stabilizer solution which consists of buffered polygeline and potassium glutamate. One dose of reconstituted vaccine contains less than 12 mg polygeline (processed bovine gelatin), less than 0.3 mg human serum albumin, 1 mg potassium glutamate, and 0.3 mg sodium EDTA. Small quantities of bovine serum are used in the cell culture process. RabAvert is intended for IM injection. The vaccine contains no preservative and should be used immediately after reconstitution with the supplied Sterile Diluent for RabAvert (water for injection). RabAvert is a white, freeze-dried vaccine for reconstitution with the diluent prior to use; the reconstituted vaccine is a clear to slightly opaque, colorless suspension.
- Raptiva® (efalizumab) is supplied as a sterile, white to off-white, lyophilized powder in single-use glass vials for SC injection. Reconstitution of the single-use vial with 1.3 mL of the supplied sterile water for injection (non-USP) yields approximately 1.5 mL of solution to deliver 125 mg/1.25 mL (100 mg/mL) of Raptiva. The sterile water for injection supplied does not comply with USP requirement for pH. After reconstitution, Raptiva is a clear to pale yellow solution with a pH of approximately 6.2. Each single-use vial of Raptiva contains 150 mg of efalizumab, 123.2 mg of sucrose, 6.8 mg of L-histidine hydrochloride monohydrate, 4.3 mg of L-histidine, and 3 mg of polysorbate 20 and is designed to deliver 125 mg of efalizumab in 1.25 mL.
- Recombinate, antihemophilic factor (recombinant, rAHF), is formulated as a sterile, nonpyrogenic, off-white to faint yellow, lyophilized powder preparation of concentrated recombinant AHF for IV injection. Recombinate (rAHF) is available in single-dose bottles which contain nominally 250, 500, and 1000 IU/bottle. When reconstituted with the appropriate volume of diluent, the product contains the following stabilizers in maximum amounts: 12.5 mg/mL albumin (human), 0.20 mg/mL calcium, 1.5 mg/mL polyethylene glycol (3350), 180 mEq/L sodium, 55 mM histidine, 1.5 μg/AHF IU polysorbate-80. Von Willebrand Factor (vWF) is coexpressed with the antihemophilic factor (recombinant) and helps to stabilize it. The final product contains not more than 2 ng vWF/IU rAHF which will not have any clinically relevant effect in patients with von Willebrand's disease. The product contains no preservative.
- Refludan [lepirudin (rDNA) for injection] is supplied as a sterile, white, freeze-dried powder for injection or infusion and is freely soluble in sterile water for injection USP or 0.9% sodium chloride injection USP. Each vial of Refludan contains 50 mg lepirudin. Other ingredients are 40 mg mannitol and sodium hydroxide for adjustment of pH to approximately 7.
- Remicade is a chimeric IgG1-kappa monoclonal antibody supplied as a sterile, white, lyophilized powder for IV infusion. Following reconstitution with 10 mL of sterile water for injection, USP, the resulting pH is approximately 7.2. Each single-use vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate, and 6.1 mg dibasic sodium phosphate, dihydrate. No preservatives are present.
- Repliva 21/7™ tablets for oral administration provide 28-day iron supplement therapy. Each red film-coated tablet contains Iron Ferrochel® (elemental iron), 70 mg; ferrous fumarate (elemental iron), 81 mg; succinic acid, 150 mg; vitamin C (ascorbic acid), 140 mg; vitamin C as Ester-C®; ascorbic acid (as calcium ascorbate), 60 mg; threonic acid (as calcium threonate), 0.8 mg; folic acid USP, 1 mg; vitamin B_{12} (cyanocobalamin), 10 μg; inactive ingredients: citric acid, croscarmellose sodium, FD&C red No. 40 aluminum lake, FD&C yellow No. 6 aluminum lake, fumed silica, hypromellose, lactose monohydrate, lecithin, magnesium stearate, maltodextrin, microcrystalline cellulose, polydextrose, polyethylene glycol, polyvinyl alcohol, povidone, silicon dioxide, sodium benzoate, sodium citrate, sorbic acid, starch, talc, titanium dioxide, triacetin. Each purple film-coated tablet contains inert ingredients: croscarmellose sodium, D&C red No. 27 aluminum lake, FD&C blue No. 1 aluminum lake, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, silicon dioxide, stearic acid, talc, titanium dioxide.
- Repronex® (menotropins for injection, USP) is a purified preparation of gonadotropins extracted from the urine of postmenopausal women. Each vial of Repronex contains 75 or 150 IU of follicle-stimulating hormone (FSH) activity and 75 or 150 IU of luteinizing hormone (LH) activity, respectively, plus 20 mg lactose monohydrate in a sterile, lyophilized form. The final product may contain sodium phosphate buffer (sodium phosphate tribasic and phosphoric acid).
- Retisert™ (fluocinolone acetonide intravitreal implant), 0.59 mg, is a sterile implant designed to release fluocinolone acetonide locally to the posterior segment of the eye at a nominal initial rate of 0.6 μg/day, decreasing over the first month to a steady state between 0.3 and 0.4 μg/day over approximately 30 months. Retisert consists of a tablet containing 0.59 mg of the active ingredient,

fluocinolone acetonide, USP, and the following inactives: microcrystalline cellulose, polyvinyl alcohol, and magnesium stearate.

- Retrovir (zidovudine) IV infusion is a sterile solution for IV infusion only. Each milliliter contains 10 mg zidovudine in water for injection. Hydrochloric acid and/or sodium hydroxide may have been added to adjust the pH to approximately 5.5. Retrovir IV Infusion contains no preservatives.
- Rev-Eyes™ (dapiprazole hydrochloride ophthalmic solution) ophthalmic eye drops is a clear, colorless, slightly viscous solution for topical application. Each milliliter (when reconstituted as directed) contains 5 mg of dapiprazole hydrochloride as the active ingredient. The reconstituted solution has a pH of approximately 6.6 and an osmolarity of approximately 415 mOsm. The inactive ingredients include mannitol (2%), sodium chloride, hydroxypropyl methylcellulose (0.4%), edetate sodium (0.01%), sodium phosphate dibasic, sodium phosphate monobasic, water for injection, and benzalkonium chloride (0.01%) as a preservative. Rev-Eyes ophthalmic eye drops, 0.5%, is supplied in a kit consisting of one vial of dapiprazole hydrochloride (25 mg), one vial of diluent (5 mL), and one dropper for dispensing.
- Rho (D) immune globulin (human)—Hyper RHO™ S/D full dose treated with solvent/detergent is a sterile solution of immune globulin containing antibodies to Rho (D) for IM administration; it contains no preservative. The fraction II solution is adjusted to a final concentration of 0.3% tri-*n*-butyl phosphate (TNBP) and 0.2% sodium cholate. After the addition of solvent (TNBP) and detergent (sodium cholate), the solution is heated to 30°C and maintained at that temperature for not less than 6 hours. Hyper RHO S/D Full Dose is formulated as a 15% to 18% protein solution at a pH of 6.4 to 7.2 in 0.21 to 0.32 M glycine. Hyper RHO S/D full dose is then incubated in the final container for 21 to 28 days at 20°C to 27°C. The potency is equal to or greater than 1500 IU. Hyper RHO S/D mini dose is formulated as a 15% to 18% protein solution at a pH of 6.4 to 7.2 in 0.21 to 0.32 M glycine. The quantity of Rho (D) antibody in Hyper RHO S/D mini dose is not less than 250 IU.
- Rhophylac® contains a maximum of 30 mg/mL of human plasma proteins of which 10 mg/mL is human albumin, which is added as a stabilizer. Prior to the addition of the stabilizer, the product purity is greater than 95% IgG. The product contains less than 5 μg/mL IgA. Additional excipients are approximately 20 mg/mL of glycine and up to 0.25 M sodium chloride. Rhophylac contains no preservative.
- Rhophylac is a sterile Rho (D) immune globulin intravenous (human) solution in a prefilled, ready-to-use syringe for either IV or IM injection. One syringe contains at least 1500 IU (300 μg) of IgG antibodies to Rho (D) in a 2-mL solution. The manufacturing process includes a solvent detergent (S/D) treatment step (using tri-*n*-butyl phosphate and Triton X-100) that is effective in inactivating enveloped viruses such as HBV, HCV, and HIV.
- Rituxan® (rituximab) antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. Rituxan is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituxan is supplied at a concentration of 10 mg/mL in either 100 (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for IV administration in 9 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and water for injection. The pH is adjusted to 6.5.
- Rozerem™ (ramelteon) tablet includes the following inactive ingredients: lactose monohydrate, starch, hydroxypropyl cellulose, magnesium stearate, hypromellose, copovidone, titanium dioxide, yellow ferric oxide, polyethylene glycol 8000, and ink containing shellac and synthetic iron oxide black.
- Sandimmune® injection (cyclosporine injection, USP) is available in a 5-mL sterile ampoule for IV administration. Each milliliter contains cyclosporine USP, 50 mg; Cremophor EL (polyoxyethylated castor oil), 650 mg; alcohol, 32.9% by volume; nitrogen, QS, which must be diluted further with 0.9% sodium chloride injection or 5% dextrose injection before use.
- Sandostatin® (octreotide acetate) injection, a cyclic octapeptide prepared as a clear sterile solution of octreotide, acetate salt, in a buffered lactic acid solution for administration by deep SC (intrafat) or IV injection. Sandostatin (octreotide acetate) injection is available as sterile 1-mL ampoules in three strengths, containing 50, 100, or 500 μg octreotide (as acetate) and sterile 5-mL multidose vials in two strengths, containing 200 and 1000 μg/mL of octreotide (as acetate). Each ampoule also contains lactic acid, USP, 3.4 mg; mannitol, USP, 45 mg; sodium bicarbonate, USP, QS to pH 4.2±0.3; water for injection, USP, QS to 1 mL. Each milliliter of the multidose vials also contains lactic acid, USP, 3.4 mg; mannitol, USP, 45 mg; phenol, USP, 5.0 mg; sodium bicarbonate, USP, QS to pH 4.2±0.3; water for injection, USP, QS to 1 mL.
- Sandostatin LAR® depot. Octreotide is the acetate salt of a cyclic octapeptide. Sandostatin LAR depot (octreotide acetate for injectable suspension) is available in a vial containing the sterile drug product, which when mixed with diluent, becomes a suspension that is given as a monthly intragluteal injection. The octreotide is uniformly distributed within the microspheres which are made of a biodegradable glucose star polymer, D,L-lactic and glycolic acids copolymer. Sterile mannitol is added to the microspheres to improve suspendability. Sandostatin LAR depot is available as sterile 5-mL vials in three strengths delivering 10, 20, or 30 mg octreotide free peptide. Each vial of Sandostatin LAR depot contains octreotide acetate, 11.2 mg, 22.4 mg, 33.6 mg; D,L-lactic and glycolic acids copolymer, 188.8 mg, 377.6 mg, 566.4 mg; mannitol, 41.0 mg, 81.9 mg, 122.9 mg. Each syringe of diluent contains carboxymethylcellulose sodium, 12.5 mg; mannitol, 15.0 mg, water for injection, 2.5 mL.
- Simulect® (basiliximab) is a sterile lyophilisate which is available in 6-mL colorless glass vials and is available in 10- and 20-mg strengths. Each 10-mg vial contains 10 mg basiliximab, 3.61 mg monobasic potassium phosphate, 0.50 mg disodium hydrogen phosphate (anhydrous), 0.80 mg sodium chloride, 10 mg sucrose, 40 mg mannitol, and 20 mg glycine, to be reconstituted in 2.5 mL of sterile water for injection, USP. No preservatives are added. Each 20-mg vial contains 20 mg basiliximab, 7.21 mg monobasic potassium phosphate, 0.99 mg disodium hydrogen phosphate (anhydrous), 1.61 mg sodium chloride, 20 mg sucrose, 80 mg mannitol and 40 mg glycine to be reconstituted in 5 mL of sterile water for injection, USP. No preservatives are added.
- Symlin® (pramlintide acetate) injection is formulated as a clear, isotonic, sterile solution for SC administration. Symlin vials contain 0.6 mg/mL of pramlintide (as acetate),

