HANDBOOK OF Pharmaceutical Manufacturing Formulations

Sterile Products

VOLUME 6

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Handbook of Pharmaceutical Manufacturing Formulations

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
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Handbook of Pharmaceutical Manufacturing Formulations: Sterile Products

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Sarfaraz K. Niazi

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Dedication

To Professor Shamsuz Zoha, my first pharmacy teacher, who inspired many with his passion for the profession and for science

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Preface to the Series

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.
Deerfield, Illinois

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Preface to the Volume

The Handbook of Pharmaceutical Manufacturing Formulations: Sterile Products (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 ANDA (Abbreviated New Drug Application) 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:

- *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.
- *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.
- *Stability.* Besides the rigor of treatment in rendering a product sterile, incompatibility issues may render a sterile product prone to instability.

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The formulations included here have been fully validated to provide sufficient shelf-life, depending on the product.

- *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 website 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 website.

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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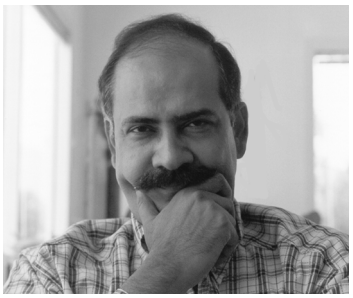

Dr. Sarfaraz K. Niazi has been teaching and conducting research in the pharmaceutical industry for over 30 years. He has authored hundreds of scientific papers, textbooks, and presentations on the topics of pharmaceutical formulation, biopharmaceutics, and pharmacokinetics of drugs. He is also an inventor with scores of patents and is licensed to practice law before the U.S. Patent and Trademark Office. Having formulated hundreds of products from consumer products to complex biotechnology-derived products, he has accumulated a wealth of knowledge in the science of formulations 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, pharmacokinetics and bioequivalence evaluation, and intellectual property issues (http://www.pharmsci.com).

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Atropine, Chlorpheniramine Maleate, and Phenylpropanolamine Injection
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Choriogonadotropin Alfa (Recombinant) for Injection
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Diazepam Injection
Diazepam Rectal Solution
Dibenzazepine Carboxamide Injection
Diclofenac Injection
Dicyclomine Hydrochloride Injection
Digoxin Injection

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Dihydroergotamine Mesylate Drops
Dihydroergotamine Mesylate Injection
Dihydroergotamine Mesylate Nasal Spray
Diisopropylphenol Injection
Diltiazem Hydrochloride Injection
Dimenhydrinate Injection
Dimethyl Sulfoxide Injection
Dinoprostone Cervical Gel
Diphenhydramine Hydrochloride Injection
Diphenylmethyl Piperazine Injection
Dipyrone Injection
Dipyrone, Papaverine HCl, and Atropine Sulfate Injection
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Disulfonic Acids Injection
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Doxercalciferol Injection
Doxorubicin for Injection
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Doxycycline Hydrochloride Injection
Ebselen Liposomal Injection
Edetate Sodium, Polyvinyl Alcohol, Sodium Sulfacetamide, Sodium Thiosulfate Ophthalmic Drops
Edrophonium Injectable
Electrolyte Maintenance Fluid
Electrolytes, TPN Injection
Emetine Hydrochloride Injection
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Ephedrine and Pyrilamine Maleate Injection Veterinary
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Famotidine Injection
Fenoldopam Mesylate Injection
Fentanyl Citrate Injection
Filgrastim Injection
Flosulide Injection
Fluconazole Injection
Flumazenil Injection

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Folic Acid and Niacinamide Injection
Follitropin Beta for Injection
Furosemide Injection
Gentamicin and Prednisolone Ophthalmic Drops
Gentamicin Injection
Gentamicin Ophthalmic Drops
Glycine Antagonist Injection
Glycopyrrolate Injection
Granisetron Hydrochloride Injection
Guaiacol-Iodide Solution Veterinary
Haloperidol Injection
Hemin for Injection
Heparin Injection
Hepatitis B Immune Globulin (Human)
Hexamethylmelamine Injection
Hydrochloric Acid
Hydrocortisone Sodium Phosphate Injection
Hydrocortisone Sodium Succinate for Injection
Hydromorphone Hydrochloride Injection
Hydroxycobalamin Injection
Hydroxyprogesterone Caproate Injection
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Ibuprofen Lysinate Injection
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Immune Globulin (Human) for Injection
Infliximab Recombinant for Injection
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Insulin Glargine Injection
Insulin Human 70/30
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Insulin Lispro Injection
Insulin Regular
Interferon Injection
Interleukin for Injection (IL-2)
Iodine Intravenous Additive
Iron Copper Solution Veterinary
Iron Dextran Injection
Iron Sucrose Injection
Isometheptene Hydrochloride Veterinary Injection
Itraconazole Injection
Ketoprofen Lysine Injection
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Ketorolac Tromethamine Ophthalmic Solution
Labetalol Hydrochloride Injection
Lactobionic Acid Injection
Lamotrigine Injection
Lazaroid Injection
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Leucovorin Calcium Injection
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Levorphanol Tartarate Injection
Levothyroxine Sodium for Injection

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Lidocaine Hydrochloride and Epinephrine Injection
Lidocaine Hydrochloride Injection
Lincomycin Hydrochloride Injection
Liothyronine Sodium Injection (T3)
Lipid Emulsion 20% for Parenteral Nutrition
Liver, Iron, and Cyanocobalamin with Procaine Injection
Liver, Iron, and Vitamin B12 Injection Veterinary
Lorazepam Injection
Magnesium Sulfate 50% Injection
Manganese Sulfate Injection
Mechlorethamine Hydrochloride for Injection Trituration
Medroxyprogesterone Acetate Sterile Aqueous Suspension
Medroxyprogesterone and Estradiol Sterile Suspension
Melphalan Hydrochloride for Injection
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Menadione Sodium Bisulfite Injection Veterinary
Menotropins for Injection
Meperidine Hydrochloride Injection
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Methohexital Sodium for Injection
Methylprednisolone Acetate Suspension Injection
Metoclopramide Injection
Metolazone Injection
Metronidazole Infusion
Metronidazole Injection
Metronidazole and Dextrose Infusion
Midazolam Hydrochloride Injection
Milrinone Lactate Injection
Mineral Complex Injection
Mitoxantrone for Injection.
Morphine Sulfate Infusion.
Morphine Sulfate Injection
Moxidectin Injection
Multiple Electrolytes and Dextrose Injection (Elliott's B Solution)
Muromonab-CD3 Injection
Nalbuphine Hydrochloride
Naloxone Hydrochloride Injection
Nandrolone Decanoate Injection
Nandrolone Phenylpropionate Injection
Naphazoline Ophthalmic Drops
Natamycin Ophthalmic Suspension
Natural Estrogenic Substances Suspension
Nedocromil Sodium Ophthalmic Solution
Neomycin and Prednisolone Acetate Ophthalmic Suspension
Neomycin Sulfate–Polymyxin B Sulfate for Irrigation
Neostigmine Methylsulfate Injection
Nesiritide for Injection
Netilmicin Injection
Niacinamide Injection

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Nicardipine Hydrochloride for Infusion
Nicardipine Hydrochloride Injection
Nikethamide Injection
Nimesulide Injection
Nimodipine Injection
Nystatin for Injection
Octreotide Acetate Injection
Ofloxacin Otic Solution
Ondansetron Hydrochloride Injection
Oprelvekin for Injection
Orphenadrine Citrate Injection
Oxacarbazepine-10 Injection
Oxazepine Injection
Oxendolone Injection
Oxymorphone Hydrochloride Injection
Oxytetracycline Injection
Oxytocin Injection
Oxytocin Injection, USP, 20 U/mL
Paclitaxel Injection
Palivizumab for Injection
Pancuronium Bromide Injection
Parenteral Nutrition Fat Emulsion
Paricalcitol Injection
Pegademase Bovine Injection
Pegaspargase Injection
Peginterferon Alfa-2b for Injection
Penicillin G Benzathine and Penicillin G Procaine Injection
Penicillin G Benzathine Injectable Suspension
Pentobarbital Sodium Solution Injection
Pentostatin for Injection
Pentylenetetrazole Injection
Pheniramine Maleate Injection
Phenol Saline Diluent
Phenylbutazone and Dipyrone Injection
Phenylbutazone Injection Veterinary
Phenylephrine and Zinc Sulfate Ophthalmic Drops
Phenylpropanolamine Hydrochloride Injection
Phenytoin Sodium Injection
Phytonadione (Vitamin K1) Injection
Piperacillin Sodium and Tazobactam Sodium Injection
Plicamycin for Injection
Polyvinyl Alcohol Ophthalmic Solution
Potassium Estrone Sulfate Injection Veterinary
Potassium Estrone Sulfate Suspension Injection
Potassium Phosphate Injection
Prednisolone and Neomycin Ophthalmic Suspension
Prednisolone Injection
Prednisolone Ophthalmic Drops
Procaine Hydrochloride Injection
Prochlorperazine Injection
Progesterone and Tocopheryl Acetate Injection
Progesterone Injection Repository Veterinary
Promazine Hydrochloride Injection
Promethazine Hydrochloride Injection
Propofol Emulsion Injection