2.25 mg/mL of metacresol as a preservative, D-mannitol as a tonicity modifier, and acetic acid and sodium acetate as pH modifiers. Symlin has a pH of approximately 4.0.

- Synagis® is available in two formulations: a lyophilized powder and a liquid solution. Lyophilized powder: Synagis is supplied as a sterile lyophilized product for reconstitution with sterile water for injection. Reconstituted Synagis (100 mg/mL) is to be administered by IM injection only. The reconstituted solution should appear clear or slightly opalescent with pH of 6.0. Each 100-mg single-use vial of Synagis lyophilized powder is formulated in 67.5 mg of mannitol, 8.7 mg histidine, and 0.3 mg of glycine and is designed to deliver 100 mg of Synagis in 1 mL when reconstituted with 1 mL of sterile water for injection. Each 50-mg single-use vial of Synagis lyophilized powder is formulated in 40.5 mg mannitol, 5.2 mg of histidine, and 0.2 mg of glycine and is designed to deliver 50 mg of Synagis in 0.5 mL, when reconstituted with 0.6 mL of sterile water for injection. Liquid solution: Synagis (100 mg/mL) is supplied as a sterile, preservative-free solution to be administered by IM injection only. The solution should appear clear or slightly opalescent with pH of 6.0. Each 100-mg single-use vial of Synagis liquid solution is formulated in 4.7 mg of histidine and 0.1 mg of glycine in a volume of 1.2 mL and is designed to deliver 100 mg of Synagis in 1 mL. Each 50-mg single-use vial of Synagis liquid solution is formulated in 2.7 mg of histidine and 0.08 mg of glycine in a volume of 0.7 mL and is designed to deliver 50 mg of Synagis in 0.5 mL.
- Systane®. Active ingredients: polyethylene glycol 400, 0.4%, and propylene glycol, 0.3%, as lubricants. Inactive ingredients: boric acid, calcium chloride, hydroxypropyl guar, magnesium chloride, polyquaternium-1 as a preservative, potassium chloride, purified water, sodium chloride, zinc chloride.
- Tenecteplase is a tissue plasminogen activator (tPA) produced by recombinant DNA technology using an established mammalian cell line (Chinese hamster ovary cells). TNKase is a sterile, white to off-white, lyophilized powder for single IV bolus administration after reconstitution with sterile water for injection (SWFI), USP. Each vial of TNKase nominally contains 52.5 mg tenecteplase, 0.55 g L-arginine, 0.17 g phosphoric acid, and 4.3 mg polysorbate 20, which includes a 5% overfill. Each vial will deliver 50 mg of tenecteplase.
- Tenormin® (atenolol) for parenteral administration is available as Tenormin IV injection containing 5 mg atenolol in 10 mL sterile, isotonic, citrate-buffered, aqueous solution. The pH of the solution is 5.5 to 6.5. Inactive ingredients: sodium chloride for isotonicity, and citric acid and sodium hydroxide to adjust pH.
- Tetanus immune globulin (human) – Hyper TET™ S/D treated with solvent/detergent is a sterile solution of tetanus hyperimmune immune globulin for IM administration; it contains no preservative. Hyper TET S/D is formulated as a 15% to 18% protein solution at a pH of 6.4 to 7.2 in 0.21 to 0.32 M glycine. Hyper TET S/D is then incubated in the final container for 21 to 28 days at 20°C to 27°C. The product is standardized against the US standard antitoxin and the U.S. control tetanus toxin and contains not less than 250 tetanus antitoxin units per container.
- Tev-Tropin™ (somatropin, rDNA origin, for injection) is a sterile, white, lyophilized powder, intended for SC administration, after reconstitution with bacteriostatic 0.9% sodium chloride injection, USP, (normal saline) (benzyl alcohol preserved). The quantitative composition of the lyophilized drug per vial is 5 mg (15 IU) vial: somatropin, 5 mg (15 IU); mannitol, 30 mg. The diluent contains bacteriostatic 0.9% sodium chloride injection, USP, (normal saline), 0.9% benzyl alcohol as a preservative, and water for injection. A 5-mL vial of the diluent will be supplied with each dispensed vial of Tev-Tropin. Tev-Tropin is a highly-purified preparation. Reconstituted solutions have a pH in the range of 7.0 to 9.0.
- The Bexxar therapeutic regimen (tositumomab and iodine I 131 tositumomab) is an antineoplastic radioimmunotherapeutic monoclonal antibody-based regimen composed of the monoclonal antibody, Tositumomab, and the radiolabeled monoclonal antibody, iodine I 131 tositumomab. Tositumomab is supplied as a sterile, pyrogen-free, clear to opalescent, colorless to slightly yellow, preservative-free liquid concentrate. It is supplied at a nominal concentration of 14 mg/mL tositumomab in 35- and 225-mg single-use vials. The formulation contains 10% (w/v) maltose, 145 mM sodium chloride, 10 mM phosphate, and water for injection, USP. The pH is approximately 7.2. iodine I 131 tositumomab is supplied as a sterile, clear, preservative-free liquid for IV administration. The dosimetric dosage form is supplied at nominal protein and activity concentrations of 0.1 mg/mL and 0.61 mCi/mL (at date of calibration), respectively. The therapeutic dosage form is supplied at nominal protein and activity concentrations of 1.1 mg/mL and 5.6 mCi/mL (at date of calibration), respectively. The formulation for the dosimetric and the therapeutic dosage forms contains 4.4 to 6.6% (w/v) povidone, 1 to 2 mg/mL maltose (dosimetric dose) or 9 to 15 mg/mL maltose (therapeutic dose), 0.85 to 0.95 mg/mL sodium chloride, and 0.9 to 1.3 mg/mL ascorbic acid. The pH is approximately 7.0.
- Rituxan (Rituximab) antibody, a genetically engineered chimeric murine/human monoclonal antibody, is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituxan is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for IV administration in 9 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and water for injection. The pH is adjusted to 6.5.
- Thrombate III®, antithrombin III (human), is a sterile, nonpyrogenic, stable, lyophilized preparation of purified human antithrombin III. When reconstituted with sterile water for injection, USP, thrombate III has a pH of 6.0 to 7.5, a sodium content of 110 to 210 mEq/L, a chloride content of 110 to 210 mEq/L, an alanine content of 0.075 to 0.125 M, and a heparin content of not more than 0.004 U/IU AT-III. Thrombate III contains no preservative and must be administered by the IV route. In addition, thrombate III has been heat-treated in solution at 60°C±0.5°C for not less than 10 hours. Each vial of thrombate III contains the labeled amount of antithrombin III in international units per vial. The potency assignment has been determined with a standard calibrated against a World Health Organization (WHO) antithrombin III reference preparation.
- Tobi® is a tobramycin solution for inhalation. It is a sterile, clear, slightly yellow, nonpyrogenic aqueous solution with the pH and salinity adjusted specifically for administration by a compressed air-driven reusable nebulizer. Each single-use 5-mL ampoule contains 300 mg tobramycin and 11.25 mg sodium chloride in sterile water for injection. Sulfuric acid and sodium hydroxide are added to adjust the pH to 6.0. Nitrogen is used for sparging.