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Pyridoxine and Thiamine Injection
Pyridoxine Hydrochloride Injection
Pyrilamine Maleate and Ephedrine Injection Veterinary
Quinidine Sulfate Injection
Quinolone Lyophilized Injections
Quinolone–Calcium Lactate Complex for Injection
Ranitidine Injection
Reteplase Recombinant for Injection
Retinol (Vitamin A) Injection
Rho (D) Immune Globulin (Human) Injection
Ringer Lactate Solution Injection
Rituximab Injection
Rubella Virus Vaccine Live
Salbutamol Aerosol for Inhalation
Sisomicin Injection
Sodium Bicarbonate and Disodium Edetate Injection
Sodium Bicarbonate Injection
Sodium Chloride Bacteriostatic Injection
Sodium Chloride Injection
Sodium Ferric Gluconate Complex in Sucrose Injection
Sodium Hyaluronate Injection
Sodium Lactate Compound (Hartmann's) Injection
Sodium Thiosulfate Injection
Somatropin (rDNA Origin) Injection
Sterile Water for Injection
Streptomycin Sulfate Injection
Succinylcholine Chloride Injection
Sumatriptan Succinate Injection
Tenecteplase for Injection
Testosterone Injection
Tetrahydrozoline Ophthalmic Drops
Theophylline and Dextrose Injection
Thiamine Hydrochloride Injection
Thiopental Sodium for Injection
Thiotepa for Injection
Thiothixene Hydrochloride Injection
Thyrotropin Alfa for injection
Timolol Ophthalmic Solution
Tinzaparin Sodium Injection
Tirofiban Hydrochloride Injection
Tobramycin Solution for Inhalation
Tobramycin Sulfate Injection
Topotecan Hydrochloride for Injection
Trace Element Concentrate Injection
Tranexamic Acid Injection
Trastuzumab for Injection
Triamcinolone Acetonide Suspension Injection
Trifluprom azine Hydrochloride Injection
Tripelennamine Hydrochloride Injection Veterinary
Tubocurarine Chloride Injection
Typhoid Vi Polysaccharide Vaccine
Uridine Triphosphate Injection
Urokinase for Injection
Valproate Sodium Injection
Valrubicin for Intravesical Instillation

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Vancomycin for Injection.
Varicella Virus Vaccine Live
Vasopressin (8-Arginine Vasopressin) Injection
Vecuronium Bromide for Injection
Verapamil Hydrochloride Injection
Vinblastine Sulfate for Injection
Vincristine Sulfate Injection
Water for Injection
Water for Injection, Bacteriostatic
Zinc Sulfate Additive Injection
Zoledronic Acid for Injection

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Part I

Sterile Manufacturing Practice

1 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 Administration [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 (CGMPRs) 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 Cleanrooms 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

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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; for example, 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 #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 indicator will be used to assure sterility, such as lag thermometers, peak controls, Steam Klox, test cultures, or biological indicators. (*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 biological indicators are used, assure that the current USP guidelines on sterilization and biological indicators are followed. In some cases, testing biological indicators may become all or part of the sterility testing.

Biological indicators are of two forms, each incorporating a viable culture of a single species of microorganism. In one form, the culture is added to representative

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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 biological indicators include:

- 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. 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 biological indicator 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

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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. Due to 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 filtered through high efficiency particulate air (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 pre-filters 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

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TABLE 1.1
Air Classifications[a]

Clean-Area Classification	>0.5-μm Particles/ft³	> 0.5-μm Particles/m³	Microbiological Limit[b] CFU/10 ft³	Microbiological Limit[b] CFU/m³
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

From Cleanrooms and Associated Controlled Environments, Classification of Air Cleanliness. Contamination Control of Aerospace Facilities. Technical Order 00-25-203, U.S. Air Force, December l, 1972.

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 1.1 summarizes clean-area air classifications.[1] 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 μm 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

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defined space.[1] (A velocity of 90 to 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 1.1) 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 inH_2O (with doors closed). When doors are open, outward airflow should be sufficient to minimize ingress of contamination.[2] 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 also should 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 (HEPA)

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

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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 dioctylphthalate (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 μm 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 μg/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 μm. 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.[2]

Any intervention or stoppage during an aseptic process can increase the risk of contamination. Personnel and

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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 air locks. 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

Sections 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 current good manufacturing practice (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

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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

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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.[7] 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 water for injection (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.