- Tobradex® (tobramycin and dexamethasone ophthalmic ointment) is a sterile, multiple-dose antibiotic and steroid combination for topical ophthalmic use. Each gram of Tobradex (tobramycin and dexamethasone ophthalmic ointment) contains the following: actives—tobramycin, 0.3%, (3 mg) and dexamethasone, 0.1% (1 mg); preservative—chlorobutanol, 0.5%; inactives—mineral oil and white petrolatum.
- Tobradex (tobramycin and dexamethasone ophthalmic suspension) suspension contains actives—tobramycin, 0.3% (3 mg), and dexamethasone, 0.1% (1 mg). Preservative: benzalkonium chloride, 0.01%. Inactives: tyloxapol, edetate disodium, sodium chloride, hydroxyethyl cellulose, sodium sulfate, sulfuric acid and/or sodium hydroxide (to adjust pH), and purified water.
- Trasylol® (aprotinin injection is supplied as a clear, colorless, sterile isotonic solution for IV administration. Each milliliter contains 10,000 KIU (Kallikrein inhibitor units) (1.4 mg/mL) and 9 mg sodium chloride in water for injection. Hydrochloric acid and/or sodium hydroxide is used to adjust the pH to 4.5 to 6.5.
- Traumeel® injection solution is officially classified as a homeopathic combination remedy. (1) Botanical ingredients: *Arnica montana*, radix (mountain arnica); *Calendula officinalis* (marigold); *Hamamelis virginiana* (witch hazel); Millefolium (milfoil); *Belladonna* (deadly nightshade); *Aconitum napellus* (monkshood); Chamomilla (chamomile); *Symphytum officinale* (comfrey); *Bellis perennis* (daisy); *Echinacea angustifolia* (narrow-leafed cone flower); *Echinacea purpurea* (purple cone flower); *Hypericum perforatum* (St. John's wort). (2) Mineral ingredients: Hepar sulphuris calcareum (calcium sulfide). Injection solution: each 2-mL ampoule contains as active ingredients Hepar sulphuris calcareum 8X. 200.0 μL; *Belladonna* 3X, 20.0 μL; *Calendula officinalis* 3X, 20.0 μL; Chamomilla 4X, 20.0 μL; Millefolium 4X, 20.0 μL; *Aconitum napellus* 3X, 12.0 μL; *Bellis perennis* 3X, 10.0 μL; *Hypericum perforatum* 3X, 6.0 μL; *E. angustifolia* 3X, 5.0 μL; *E. purpurea* 3X, 5.0 μL; *Arnica montana*, radix 2X, 2.0 μL; *Hamamelis virginiana* 2X, 2.0 μL; *Symphytum officinale* 6X, 2.0 μL. Each 2-mL ampoule contains as an inactive ingredient—sterile isotonic sodium chloride solution.
- Travoprost is a synthetic prostaglandin F 2(alpha) analogue. Travatan® ophthalmic solution, 0.004%, is supplied as sterile, buffered aqueous solution of travoprost with a pH of approximately 6.0 and an osmolality of approximately 290 mOsm/kg. Each milliliter of Travatan ophthalmic solution, 0.004%, contains 40 μg travoprost. Benzalkonium chloride, 0.015%, is added as a preservative. Inactive ingredients are polyoxyl-40 hydrogenated castor oil, tromethamine, boric acid, mannitol, edetate disodium, sodium hydroxide and/or hydrochloric acid (to adjust pH), and purified water.
- Trelstar LA contains a pamoate salt of triptorelin, is a sterile, lyophilized biodegradable microgranule formulation supplied as a single-dose vial containing triptorelin pamoate (11.25 mg as the peptide base); 145 mg poly-D,L -lactide-co-glycolide; 85 mg mannitol, USP; 30 mg carboxymethylcellulose sodium, USP; 2 mg polysorbate 80, NF. When 2 mL sterile water for injection is added to the vial containing Trelstar LA and mixed, a suspension is formed which is intended as an IM injection to be administered every 84 days (i.e., every 12 weeks). Trelstar LA is available in two packaging configurations: (a) Trelstar LA vial alone or (b) Trelstar LA vial plus a separate prefilled syringe that contains sterile water for injection, USP, 2 mL, pH 6 to 8.5 (Clip'n'Ject®). Trelstar depot contains a pamoate salt of triptorelin and triptorelin is a synthetic decapeptide agonist analog of luteinizing hormone-releasing hormone (LHRH or GnRH) with greater potency than the naturally occurring LHRH. Trelstar depot is a sterile, lyophilized biodegradable microgranule formulation supplied as a single-dose vial containing triptorelin pamoate (3.75 mg as the peptide base), 170 mg poly- D, L-lactide-co-glycolide, 85 mg mannitol, USP, 30 mg carboxymethylcellulose sodium, USP, 2 mg polysorbate 80, NF. When 2 mL sterile water for injection is added to the vial containing Trelstar depot and mixed, a suspension is formed which is intended as a monthly IM injection.
- Trisenox® is a sterile injectable solution of arsenic trioxide. Trisenox is available in 10-mL single-use ampoules containing 10 mg of arsenic trioxide. Trisenox is formulated as a sterile, nonpyrogenic, clear solution of arsenic trioxide in water for injection using sodium hydroxide and dilute hydrochloric acid to adjust to pH 8. Trisenox is preservative-free. Arsenic trioxide, the active ingredient, is present at a concentration of 1.0 mg/mL. Inactive ingredients and their respective approximate concentrations are sodium hydroxide (1.2 mg/mL) and hydrochloric acid, which is used to adjust the pH to 7.5 to 8.5.
- Tygacil (tigecycline) is an orange lyophilized powder or cake. Each Tygacil vial contains 50 mg tigecycline lyophilized powder for IV infusion. The product does not contain excipients or preservatives.
- Ultane (sevoflurane) is a clear, colorless liquid containing no additives. Sevoflurane is nonpungent. It is miscible with ethanol, ether, chloroform, and benzene and it is slightly soluble in water. Sevoflurane is stable when stored under normal room lighting conditions according to instructions. Sevoflurane is not corrosive to stainless steel, brass, aluminum, nickel-plated brass, chrome-plated brass, or copper beryllium.
- Vancocin® HCl (vancomycin hydrochloride capsules, USP) contain vancomycin hydrochloride equivalent to 125 mg (0.08 mmol) or 250 mg (0.17 mmol) vancomycin. The capsule also contain FD&C blue No. 2, gelatin, iron oxide, polyethylene glycol, titanium dioxide, and other inactive ingredients.
- Vantas™ (histrelin implant) is a sterile, nonbiodegradable, diffusion-controlled reservoir drug delivery system designed to deliver histrelin continuously for 12 months upon SC implantation. The Vantas implant contains 50 mg of histrelin acetate. The sterile Vantas implant consists of a 50-mg histrelin acetate drug core inside a nonbiodegradable, 3 cm × 3.5 mm cylindrically shaped hydrogel reservoir. The drug core also contains the inactive ingredient stearic acid NF. The hydrogel reservoir is a hydrophilic polymer cartridge composed of 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, trimethylolpropane trimethacrylate, benzoin methyl ether, Perkadox-16, and Triton X-100. The hydrated implant is packaged in a glass vial containing 2 mL of 1.8% NaCl solution. The implant is primed for release of the drug upon insertion.
- Vaprisol (conivaptan hydrochloride injection) is supplied as a sterile liquid in an ampoule. Each ampoule will deliver 20 mg conivaptan hydrochloride, 1.2 g propylene glycol, 0.4 g ethanol, and water for injection, QS. Lactic acid is added for pH adjustment to 3.0.
- Velcade® (bortezomib) for injection is an antineoplastic agent available for IV injection use only. Each single-dose vial contains 3.5 mg of bortezomib as a sterile lyophilized powder. Inactive ingredient: 35 mg mannitol, USP. The sol-

ubility of bortezomib, as the monomeric boronic acid, in water is 3.3 to 3.8 mg/mL in a pH range of 2.0 to 6.5.

- Ventavis (iloprost) inhalation solution is a clear, colorless sterile solution containing 10 μg/mL iloprost formulated for inhalation via the Prodose® AAD® (adaptive aerosol delivery) system, a pulmonary drug delivery device. Each single-use glass ampoule contains 2 mL (20 μg) of the solution to be added to the Prodose AAD system medication chamber. Each milliliter of the aqueous solution contains 0.01 mg iloprost, 0.81 mg ethanol, 0.121 mg tromethamine, 9.0 mg sodium chloride, and approximately 0.51 mg hydrochloric acid (for pH adjustment to 8.1) in water for injection. The solution contains no preservatives.
- Vfend® (voriconazole is available as a lyophilized powder for solution for IV infusion, film-coated tablets for oral administration, and as a powder for oral suspension. Vfend IV is a white lyophilized powder containing nominally 200 mg voriconazole and 3200 mg sulfobutyl ether beta-cyclodextrin sodium in a 30-mL type I clear glass vial. Vfend IV is intended for administration by IV infusion. It is a single-dose, unpreserved product. Vials containing 200 mg lyophilized voriconazole are intended for reconstitution with water for injection to produce a solution containing 10 mg/mL Vfend and 160 mg/mL of sulfobutyl ether beta-cyclodextrin sodium. The resultant solution is further diluted prior to administration as an IV infusion.
- Viadur® (leuprolide acetate implant) is a sterile, nonbiodegradable, osmotically driven miniaturized implant designed to deliver leuprolide acetate for 12 months at a controlled rate. Viadur contains 72 mg of leuprolide acetate (equivalent to 65 mg leuprolide free base) dissolved in 104 mg dimethyl sulfoxide. The 4 mm × 45 mm titanium alloy reservoir houses a polyurethane rate-controlling membrane, an elastomeric piston, and a polyethylene diffusion moderator. The reservoir also contains the osmotic tablets, which are not released with the drug formulation. The osmotic tablets are composed of sodium chloride, sodium carboxymethyl cellulose, povidone, magnesium stearate, and sterile water for injection. Polyethylene glycol fills the space between the osmotic tablets and the reservoir. A minute amount of silicone medical fluid is used during manufacture as a lubricant. The weight of the implant is approximately 1.1g.
- Visudyne® (verteporfin for injection) is a light activated drug used in photodynamic therapy. The finished drug product is a lyophilized dark green cake. Verteporfin is a 1:1 mixture of two regioisomers (I and II). Each milliliter of reconstituted Visudyne contains active—verteporfin, 2 mg; Inactives—lactose, egg phosphatidylglycerol, dimyristoyl phosphatidylcholine, ascorbyl palmitate, and butylated hydroxytoluene.
- VISUtein provides 18 mg of lutein, along with 200 mg of *N*-acetyl cysteine and 60 mg anthocyanidins from bilberry. Other ingredients are mixed carotenoids, vitamins A, B_2, and zinc.
- Viva® lubricating eye drops are 1% polysorbate 80 preservative-free in a multidose bottle. It is a patented, nonoily/glycerin free (no blurring of vision) sterile ophthalmic lubricant that is designed to provide instant moisturizing. Inactive ingredients: citric acid, edetate disodium, purified water, sodium chloride and the antioxidants: mannitol, pyruvate, retinyl palmitate, and sodium citrate.
- Vivotif® (typhoid vaccine live oral Ty21a) is a live attenuated vaccine. The lyophilized bacteria are mixed with lactose and magnesium stearate and filled into gelatin capsules which are coated with an organic solution to render them resistant to dissolution in stomach acid. The enteric-coated, salmon/white capsules are then packaged in four-capsule blisters for distribution. The contents of each enteric-coated capsule are viable *Salmonella typhi* Ty21a, 2 to 6 × 10^9 CFU (colony-forming unit); nonviable *S. typhi* Ty21a, 5 to 50 × 10^9 bacterial cells; sucrose, 26 to 130 mg; ascorbic acid, 1 to 5 mg; amino acid mixture, 1.4 to 7 mg; lactose, 100 to 180 mg; magnesium stearate, 3.6 to 4.4 mg.
- Voltaren ophthalmic (diclofenac sodium ophthalmic solution), 0.1%, solution is a sterile, topical, nonsteroidal, anti-inflammatory product for ophthalmic use. Inactive ingredients: polyoxyl 35 castor oil, boric acid, tromethamine, sorbic acid (2 mg/mL), edetate disodium (1 mg/mL), and purified water.
- WinRho® SDF is a sterile, freeze-dried gamma-globulin (IgG) fraction containing antibodies to the Rho (D) antigen (D antigen). The product is stabilized with 0.1 M glycine, 0.04 M sodium chloride, and 0.01% polysorbate 80. It contains no preservative.
- Xigris® [drotrecogin-alpha (activated)] is a recombinant form of human activated protein C. Xigris is supplied as a sterile, lyophilized, white to off-white powder for IV infusion. The 5- and 20-mg vials of Xigris contain 5.3 and 20.8 mg of drotrecogin-alpha (activated), respectively. The 5- and 20-mg vials of Xigris also contain 40.3 and 158.1 mg of sodium chloride, 10.9 and 42.9 mg of sodium citrate, and 31.8 and 124.9 mg of sucrose, respectively.
- Xolair (omalizumab) is a recombinant DNA-derived humanized IgG1(kgr) monoclonal antibody that selectively binds to human immunoglobulin E (IgE). Xolair is a sterile, white, preservative-free, lyophilized powder contained in a single-use vial that is reconstituted with sterile water for injection (SWFI), USP, and administered as an SC injection. A Xolair 75-mg vial contains 129.6 mg of omalizumab, 93.1 mg sucrose, 1.8 mg L-histidine hydrochloride monohydrate, 1.2 mg L-histidine, and 0.3 mg polysorbate 20 and is designed to deliver 75 mg of omalizumab in 0.6 mL after reconstitution with 0.9 mL SWFI, USP. A Xolair 150 mg vial contains 202.5 mg of omalizumab, 145.5 mg sucrose, 2.8 mg L-histidine hydrochloride monohydrate, 1.8 mg L-histidine, and 0.5 mg polysorbate 20, and is designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI, USP.
- Zaditor™ is a sterile ophthalmic solution containing ketotifen for topical administration to the eyes. Each milliliter of Zaditor contains active—0.345 mg ketotifen fumarate equivalent to 0.25 mg ketotifen. Inactives—glycerol, sodium hydroxide/hydrochloric acid (to adjust pH), and purified water. Preservative: benzalkonium chloride, 0.01%. It has a pH of 4.4 to 5.8 and an osmolality of 210 to 300 mOsm/kg.
- Zeel® injection solution is a combination formulation consisting of five botanical substances, five mineral substances, and four animal-derived substances. Zeel injection solution is officially classified as a homeopathic combination remedy. (1) Botanical ingredients: *Arnica montana*, radix (mountain arnica), Dulcamara (bittersweet), *Rhus toxicodendron* (poison oak), *Sanguinaria canadensis* (blood root), *Symphytum officinale* (comfrey). (2) Mineral ingredients: sulfur, (alpha)-lipoicum acid (thioctic acid), coenzyme A, nadidum (nicotinamide adenine dinucleotide), Natrum oxalaceticum (sodium oxalacetate). (3) Animal-derived ingredients: Cartilago suis (porcine cartilage), Embryo totalis suis (porcine embryo), Funiculus umbilicalis suis (porcine umbilical cord), Placenta suis (porcine placenta). Injection solution: each 2-mL ampoule contains as active ingredi-

ents *Arnica montana*, radix, 4 × 200 μL; *Rhus toxicodendron* 2 × 10 μL; Dulcamara, 3 × 10 μL; *Symphytum officinale*, 6 × 10 μL; sulfur, 6 × 3.6 μL; *Sanguinaria canadensis*, 4 × 3 μL; Cartilago suis, 6 × 2 μL; Embryo totalis suis, 6 × 2 μL; Funiculus umbilicalis suis, 6 × 2 μL; Placenta suis, 6 × 2 μL; coenzyme A, 8 × 2 μL; (alpha)-Lipoicum acidum, 8 × 2 μL; Nadidum, 8 × 2 μL; Natrum oxalaceticum, 8 × 2 μL. Each 2.0 mL ampoule contains as an inactive ingredient sterile isotonic sodium chloride solution.