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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 water for injection, 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. Biological indicators 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.

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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.[5–7] 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 endo-toxins. 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 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

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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
- 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.

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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 <71> indicator microorganisms as well as isolates that have been identified by environmental monitoring, personnel monitoring, and positive sterility test results. Positive control units should be inoculated with a <100 CFU challenge and incubated. For instances in which the growth promotion testing fails, the origin of any contamination found during the simulation should nonetheless be investigated and the media fill should be promptly repeated. The production process should be accurately simulated using media and conditions that optimize detection of any microbiological contamination. Each unit should be filled with an appropriate quantity and type of microbial growth medium to contact the inner container/closure surfaces (when the unit is inverted and swirled) and permit visual detection of microbial growth. Some drug manufacturers have expressed concern over the possible contamination of the facility and equipment with the nutrient media during media fill runs. However, if the medium is handled properly and is promptly followed by the cleaning, sanitizing, and, where necessary, sterilization of equipment, subsequently processed products are not likely to be compromised.

g. Incubation and Examination of Media-Filled Units

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.

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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.

h. 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[8] 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 μm 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 microorgan-

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isms 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-μm 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 *Brevundimonas 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.[9] The probability of such passage is considered to increase as the number of organisms (bioburden) in the material to be filtered increases.[10] 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.[9–11] 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 (Section 211.63 and Section 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.

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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 biological indicator within the sterilization load. *D*-value of the biological indicator can vary widely depending on the material (e.g., glass versus 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,[4] 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 biological indicators (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 (TC) 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. Biological indicators 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 biological indicator 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

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components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity."

Section 211.165 and Section 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 (Section 211.42 and Section 211.113).

Evaluating the quality of air and surfaces in the cleanroom 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

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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

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be obtained by incubating at 30°C to 35°C for 48 to 72 h. 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 cleanroom 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 Sec. 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 Section 211.194 and Section 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.

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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."[12] 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.

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A good error record can help eliminate a lab 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

Section 211.100, Section 211.186, and Section 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

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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 (Section 211.100 and Section 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

Due to 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.

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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 in. 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

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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) 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 six-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).

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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.[13] 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

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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 Section 211.100 and Section 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:

- 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:

- 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-μm 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

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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

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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 min. 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.

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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

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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, biological indicators are used in lyophilizers to validate the steam sterilization cycle. One manufacturer of a biopharmaceutical product was found to have a positive biological indicator after sterilization at 121°C for 45 min. 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 biological indicator 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, 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

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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 clean-room 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

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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 to 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.

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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

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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 non-sterile 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 reverse osmosis (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 U.S.), 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 water side) 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 water side. Thus, it is recommended that, when not in use, heat exchangers not be drained of the cooling water.

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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 "deadlegs," 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 to 80°C) circulating systems. With colder systems (65°C to 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 reverse osmosis (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 ultraviolet (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-μm point-of-use filters that can mask the level of microbiological contamination in the system. Although it is recognized that endo-toxins 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-μm 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.

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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-μm 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 ultrafiltration (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

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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.

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GLOSSARY

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

Air Lock: 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

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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 mmHg, or 760,000 μm.

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 μm. 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 (min) 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.

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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 to 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.

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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 μm = 1 Mtorr or 25,400 μm = 1 inHg, or 760,000 μm = 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 set-up, 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 min.

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 (SAL) of usually less than 10^6 (i.e., a probability of a nonsterile unit of greater than one in a million).

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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 μm. 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-μm particle-retaining efficiency of 99.999%.

Unloading Valve: The valve that connects the interstage with suction to equalize both pressures during pump-down.

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 balI 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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2 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

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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.

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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 Endotoxin 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

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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 Code of Federal Regulations (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

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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

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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.

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3 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:
   - Where there is more than one active component in the formulation, the ingredients appear in alphabetical order.
   - Where there is a large number of active ingredients, such as in vitamin B-complex formulations, the ingredients are listed under the generic category, e.g., B-complex vitamin.
   - Individual vitamins are listed with their name first; for example, Vitamin C appears as ascorbic acid, Vitamin E as alpha 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.
   - 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, though 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

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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.
   - 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-μm 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 aswhen 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 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.

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- 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 transfering 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 Chapter 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-µm prefilter is recommended, followed by a 0.22-µm 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 website (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

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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.westpharma.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.wheatonsci.com); ampoules are also supplied by Wheaton (http://www.alcanpackaging.com/pharma/eng/html/tubularampoules.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.

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

Santasolo-Sohlberg Corp.
Hankasuontie 4
SF-00390 Helsinki, Finland

Aseptic Contract Manufacturers

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

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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

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

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

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Klenzade
Osborn Building
St. Paul, MN 55102, USA

Ladish-Triclover
9201 Wilmot Road
Kenosha, WI 53141, USA

National Sonies
250 Marcus Boulevard
Hauppage, 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

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

Consultants

Bio-Separation Consultants
3935 Falcon Ave.
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, 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

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

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Mallinckrodt, Inc.
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 Ave.
St. Louis, MO 63110, USA
Telephone: (800) 325-8690

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 St.
New Orleans, LA 70130, USA
Telephone: (504) 523-7271

Pennwalt Corp.
Stokes Vacuum Components Dept.
5500 Tabor Road
Philadelphia, PA 19120, USA

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Hankasuontie, 4-6
SF-00390 Helsinki 39, Finland

Stilmas S.p.a.
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I-20090 Settala
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Vaponies, Inc.
Cordage Park
Plymouth, MA 02360, USA
Telephone: (617) 746-7555

Engineering and Construction

CRS Sirrine, Inc.
P. O. Box 5456
Greenville, SC 29606
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

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

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Vetter Pharma Fertigung
P. O. Box 2380
D-7980 Ravensburg, Germany
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Filter Aids

Cuno, Inc.
400 Research Parkway
Meriden, CT 06450, USA
Telephone: (800) 243-6894

Eagle-Picher Industries
580 A Walnut St.
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

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

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
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Telephone: (06181) 34-0

Pennwalt (Stokes Division)
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Philadelphia, PA 19120, USA
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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

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
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Cumo, Inc.
400 Research Parkway
Meriden, CT 06450, USA
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Domnick Hunter Filters, 1Ad
Durham Road D-3400
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Telephone: (091) 4105121

Ertel Engineering
20 Front Street
Kingston, NY 12401, USA
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Filterite Corp.
4116 Sorrento Valley Blvd.
San Diego, CA 92121, USA
Telephone: (800) 854-1571

Filtrox Werk AG
CH-9001 St. Gallen, Switzerland

FPI (Filter Products, Inc.)
8314 Tiogawoods Drive
Sacramento, CA 95828, USA
Telephone: (916) 689-2328

Fuji Filter Mfg. Co. Ltd.
Shiu-Muromachi Bldg. 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 Ave. East
Cranford, NJ 07016, USA
Telex: 96113

Kurita Machinery, Mfg. Co.
1-44 2-Chome, Sakaigawa,
Nishi-ku, 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 Ave.
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
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Schenk Filterbau GmbH
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D-7070 Schwabisch Gmund
Germany
Telephone: (07171) 82091

Schleicher u. Schull GmbH
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D-3354 Dassel, Germany
Telephone: (05564) 8995

Seitz-Filter-Werke GmbH
Planiger Str. 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

PUMPS (SANITARY)

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Waukesha Foundry
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Waukesha, WI 53186, USA
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Randolph Corp.
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Houston, TX 77019, USA
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Warren Rupp-Houdaille Co.
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Mansfield, OH 44901, USA
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Wilden Pump & Engineering
22069 Van Buren Street
Colton, CA 92324, USA
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The Ladish Co.
9201 Wilmot Road
Kenosha, WI 53141, USA
Telephone: (414) 694-5511
Fax: (414) 694-7104

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
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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
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Stainless Metals, Inc.
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Long Island City, NY 11101, USA
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Valex
6080 Leland Street
Ventura, CA 93003, USA
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Walker Stainless Equipment
New Lisbon, WI 53950, USA
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Sterility Test Equipment

Gelman Sciences
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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
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Vial and Bottle Washers

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Part II

Sterile Pharmaceutical Formulations

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Abciximab Injection

Bill of Materials (Batch Size 1 L)					
Scale /mL		Item	Material	Quantity	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 47,615 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	Quantity	UOM
500.00	mg		Acetazolamide Sodium	500.00	mg
QS	mL		Sodium Hydroxide[a]	QS	mL
QS	mL		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.

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Acetylcholine Chloride Intraocular Solution

Bill of Materials for Lower Chamber					
Scale/Vial		Item	Material	Quantity	UOM
20.00	mg	1	Acetylcholine Chloride	20.00	mg
56.00	mg	2	Mannitol	56.00	mg

Bill of Materials for Upper Chamber (2-mL Diluent)
Sodium Acetate Trihydrate
Potassium Chloride
Magnesium Chloride Hexahydrate
Calcium Chloride Dihydrate
Sterile Water for Injection

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 to 330 milliosmoles/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.