- Zemaira®, alpha-1 proteinase inhibitor (human), is a sterile, stable, lyophilized preparation of highly purified human alpha-1 proteinase inhibitor (A1-PI), also known as alpha-1 antitrypsin, is supplied as a sterile, white, lyophilized powder to be administered by the IV route. The specific activity of Zemaira ≥0.7 mg of functional A1-PI per milligram of total protein. The purity is ≥90% A1-PI. Following reconstitution with 20 mL of sterile water for injection, USP, each vial contains approximately 1000 mg of functionally active A1-PI, 81 mM sodium, 38 mM chloride, 17 mM phosphate, and 144 mM mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust the pH. Zemaira contains no preservatives. Each vial of Zemaira contains the labeled amount of functionally active A1-PI in milligrams as stated on the vial label as determined by its capacity to neutralize human neutrophil elastase.
- Zemplar® (paricalcitol injection, USP). Each mL contains paricalcitol, USP, 5 μg, propylene glycol, 30% (v/v), and alcohol, 20% (v/v).
- Zevalin (ibritumomab tiuxetan) is ibritumomab, is supplied as two separate and distinctly labeled kits that contain all of the nonradioactive ingredients necessary to produce a single dose of In-111 Zevalin and a single dose of Y-90 Zevalin, both essential components of the Zevalin therapeutic regimen. Each of the two Zevalin kits contains four vials that are used to produce a single dose of either In-111 Zevalin or Y-90 Zevalin, as indicated on the outer container label: One Zevalin vial containing 3.2 mg of ibritumomab tiuxetan in 2 mL of 0.9% sodium chloride solution; a sterile, pyrogen-free, clear, colorless solution that may contain translucent particles; no preservative present. One 50 mM sodium acetate vial containing 13.6 mg of sodium acetate trihydrate in 2 mL of water for injection; a sterile, pyrogen-free, clear, colorless solution; no preservative present. One formulation buffer vial containing 750 mg of albumin (human), 76 mg of sodium chloride, 28 mg of sodium phosphate dibasic dodecahydrate, 4 mg of pentetic acid, 2 mg of potassium phosphate monobasic, and 2 mg of potassium chloride in 10 mL of water for injection adjusted to pH 7.1 with either sodium hydroxide or hydrochloric acid; a sterile, pyrogen-free, clear yellow to amber-colored solution; no preservative present. One empty reaction vial, sterile, pyrogen-free.
- Zithromax (azithromycin for injection) contains the active ingredient azithromycin. Zithromax (azithromycin for injection) is supplied in lyophilized form in a 10-mL vial equivalent to 500 mg of azithromycin for IV administration. Reconstitution, according to label directions, results in approximately 5 mL of Zithromax for IV injection with each milliliter containing azithromycin dihydrate equivalent to 100 mg of azithromycin.
- Zoladex® (goserelin acetate implant) 10.8-mg implant is supplied as a sterile, biodegradable product containing goserelin acetate equivalent to 10.8 mg of goserelin. Zoladex is designed for SC implantation with continuous release over a 12-week period. Goserelin acetate is dispersed in a matrix of D,L-lactic and glycolic acids copolymer (12.82–14.76 mg/dose) containing less than 2% acetic acid and up to 10% goserelin-related substances and presented as a sterile, white to cream-colored 1.5-mm diameter cylinder, preloaded in a special single-use syringe with a 14-gauge × 0.5 mm needle and protective needle sleeve (SafeSystem™ Syringe) in a sealed, light- and moisture-proof, aluminum foil laminate pouch containing a desiccant capsule. Studies of the D,L-lactic and glycolic acids copolymer have indicated that it is completely biodegradable and has no demonstrable antigenic potential. Zoladex is also supplied as a sterile, biodegradable product containing goserelin acetate equivalent to 3.6 mg of goserelin designed for administration every 28 days. Zoladex is also supplied as a sterile, biodegradable product containing goserelin acetate equivalent to 3.6 mg of goserelin. Zoladex is designed for SC injection with continuous release over a 28-day period. Goserelin acetate is dispersed in a matrix of D,L-lactic and glycolic acids copolymer (13.3–14.3 mg/dose) containing less than 2.5% acetic acid and up to 12% goserelin-related substances and presented as a sterile, white to cream-colored 1-mm diameter cylinder, preloaded in a special single use syringe with a 16-gauge needle × 0.5 mm needle and protective needle sleeve (SafeSystem Syringe) in a sealed, light- and moisture-proof, aluminum foil laminate pouch containing a desiccant capsule.
- Zometa® contains zoledronic acid. Zometa (zoledronic acid) injection is available in vials as a sterile liquid concentrate solution for IV infusion. Each 5-mL vial contains 4.264 mg of zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis. Inactive ingredients: mannitol, USP, as bulking agent; water for injection; and sodium citrate, USP, as buffering agent.
- Zosyn (piperacillin and tazobactam for injection) formulation also contains edetate disodium dihydrate (EDTA) and sodium citrate. Each Zosyn 2.25 g single-dose vial or ADD-Vantage vial contains an amount of drug sufficient for withdrawal of piperacillin sodium equivalent to 2 g of piperacillin and tazobactam sodium equivalent to 0.25 g of tazobactam. The product also contains 0.5 mg of EDTA per vial. Each Zosyn 3.375 g single-dose vial or ADD-Vantage vial contains an amount of drug sufficient for withdrawal of piperacillin sodium equivalent to 3 g of piperacillin and tazobactam sodium equivalent to 0.375 g of tazobactam. The product also contains 0.75 mg of EDTA per vial. Each Zosyn 4.5 g single-dose vial or ADD-Vantage vial contains an amount of drug sufficient for withdrawal of piperacillin sodium equivalent to 4 g of piperacillin and tazobactam sodium equivalent to 0.5 g of tazobactam. The product also contains 1 mg of EDTA per vial.
- Zylet (loteprednol etabonate and tobramycin ophthalmic suspension) contains (per milliliter) actives—loteprednol etabonate, 5 mg (0.5%), and tobramycin, 3 mg (0.3%); inactives—edetate disodium, glycerin, povidone, purified water, tyloxapol, and benzalkonium chloride 0.01% (preservative). Sulfuric acid and/or sodium hydroxide may be added to adjust the pH to 5.7 to 5.9. The suspension is essentially isotonic with a tonicity of 260 to 320 mOsm/kg.
- Zymar® (gatifloxacin ophthalmic solution), 0.3%, is a sterile ophthalmic solution. Active: gatifloxacin 0.3% (3 mg/mL). Preservative: benzalkonium chloride, 0.005%. Inactives: edetate disodium, purified water, and sodium chloride. May contain hydrochloric acid and/or sodium

hydroxide to adjust pH to approximately 6. Zymar is a sterile, clear, pale yellow colored isotonic unbuffered solution. It has an osmolality of 260 to 330 mOsm/kg.

- Zyprexa IM (olanzapine for injection) is intended for IM use only. Each vial provides for the administration of 10 mg (32 μmol) olanzapine with inactive ingredients 50 mg lactose monohydrate and 3.5 mg tartaric acid. Hydrochloric acid and/or sodium hydroxide may have been added during manufacturing to adjust pH.

Index

Abciximab injection, 172
Acetate
  otic suspension, 237
  suspension injection, 363
Acetazolamide injection, 172
Acetylcholine chloride intraocular solution, 173
Active air monitoring, 33, 44
Acyclovir sodium injection, 173
Adenosine injection, 173
Adrenal cortex injection, 174
Adrenaline tartarate injection, 174
Adventitious viruses, 72
Alatrofloxacin mesylate injection, 174, 175
Albuterol sulfate inhalation solution, 176
Aldesleukin for injection, 176
Alemtuzumab injection, 177
Alpha-tocopherol (vitamin E) injection, 177
Alprostadil for injection, 177
Alteplase recombinant injection, 177
Amikacin sulfate injection, 178, 179
Amino acid
  parenteral injection, 183
  parenteral nutrition solution, 180–182
Aminohippurate sodium for injection, 183
Aminophylline injection, 184
Amiodarone injection, 184–185
Amoxicillin-clavulanic acid injection, 185
Amoxicillin powder for injection, 185
Amphotericin B
  cholesteryl sulfate complex for injection, 186
  injection, 186
  lipid complex injection, 187
  liposome for injection, 187
Antibody production tests, 72
Antithymocyte globulin (rabbit) for injection, 190
Aprotinin injection, 190
Argatroban (thrombin inhibitor) injection, 190
Arsenic trioxide injection, 190
Ascorbic acid injection, 196
Aseptic fill manufacturing
  actions concerning product, 65
  buildings and facilities, 32–36, 64
  containers and closures, 64–65
  of formal written procedures, 65
  manufacturing operation, 64
  microbiological monitoring of the environment, 65
  and specifications for media fills, 65
Aseptic processing, 32–33
Asparaginase for injection, 197
Atropine, chlorpheniramine maleate, and phenylpropanolamine injection, 197
Atropine sulfate injection, 197, 198
Aztreonam for injection, 198

Bacterial endotoxins test, 65
Basiliximab for injection, 198
Batch monitoring and control
  in blow-fill-seal technology, 49–50
B complex injection, 200
B complex vitamin
  ascorbic acid and, 191
  with beta-carotene injection, 195
  with hormones, 208
  with liver extract injection, 208
  lyophilized in covial, 193
  lyophilized with diluent, 194
B complex vitamin veterinary, 206, 207
B complex with minerals injection (veterinary), 207
Benzodiazepine injection, 208
Benztropine mesylate injection, 209
Beta-carotene injection, 209
Betamethasone suspension injection, 209
Bethanechol chloride injection, 209
Biological safety cabinets (BSC), 124
Biotechnological/biological products
  analytical consideration of, 103
  characterization of, 101–103
  drug product specification of, 105–106
  drug substance specification, 105
  pharmacopoeial specifications, 104
  physicochemical characterization, 107
  process controls, 103–104
  process-related impurities and contaminants, 108
  product-related impurities including degradation products, 108
  release limits *vs.* Shelf life limits, 104
  statistical concepts, 104
Biotin injection, 210
Biperiden lactate injection, 210
Bisantrene emulsion injection, 210
Blow-fill-seal technology, 49–50
Botulinum toxin
  type A purified neurotoxin complex, 211
  type B injectable solution, 212
Bretylium tosylate in dextrose injection, 212
BSC. *See* Biological safety cabinets
Buflomedil injection, 213
Bupivacaine
  with epinephrine injection, 214
  hydrochloride injection, 213, 214
Buprenorphine hydrochloride injection, 215

CACI, 125
Caffeine citrate injection, 215
CAI, 124
Calcitonin injection, 215
Calcitriol injection, 216, 217
Calcium gluconate injection, 218

Calcium glycerophosphate injection
human and veterinary, 218
with lactate, 217
Camphor injection, 219
Camptothecin injection, 219
Carboplatin
for infusion, 219
injection, 219
Carprofen injection, 220
Cefamandole nafate for injection, 220
Cefazolin injection, 220
Cefepime hydrochloride for injection, 220
Cefotaxime injection, 221
Cefotetan injection, 221
Cefoxitin injection premixed IV solution, 221
Ceftazidime
for injection: l-arginine formulation, 221
injection dry powder, 222
injection premix, 222
Ceftriaxone injection
250-mg (IM and IV), 223
500-mg (IM and IV), 222
premix, 223
Cefuroxime for injection, 223
Cell
banking, 90–91
bank system, 83
lines, acceptability of, 72
substrate, generation of, 90
Cell banks, testing of
cell substrate stability, 92
tests for karyology and tumorigenicity, 93
tests of identity, 91–92
tests of purity, 92
Cell-based therapy products, 44
Cetrorelix acetate for injection, 223
cGMP compliance
air, 30
buildings, 30
containers and closures, 31
environmental controls, 30
equipment, 30–31
laboratory controls, 32
personnel, 30
personnel practices, 32
sterilization, 31–32
water for injection, 31
Chloramphenicol
injection, 226
for injection, 225
and phenylmercuric nitrate ophthalmic drops, 224
sodium succinate for injection, 226
Chloroquine phosphate injection, 227
Chlorothiazide sodium for injection, 228
Chlorpheniramine maleate injection, 228
Chlorpromazine hydrochloride injection, 228–229
Choriogonadotropin-alpha (recombinant) for injection, 229
Chorionic gonadotropin for injection, 229–230
Chromium chloride additive injection, 230, 231
Cidofovir injection, 231
Cimetidine injection, 231, 232
Ciprofloxacin
hydrochloride ophthalmic solution, 232
injection, 232
Cisplatin diaminedichloride injection, 233
Cisplatin with 2,2′-dithio-*bis*-ethane sulfonate injection, 233
Cladribine injection infusion, 234
Clarithromycin injection, 234
Clean-area classifications, 48
Cleaning validation
analytical methods, 68
equipment design, 68
sampling, 68–69
written procedure, and documentation, 68
Clean rooms
horizontal laminar flow, 115–124
laminar flow, 115
optimized designs, 111–114
turbulent type, 114
vertical flow, 114–115
Clindamycin injection in 5% dextrose, 235
Clindamycin phosphate injection, 235
Clonidine hydrochloride injection, 236
Coagulation factor ix (recombinant) for injection, 236
Coagulation factor VIIa (recombinant) for injection, 236
Code of federal regulations (CFR), 30
Comparability during development, drug, 99
Compounded sterile preparations. *See* CSPs
Compounding aseptic containment isolator. *See* CACI
Compounding aseptic isolator. *See* CAI
Conjugated estrogens for injection, 237
Containers/closures
aseptic fill manufacturing, 64–65
components of, 37
and package integrity, 65
preparation, 37–38
sterilization of equipment and, 42–43
Copper sulfate additive injection, 237–238
Corticorelin ovine triflutate for injection, 238
Cortisone acetate injectable suspension, 238
Cosyntropin for injection, 238
Cromolyn sodium ophthalmic solution, 239
Crude liver extract injection, 239
CSPs, 124
Cyanocobalamin
choline, and niacinamide injection, 239
injection, 240
injection for veterinary use, 241
pyridoxine, and thiamine injection, 242–244
repository injection, 241
and thiamine injection, 239
Cyclosporine ampoules for infusion, 244
Cytarabine liposome injection for intrathecal use, 245
Cytomegalovirus immune globulin IV (human), 245

Dacarbazine injection, 246
Daclizumab for injection, 246
Dactinomycin for injection, 246
Dantrolene sodium for injection, 247
Dapiprazole hydrochloride ophthalmic solution, 248
Daunorubicin
citrate liposome injection, 248
HCL injection, 248
Desmopressin acetate injection (intranasal), 249
Detergent, 69
Dexamethasone
acetate/sodium phosphate suspension, 249
injection, veterinary, 251
sodium phosphate injection, 250, 251
Dexamethasone acetate suspension, 249
Dexpanthenol, niacinamide, pyridoxine, riboflavin, and thiamine injection, 252

Dexrazoxane for injection, 253
Dextrose
injection (5% and 10% LVP), 253
25% injection (flexible container), 253
with sodium chloride injection LVP, 254
Diazepam
emulsion injection, 254, 255
injection, 255
rectal solution, 256
Dibenzazepine carboxamide injection, 256
Diclofenac
with acetylcysteine injection, 258
lecithin injection, 258
lyophilized injection, 258, 259
sodium injection, 257
Dicyclomine hydrochloride injection, 259
Digoxin injection, 259
Dihydroergotamine
mesylate drops, 260
mesylate injection, 261
mesylate nasal spray, 261
Diisopropylphenol injection, 261
Diltiazem hydrochloride injection, 262
Dimenhydrinate injection, 262
Dimethyl sulfoxide injection, 262
Dinoprostone cervical gel, 263
Dioctyl phthalate (DOP), 30
Diphenhydramine hydrochloride injection, 263
Diphenylmethyl piperazine injection, 263
Dipyrone
injection, 264
papaverine HCL, and atropine sulfate injection, 264
Disodium edetate injection, 265
Disulfonic acids injection, 265
DOP. *See* Dioctyl phthalate
Dopamine hydrochloride injection, 266
Doxercalciferol injection, 267
Doxorubicin for injection, 267
Doxycycline hyclate injection, 268
Doxycycline hydrochloride injection, 268
Drug product, 85
Drug substance (bulk material), 84–85

Ebselen liposomal injection, 269
Edrophonium injectable, 272
Electrolyte fluid
for maintenance, 273
for maintenance, pediatric, 273
for rehydration, 272
Electrolyte maintenance fluid rehydration, 274
Electrolytes, TPN injection, 275
Elliott's B solution, 335
Emetine hydrochloride injection, 275
Enalaprilat injection, 275
Endotoxin control, 38
Environmental monitoring, 43–44
Environmental protection agency. *See* EPA
EPA, 56
Ephedrine
and pyrilamine maleate injection veterinary, 275
sulfate injection, 276
Epinephrine
auto injector injection, 276
injection, 277
Epoetin-alpha, for injection, 277
Epoprostenol sodium for injection, 277
Ergocalciferol injection (vitamin D), 278
Ergonovine maleate injection
for human use, 278
veterinary, 278
Erythromycin injection, 279
Esmolol hydrochloride injection infusion, 280
Estradiol
and cyanocobalamin injection, 281
cypionate injection, 280
suspension injection, 281
valerate injection, 281
Estrogenic substances
in oil injection, 281
Estrone
estradiol, and cyanocobalamin injection, 281
sterile suspension veterinary injection, 282
Etanercept injection, 282
Ethylene oxide
in terminal sterilization, 66
Etorphine hydrochloride veterinary, 282
Exemestane aqueous suspension injection, 283

Famotidine injection, 283
FDA. See Food and drug administration
Fenoldopam mesylate injection, 284
Fentanyl citrate injection, 284
Filgrastim injection, 284
Filtration efficacy, 42–43
Flosulide injection, 285
Fluconazole injection, 285
Flumazenil injection, 285
Folic acid and niacinamide injection, 286
Follitropin-beta for injection, 286
Food and drug administration, 30
Furosemide injection, 287

Gentamicin
injection, 289–290
ophthalmic drops, 291
and prednisolone ophthalmic drops, 288
Glycine antagonist injection infusion, 292
Glycopyrrolate injection, 292
Granisetron hydrochloride injection
multiple dose, 293
single dose, 293
Guaiacol-iodide solution veterinary, 293

Haloperidol injection, 293
Heat exchangers, 56
Hemin for injection, 293
Heparin injection, 294
Hexamethylmelamine injection, 295
High-efficiency particulate air (HEPA), 30, 33–35, 46, 49, 111
High-purity water system
microbial limits of, 55–56
still, 56
system design of, 54–55
system validation of, 55
Hydrochloric acid, 295
Hydrocortisone sodium phosphate injection, 295
Hydrocortisone sodium succinate
for injection (nonlyophilized), 297
for injection (single-unit system lyophilized), 296
Hydromorphone hydrochloride injection
multiple dose, 299
single dose, 299

Hydroxycobalamin injection, 299
Hydroxyprogesterone caproate injection, 300
Hydroxypropylmethylcellulose ophthalmic solution, 300
Hyoscine butylbromide injection, 301