Acyclovir Sodium Injection

Bill of Materials per Vial (10 mL)					
Scale/mL		Item	Material	Quantity	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 intravenous administration only. The pH of the reconstituted solution is ca. 11. Further dilution in any appropriate intravenous solution must be performed before infusion.

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Adenosine Injection

1: 5′ Monophosphate Injection 200 mg/mL Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

2: Adenosine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	UOM
200.00	µg	1	Adrenal Cortex equivalent to 200 µg 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	Quantity	UOM
1.80	mg	1	Adrenaline Bitartarate (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 min. Sample.
7. Check for clarity. Sample.

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Alatrofloxacin Mesylate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
7.86	mg	1	Alatrofloxacin Mesylate	7.86	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

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 to 4.1) by Item 2 or 3.
3. Filter and fill 30 mL into a 40-mL vial or ampoule.
4. Autoclave at 115°C for 15 min.
5. Finish and sample.

An isotonic form of the above is obtained as follows.

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	
QS	mL	4	Sodium Hydroxide for pH adjustment	QS	
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 (3.7to 4.1) by Item 3 or 4.
3. Filter and fill 30 mL into a 40-mL vial.
4. Autoclave at 115°C for 15 min.
5. Finish and sample. Final concentration is 3.14 mg/mL.

A lyophilized form of the above is obtained as follows:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	
QS	mL	4	Sodium Hydroxide for pH adjustment	QS	
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 to 4.1) by Item 3 or 4.
3. Filter and fill 30 mL into a 40-mL vial.
4. Lyophilize for 24 h under a 0.1-atm vacuum.
5. Autoclave at 115°C for 15 min.
6. Finish and sample. Final concentration is 3.14 mg/mL.

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Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
5.00	mg	1	Trovafloxacin, use Alatrofloxacin Mesylate	5.00	g
QS	mL	2	Sodium Hydroxide for pH adjustment	QS	mL
QS	mL	3	Hydrochloric Acid for pH adjustment	QS	mL
QS	mL	4	Water for Injection, QS to	1.00	L

* For pH adjustment.

DESCRIPTION

Available in 40-mL and 60-mL single-use vials as a sterile, preservative-free aqueous concentrate intended for dilution prior to intravenous administration of doses of 200 mg or 300 mg of trovafloxacin, respectively. The pH range for the 5 mg/mL aqueous concentrate is 3.5 to 4.3.

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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 vial is heat treated at 60°C for 10 h against the possibility of transmitting the hepatitis viruses. The product is available in 50-mL and 100-mL rubber-stoppered single-dose vials.

1: 5%

Bill of Materials (Batch Size 1 L)					
Scale/100 mL		**Item**	**Material**	**Quantity**	**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*-Acetyltryptophanate (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.

2: 20%

Bill of Materials (Batch Size 1 L)					
Scale/100 mL		**Item**	**Material**	**Quantity**	**UOM**
20.00	g	1	Albumin	200.00	g
QS	mL	2	Sodium Caprylate (0.016 *M*)	QS	mL
QS	mL	3	Sodium *N*-Acetyltryptophanate (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.

3: 25%

Bill of Materials (Batch Size 1 L)					
Scale/100 mL		**Item**	**Material**	**Quantity**	**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*-Acetyltryptophanate (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 ± 0.5.

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Albuterol Sulfate Inhalation Solution

Bill of Materials (Batch Size 1 L)					
Scale/3 mL		**Item**	**Material**	**Quantity**	**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**	**Quantity**	**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 mL 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**	**Quantity**	**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

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Alpha Tocopherol (Vitamin E) Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 96.0 to 102.0% 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	Quantity	UOM
5.40	µg	1	Alprostadil	5.40	mg
172.00	mg	2	Lactose	172.00	g
47.00	µg	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	Quantity	UOM
58MM	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.

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Amikacin Sulfate Injection

50 mg /mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

250 mg /mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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°C to 30°C) while sparging with filtered Item 6. Bubble for not less than 30 min.
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, 2, 3, and 4, one at a time and slowly.
5. Check pH to 4.5 (4.0 to 5.0); 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-µm 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-µm or finer membrane filter.
10. Fill container, protect head space with Item 6, and sterilize using an approved cycle.

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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).