Ibuprofen lysinate injection, 301
Ibutilide fumarate injection, 302
Idarubicin hydrochloride injections, 302
Imiglucerase for injection, 302
Immune globulin (human) for injection, 303
Infliximab recombinant for injection, 303
Inhalation
  albuterol sulfate solution for, 176
  salbutamol aerosol for, 375
  tobramycin solution for, 390
Injection
  abciximab, 172
  acetate suspension, 363
  acetazolamide, 172
  acyclovir sodium, 173
  adenosine, 173
  adrenal cortex, 174
  adrenaline tartarate, 174
  alatrofloxacin mesylate, 174, 175
  aldesleukin for, 176
  alemtuzumab, 177
  alpha-tocopherol (vitamin E), 177
  alprostadil for, 177
  alteplase recombinant, 177
  amikacin sulfate, 178
  aminohippurate sodium for, 183
  aminophylline, 184
  amiodarone, 184–185
  amoxicillin-Clavulanic acid, 185
  amoxicillin powder for, 185
  antithymocyte globulin (rabbit) for, 190
  aprotinin, 190
  argatroban (thrombin inhibitor), 190
  arsenic trioxide, 190
  ascorbic acid, 196
  asparaginase for, 197
  atropine, chlorpheniramine maleate, and phenylpropanolamine, 197
  atropine sulfate, 197, 198
  aztreonam for, 198
  basiliximab for, 198
  B complex, 200
  B complex with minerals (veterinary), 207
  benzodiazepine, 208
  benztropine mesylate, 209
  beta-carotene, 209
  betamethasone suspension, 209
  bethanechol chloride, 209
  biotin, 210
  biperiden lactate, 210
  bisantrene emulsion, 210
  bretylium tosylate in dextrose, 212
  buflomedil, 213
  buprenorphine hydrochloride, 215
  caffeine citrate, 215
  calcitonin, 215
  calcitriol, 216, 217
  calcium gluconate, 218
  camphor, 219
  camptothecin, 219
  carprofen, 220
  cefamandole nafate for, 220
  cefazolin, 220
  cefepime hydrochloride for, 220
  cefotaxime, 221
  cefotetan, 221
  cefuroxime for, 223
  cetrorelix acetate for, 223
  choriogonadotropin-alpha (recombinant) for, 229
  chorionic gonadotropin for, 229–230
  chromium chloride additive, 230, 231
  cidofovir, 231
  cimetidine, 231, 232
  clarithromycin, 234
  clindamycin phosphate, 235
  clonidine hydrochloride, 236
  coagulation factor ix (recombinant) for, 236
  coagulation factor VIIa (recombinant) for, 236
  conjugated estrogens for, 237
  copper sulfate additive, 237–238
  corticorelin ovine triflutate for, 238
  cosyntropin for, 238
  crude liver extract, 239
  dacarbazine, 246
  daclizumab for, 246
  dactinomycin for, 246
  dantrolene sodium for, 247
  desmopressin acetate (intranasal), 249
  dexrazoxane for, 253
  dibenzazepine carboxamide, 256
  dicyclomine hydrochloride, 259
  digoxin, 259
  diisopropylphenol, 261
  diltiazem hydrochloride, 262
  dimenhydrinate, 262
  dimethyl sulfoxide, 262
  diphenhydramine hydrochloride, 263
  diphenylmethyl piperazine, 263
  dobutamine, 265
  dopamine hydrochloride, 266
  doxercalciferol, 267
  doxorubicin for, 267
  doxycycline hyclate, 268
  doxycycline hydrochloride, 268
  ebselen liposomal, 269
  emetine hydrochloride, 275
  enalaprilat, 275
  epoprostenol sodium for, 277
  exemestane aqueous suspension, 283
  famotidine, 283
  fenoldopam mesylate, 284
  fentanyl citrate, 284
  filgrastim, 284
  flosulide, 285
  fluconazole, 285
  flumazenil, 285
  folic acid and niacinamide, 286
  follitropin-beta for, 286
  furosemide, 287
  haloperidol, 293
  hemin for, 293
  heparin, 294
  hexamethylmelamine, 295
  hydrocortisone sodium phosphate, 295
  hydroxycobalamin, 299
  hydroxyprogesterone caproate, 300

hyoscine butylbromide, 301
ibuprofen lysinate, 301
ibutilide fumarate, 302
idarubicin hydrochloride, 302
imiglucerase for, 302
immune globulin (human) for, 303
infliximab recombinant for, 303
interferon alphacon-1, 309
interferon alpha-n3, 309
interferon beta-1a, 308
interferon beta-1b, 308
interferon gamma-1b, 309
isometheptene hydrochloride (veterinary), 311
itraconazole, 311
ketoprofen lysine, 311
labetalol hydrochloride, 312
lamotrigine, 313
lazaroid, 314
lepirudin for, 314
leuprolide acetate, 316
levorphanol tartarate, 317
levothyroxine sodium for, 317
lincomycin hydrochloride, 319
lorazepam, 321
melphalan hydrochloride for, 325
menadione, 325
menadione sodium bisulfite, 325–326
menotropins for, 326
meperidine hydrochloride, 326
meropenem for, 328
mesoridazine besylate, 328
methocarbamol, 329
methohexital sodium for, 329
methylprednisolone acetate suspension, 329
midazolam hydrochloride, 333
milrinone lactate, 333
mineral complex, 333
mitoxantrone for, 334
monophosphate 200 mg/ml (veterinary), 173
moxidectin, 335
muromonab-CD3, 336
naloxone hydrochloride, 336–337
nandrolone decanoate, 337
nandrolone phenylpropionate, 338
nesiritide for, 342
netilmicin, 343
nicardipine hydrochloride, 344
nikethamide, 344
nimesulide, 344
nimodipine, 345
nystatin for, 345
oprelvekin for, 347
orphenadrine citrate, 347
oxacarbazepine-10, 347
oxazepine, 348
oxendolone, 348
oxymorphone hydrochloride, 349
oxytetracycline, 349
pancuronium bromide, 351
paricalcitol, 352
pegademase bovine, 353
pegaspargase, 353
peginterferon alpha-2b for, 353
pentobarbital sodium solution, 354
pentostatin for, 354
pentylenetetrazol, 354
pheniramine maleate, 355
phenylbutazone and dipyrone, 355
phenylpropanolamine hydrochloride, 357
phenytoin sodium, 357
potassium phosphate, 360
procaine hydrochloride, 366
prochlorperazine, 366
promazine hydrochloride, 367
reteplase recombinant for, 372
retinol (vitamin A), 372
Rho (D) immune globulin (human), 373
ringer lactate solution, 373
rituximab, 374
sodium hyaluronate, 379
sodium thiosulfate, 380
sterile water for, 381
streptomycin sulfate, 381
Institute of Environmental Science And Technology (IEST), 112, 113
Insulin
aspart injection, 303
glargine injection, 304
human 70/30, 304
insulin human isophane suspension (NPH), 306
lispro injection, 307
regular, 307
Interferon alpha-2a, 308
Interferon alpha-2a (prefilled syringe), 308
Interferon alphacon-1 injection, 309
Interferon alpha-n3 injection, 309
Interferon beta-1a injection, 308
Interferon beta-1b injection, 308
Interferon gamma-1b injection, 309
Interleukin for injection (IL-2), 310
In vitro cell age for production, 83
Iodine IV additive, 310
Iron
copper solution veterinary, 310
dextran injection, 310
sucrose injection, 311
Isolators
decontamination, 48
design, 47–48
environmental monitoring, 49
filling line sterilization, 48–49
maintenance of, 47
transfer of materials and supplies of, 48
Isometheptene hydrochloride veterinary injection, 311
Itraconazole injection, 311

Ketoprofen lysine injection, 311
Ketorolac tromethamine
injection, 312
ophthalmic solution, 312

Labetalol hydrochloride injection, 312
Lactobionic acid
injection, 313
12% w/v solution, 234
LAFW, 124, 126
Laminar airflow workstation. *See* LAFW
Lamotrigine injection, 313
Large volume parenterals. *See* LVP
Lazaroid injection, 314

Leucovorin calcium injection
3 mg/ml, 2-ml vial, 315
50 mg/5 ml, 10-ml vial lyophilized, 314
5 mg/ml injection, 315
Leuprolide acetate injection, 315–316, 316
Levorphanol tartarate injection, 317
Levothyroxine sodium for injection, 317
Lidocaine hydrochloride
and epinephrine injection, 318
injection, 319
Lincomycin hydrochloride injection, 319
Liothyronine sodium injection (T3), 320
Lipid emulsion 20% for parenteral nutrition, 320
Liver
iron, and cyanocobalamin with procaine injection, 320
iron, and vitamin B12 injection veterinary, 321
Lorazepam injection, 321
LVP, 4, 30, 32, 254
Lyophilization, parenteral
cycle/controls, 51–52
cycle validation, 52
filling, 50–51
finished product inspection, 54
finished product testing, 53–54
product type and formulation, 50
sterilization and design, 52–53
Lyophilized injection
B complex, vitamin D, vitamin E, 204
diclofenac, 258, 259

Magnesium sulfate 50% injection, 321
Manganese sulfate injection, 322
Manufacturing process, drug, 98
Master cell bank
cell clone used to develop, 82
virus, 70
MCB test
master cell bank/working cell bank/in vitro cell age, 71
Mechlorethamine hydrochloride for injection trituration, 322
Medroxyprogesterone
acetate sterile aqueous suspension, 323, 324
and estradiol sterile suspension, 324
Melphalan hydrochloride for injection, 325
Meltback. *See* lyophilization, finished product inspection
Menadione injection, 325
Menadione sodium bisulfite injection, 325–326
Menotropins for injection, 326
Meperidine hydrochloride
injection multidose vials, 327
injection single-dose vials, 327
and promethazine hydrochloride injection, 327
Meperidine hydrochloride injection, 326
Meropenem for injection, 328
Metaraminol
bitartrate injection, 328
dipropionate injection, 328
Methocarbamol injection, 329
Methohexital sodium for injection, 329
Methylprednisolone acetate suspension injection, 329
Metoclopramide injection
preservative formula, 330
preservative-free formula, 331
Metolazone injection, 331
Metronidazole
and dextrose infusion, 332
infusion, 331
injection, 332
Midazolam hydrochloride injection, 333
Milrinone lactate injection, 333
Mineral complex injection, 333
Mitoxantrone for injection, 334
Monophosphate injection 200 mg/ml veterinary, 173
Morphine sulfate
infusion, 334
injection, 334
Moxidectin injection, 335
Muromonab-cd3 injection, 336

Nalbuphine hydrochloride, 336
Naloxone hydrochloride injection, 336–337
Nandrolone decanoate injection, 337
Nandrolone phenylpropionate injection, 338
Naphazoline ophthalmic drops, 338
Natamycin ophthalmic suspension, 339
Natural estrogenic substances suspension, 339
Nedocromil sodium ophthalmic solution, 339
Neomycin and prednisolone acetate ophthalmic suspension, 340
Neomycin sulfate-polymyxin B sulfate for irrigation, 342
Neostigmine methylsulfate injection
multidose vial, 342
single-dose vial, 342
Nesiritide for injection, 342
Netilmicin injection, 343
Niacinamide
injection, 343
pyridoxine, riboflavin, and thiamine injection, 199
Nicardipine hydrochloride for infusion, 344
Nicardipine hydrochloride injection, 344
Nikethamide injection, 344
Nimesulide injection, 344
Nimodipine injection, 345