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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 µS/cm and pH range of 5.0 to 7.0.
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 2-a preparation vessel. Mix well by stirring to make clear solution.
   c. Add and dissolve Item 3 and Item 2 into the solution of Step 2-b, mix well, and make clear solution.
   d. Check pH (4.0 to 5.0).
   e. Adjust pH by 2 *N* H_2SO_4/1 *N* NaOH solution (4.0 to 5.0).
   f. After adjustment of pH make up volume to 1l by Item 4 and mix during bubbling Item 5 until O_2% is less than 1.
   g. Check final pH (4.0 to 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-µm 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-µm 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 to 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 min
9. *Optical checking.* Check the ampoules under the optical checking machine.

PACKAGING MATERIAL SPECIFICATIONS

Ampoule, 2 mL, flint glass Type I

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Amino Acid Parenteral Nutrition Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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		19	Nitrogen Gas, NF	QS	

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 to 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°C to 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 to 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-µm 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 to 1000 mL), 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.

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1: 8.5%

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	

2: 10.00%

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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		

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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 to 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°C to 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 to 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 to 1000 mL), 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

Isoleucine	4.0 to 5.5 g/L
Leucine	8.0 to 10.0 g/L
Lysine	6.0 to 8.0 g/L
Methionine	4.0 to 6.0 g/L
Phenylalanine	4.0 to 6.0 g/L
Threonine	4.0 to 6.0 g/L
Tryptophan	1.0 to 2.0 g/L
Valine	6.0 to 8.0 g/L
Arginine	10.0 to 12.0 g/L
Histidine	1.5 to 3.5 g/L
Alanine	9.0 to 12.0 g/L
Aminoacetic Acid (Glycine)	11.0 to 16.0 g/L
Asparagine	0 to 1.0 g/L
Aspartic Acid	5.5 to 8.0 g/L
Acetylcysteine	0 to 2.5 g/L
Glutamic Acid	6.0 to 10.0 g/L
Ornithine	0 to 1.0 g/L
Proline	4.0 to 6.0 g/L
Serine	1.0 to 3.0 g/L
Tyrosine	0.1 to 0.5 g/L
(as Acetyltyrosine)	0 to 2.0 g/L
Taurine	0 to 4.0 g/L

Aminohippurate Sodium for Injection

Bill of Materials (Batch Size 1 L)

Scale/mL		Item	Material	Quantity	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.

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Aminophylline Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min 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 subzero 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.

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Amiodarone Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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] Preprepared 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 to 3.6).
8. Make up the volume with Item 5.

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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		Water for Injection, USP, QS to	1.00	L

Note: Fill 3 mL per ampoule.

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Amoxicillin–Clavulanic Acid Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Quantity	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	Quantity	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 × 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-mL 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 min (–0, +360 min). 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 h at 121°C and vacuum dry with heat for a minimum of 4 h at a temperature not exceeding 90°C.
   d. Deliver to sterile area for filling.
4. *Filling*.
   a. Sterile-fill required grams 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-min 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.

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Amphotericin B Cholesteryl Sulfate Complex for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		**Item**	**Material**	**Quantity**	**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.

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Amphotericin B Injection

Bill of Materials (Batch Size 15 L)					
Scale/mL		Item	Material	Quantity	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 below 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 below 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 to 7.7). *Note*: pH *must not* drop below 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 min. Keep tank covered. Sample and keep solution cool until QC approval.
9. Aseptically filter the solution through a 0.22-µm 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 below, hold for at least 30 min. Turn condenser on. After condenser temperature reaches –40°C or below, turn vacuum on.
12. When the vacuum reading is less than 250 µm, 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.

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Amphotericin B Lipid Complex Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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.

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Antazoline Sulfate and Xylometazoline Hydrochloride Ophthalmic Drops

Bill of Materials (Batch Size 1 L)					
Scale/5 mL		Item	Material	Quantity	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 (#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 min 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.

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Antipyrine, Phenylephrine, and Pyrilamine Maleate Ophthalmic Drops

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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, 3, 4, 5, 6, 7, 8, and 9, in order, allowing each to dissolve before adding the next.
2. QS to 45 L with Item 10 and mix well for 15 min.
3. Sterile filtration.
4. Sterilize for 1 h (range 45 to 60 min) at 121°C (–0, +5°C) in autoclave at 15 psi the Sartorius mini cartridge, filter, and a stainless steel pressure vessel.
5. Mix the product for at least 10 min before filtration. Before sterile filtration to the 100-L pressure vessel, perform the bubble point test at NLT 46 psi.
6. After completion of product filtration, flush the sterilizing filter with at least 20 L of water purified (distilled). Sample.
7. Aseptically fill sterile solution through sintered glass into sterilized containers. Perform the bubble point test on a 0.22-μm in-line gas filter before and after filtration at 18 psi.