Octreotide acetate injection
depot, 346
multidose vial, 345
single-dose ampoule, 345
Ofloxacin otic solution, 346
Ondansetron hydrochloride injection
multidose vial, 346
premixed for infusion, 347
single-dose vial, 346
Ophthalmic drops
antazoline sulfate and xylometazoline hydrochloride, 187
antipyrine, phenylephrine, and pyrilamine maleate, 188
antipyrine, phenylephrine, and sodium thiosulfate, 189
borax sodium lubricating, 211
edetate sodium, polyvinyl alcohol, sodium sulfacetamide, sodium thiosulfate, 269, 271
Ophthalmic solution
antipyrine, phenylephrine, and sodium thiosulfate, 189
ciprofloxacin hydrochloride, 232
cromolyn sodium, 239
dapiprazole hydrochloride(0.5%), 248
hydroxypropylmethylcellulose, 300
ketorolac tromethamine, 312
nedocromil sodium, 339
polyvinyl alcohol, 359
timolol, 390
Oprelvekin for injection, 347

Orphenadrine citrate injection, 347
Oxacarbazepine-10 injection, 347
Oxazepine injection, 348
Oxendolone injection, 348
Oxymorphone hydrochloride injection, 349
Oxytetracycline injection, 349
Oxytocin injection, 350–351

Paclitaxel injection, 351
Palivizumab for injection, 351
Pancuronium bromide injection, 351
Parenteral nutrition fat emulsion, 352
Paricalcitol injection, 352
Passive air monitoring (settling plates), 45
Pegademase bovine injection, 353
PEC, 124, 125, 126, 127
Pegaspargase injection, 353
Peginterferon alpha-2b for injection, 353
Penicillin g benzathine
  injectable suspension, 354
  and penicillin g procaine injection, 353
Pentobarbital sodium solution injection, 354
Pentostatin for injection, 354
Pentylenetetrazol injection, 354
Pheniramine maleate injection, 355
Phenol saline diluent, 355
Phenylbutazone and dipyrone injection, 355
Phenylbutazone injection veterinary, 356
Phenylephrine and zinc sulfate ophthalmic drops, 356
Phenylpropanolamine hydrochloride injection, 357
Phenytoin sodium injection, 357
Phytonadione
  vitamin K1 injection, 357–358
Phytonadione injection
  aqueous colloidal solution of vitamin K1, 358
Piperacillin sodium and tazobactam sodium injection, 358
Piping, 58
Placebo product, 69
Plicamycin for injection, 359
Polyvinyl alcohol ophthalmic solution, 359
Potassium estrone sulfate
  injection veterinary, 360
  suspension injection, 360
Potassium phosphate injection, 360
Prednisolone
  acetate/phosphate injection, 362
  acetate suspension with niacinamide injection, 363
  and neomycin ophthalmic suspension, 361
  ophthalmic drops, 364
Primary engineering control. *See* PEC
Procaine hydrochloride injection, 366
Process control documentation, 46–47
Process simulation
  frequency and number of runs, 39–40
  interpretation of test results, 41
  line speed, 40
  media, 40
  size and duration of runs, 40
  study design, 39
Process validation
  in blow-fill-seal technology, 49
  filtration efficacy, 41–42
  process simulations, 39–41
  sterilization of equipment and container/closure, 42–43
Process water, 58
Prochlorperazine injection, 366
Progesterone
  injection repository veterinary, 367
  and tocopheryl acetate injection, 366
Promazine hydrochloride injection, 367
Promethazine hydrochloride injection
  cartridge unit, 368
  vial, 368
Propofol emulsion injection, 369
Pumps, 58
Purified water systems, 57–58
Pyridoxine
  hydrochloride injection, 369, 370
  and thiamine injection, 369
Pyrilamine maleate and ephedrine injection veterinary, 370

Quality considerations, drug
  analytical techniques, 96–97
  characterization, 97–98
  specifications, 98
  stability, 98
Quinidine sulfate injection, 370
Quinolone-calcium lactate complex for injection, 371

Radiation
  in terminal sterilization, 63
Ranitidine injection ampoule, 371, 372
Reteplase recombinant for injection, 372
Retinol (vitamin A) injection, 372
Retrovirus test, 72
Reverse osmosis, 57
Rho (D) immune globulin (human) injection, 373
Ringer lactate solution injection, 373
Rituximab injection, 374
Room area classification, 33t
Rubella virus vaccine live, 374

Salbutamol aerosol for inhalation, 375
Sample selection, 85
Sisomicin injection, 376
Sodium bicarbonate
  and disodium edetate injection, 377
  injection, 378
Sodium chloride
  bacteriostatic injection, 379
  injection, 379
Sodium ferric gluconate complex in sucrose injection, 379
Sodium hyaluronate injection, 379
Sodium injection
  dalteparin, 247
  danaparoid, 247
Sodium lactate compound (Hartmann's) injection, 380
Sodium thiosulfate injection, 380
Solution
  acetylcholine chloride intraocular, 173
  albuterol sulfate inhalation, 176
  amino acid parenteral nutrition, 180–182
  aqueous colloidal of vitamin K1, 358
  cefoxitin injection premixed IV, 221
  diazepam rectal, 256
  guaiacol-iodide veterinary, 293
  iron copper veterinary, 310
  pentobarbital sodium injection, 354
  ringer lactate injection, 373
Somatropin (RDNA origin) injection, 380–381
SOPs, 32, 39, 40, 43, 55, 57, 65, 67, 116, 350, 377, 378, 402

Stability-indication, drug
other product characteristics, 86
potency, 85–86
protocol, 85
purity and molecular characterization, 86
Standard operating procedures. *See* SOPs
Sterile drug
aseptic processing, 32–33
cGMP compliance of, 30–32
Sterile water for injection, 381
Sterility testing, 44–47
methods, 65
Storage conditions, drug
accelerated and stress conditions, 86
container/closure, 87
humidity, 86
light, 87
stability after reconstitution of freeze-dried product, 87
temperature, 86
Streptomycin sulfate injection, 381
Succinylcholine chloride injection
ampoule, 383
lyophilized, 382
veterinary nonsterile, 383
Sulfate injection
amikacin, 178
atropine, 197, 198
Sumatriptan succinate injection, 384
Surface monitoring, 44

Tenecteplase for injection, 384
Terminal heat sterilization
bacterial endotoxins test and method, 63
evidence of formal written procedures, 63
microbiological efficacy of the cycle, 62–63
microbiological monitoring of the environment, 63
process and product, 62
sterility testing methods and release criteria, 63
Testosterone
cypionate injection, 384
propionate injection, 385, 386
repository veterinary injection, 385
suspension injection, 384
Testosterone enanthate
estradiol valerate injection, 385
injection, 385
Test until clean, 69
Tetrahydrozoline ophthalmic drops, 386
Theophylline and dextrose injection, 387
Thiamine hydrochloride injection
buffered, 388
buffered and gelatin, 388
with citric acid and gelatin, 388
with sodium formaldehyde sulfoxylate, 388
unbuffered, 387
Thiopental sodium for injection, 389
Thiotepa for injection, 389
Thiothixene hydrochloride injection, 389
Thyrotropin-alpha for injection, 389
Time limitation, 38–39
Timolol ophthalmic solution, 390
Tinzaparin sodium injection, 390
Tirofiban hydrochloride injection, 390
Tobi®, 422
Tobramycin
solution for inhalation, 390
sulfate injection, 391–392
Topotecan hydrochloride for injection, 392
Trace element concentrate injection, 392–393
Tranexamic acid injection, 393
Trastuzumab for injection, 393
Triamcinolone acetonide suspension injection, 394
Trifluprom azine hydrochloride
injection, 394, 395
veterinary, 395
Tubocurarine chloride injection, 396
Typhoid vi polysaccharide vaccine, 396

Urokinase for injection, 397

Valproate sodium injection, 397
Valrubicin for intravesical instillation, 397
Vancomycin for injection, 398
Varicella virus vaccine live, 399
Vasopressin (8-arginine vasopressin) injection, 399
Vecuronium bromide for injection, 399
Verapamil hydrochloride injection, 400
Vinblastine sulfate for injection, 400
Vincristine sulfate injection, 401
Viral clearance evaluation
analysis of stepwise elimination of virus, 76
choice of studies, 79t
facility and staff, 76
function and regeneration of columns, 76
inactivation assessment, 76
interpretation of, 77
limitation, 77–78
physical removal vs. Inactivation, 76
of reduction factors calculation, 80
reevaluation, 78
scaled-down production system, 76
specific precautions in, 76–77
viruses, 79t
Viruses/model viruses, 75

Water
bacteriostatic injection, 403
for injection, 402
Water for injection (WFI), 31, 55, 56
WFI systems, 56

Zinc sulfate additive injection, 403
Zoledronic acid for injection, 404

Pharmaceutical Science

about the book...

No other area of regulatory compliance receives more attention and scrutiny by regulatory authorities than the regulation of sterile products, for obvious reasons. With the increasing number of potent products, particularly the new line of small protein products, joining the long list of proven sterile products, the technology of manufacturing sterile products has evolved into a very sophisticated industry.

Highlights from ***Sterile Products, Volume Six*** include:

- formulations of sterile dosage forms, regulatory filing requirements of sterile preparations, and cGMP compliance, all of which are tied together in the final preparation of the CMC sections of regulatory applications
- specifications of a manufacturing facility to manufacture compliant sterile products
- NDA or aNDA filing requirements of sterile products
- an alphabetical presentation of formulations of pharmaceutical products based on their generic names

about the author...

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