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Antipyrine, Phenylephrine, and Sodium Thiosulfate Ophthalmic Solution

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Quantity	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 min 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, 5, 6, 7, 8, and 9, in order, allowing each to dissolve before adding the next.
3. Check pH (range 6.7 to 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 min.

STERILE FILTRATION

1. Sterilize for 1 h (range 45 to 60 min) 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 min before filtration.
4. Connect the sterilized Sartorius mini cartridge filter and sterile-filter with the aid of N_2 pressure (15 to 30 lb). Discard initial 10 L of filtrate, attach sterilized hose to sterilized filter holder,

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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 h 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 in-line 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	Quantity	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	10.00	g
			Diluent vial		
5.00	mL	1	Water for Injection, USP, QS to	5.00	L

Note: A 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	Quantity	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.

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Argatroban (Thrombin Inhibitor) Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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.

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Ascorbic Acid and B-Complex Vitamins

1: 2 Vials

Bill of Materials Vial 1 (Batch Size 561 L)					
Scale/mL		Item	Material	Quantity	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 units, factored for potency (e.g., 1.5 million units/g)	—	—
40	IU	3	Vitamin D, 25% excess, labeled for 40 million units, factored for potency such as 28 million units/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	12,807.63	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 Vitamin A and Vitamin 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 min, and then blanket with Item 13.
2. Dissolve Item 7 in 13.3 L of hot Item 14 (50°C to 60°C). Allow to cool. Add to the vessel above.
3. Add, with constant stirring, Items 15, 1, 10, 6, 5, and 4. 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, 8, and 3 to Item 9 and allow for 5 to 6 min 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.

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Bill of Materials Vial 2 (Batch Size 561 L)					
Scale/mL		Item	Material	Quantity	UOM
80.00	µg	1	Folic Acid, USP, 25% excess	56.10[a]	g
1.00	µg	2	Cyanocobalamin, USP, 25% excess	701.25[b]	mg
12.00	µg	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 five 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 about 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 h. Rinse stoppers at least three times with RO water.

2: Lyophilized in Covial

Bill of Materials Lower Chamber (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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).

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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 min.
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 below.
    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 h.
    e. Start condenser; let the condenser cool to –55°C or below.
    f. Start vacuum and let the chamber achieve a level of 100 microns or below.
    g. Set the temperature controller at –30°C and let the lyophilizer run for 24 h.
    h. Raise the shelf temperature to 0°C and let run for additional 6 h.
    i. Raise the shelf temperature to +20°C and run for additional 12 h.
    j. Raise shelf temperature to +35°C and run additional 6 h.
    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.

Bill of Materials Upper Chamber (Batch Size 1 L)

Scale/mL		Item	Material	Quantity	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 about 500 mL of Item 5 into a clean compounding tank and bubble Item 7 for 10 min. 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 about 800 mL with Item 5 and check pH.

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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.

3: Lyophilized with Diluent

Bill of Materials B-Complex Lyophilized (Batch Size 3.9 L)					
Scale/mL		Item	Material	Quantity	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 3.0 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 h.
   b. Turn vacuum on to less than 300 microns for a 20-h cycle time.
   c. Raise the temperature to +15°C for at least 8 h. Break vacuum with N_2 and open under aseptic conditions.
   d. Stopper and seal with aluminum three-piece caps.

Bill of Materials (Batch Size 45 L)					
Scale/10 mL		Item	Material	Quantity	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 min.
7. Remove from autoclave and cool rapidly by squelching into 21°C water.

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Ascorbic Acid, B-Complex Vitamin, with Beta Carotene Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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, 5, 6, 7, and 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-Turrax® 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.

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Ascorbic Acid Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 about 110% of Item 4 in a separate vessel and allow to cool to room temperature.
2. In another vessel, take about 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 to 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 min.
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	Quantity	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

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Ascorbic Acid, USP, 250 mg/mL Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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	Quantity	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

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Atropine Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min.
7. Sample for final testing, clarity, and sterility.

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 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 min.
8. Sterilize all Pyrex bottle fittings and filling parts in autoclave at 121°C for 30 to 35 min.
9. Sterilize sufficient number of Pyrex bottles with dry heat (270°C to 280°C for 2 h and 50 min (range 2 h and 45 min to 3 h). Use bottles within 72 h.
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 h.
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 h and 50 min to 3 h. Use them within 24 h.
14. Aseptically fill 1.15 mL (1.10 to 1.18 mL), flush each ampoule with sterile-filtered N_2 gas. Seal.
15. Autoclave at 122°C (121°C to 124°C) for 12 min (10 to 14 min).
16. Sample for complete testing.

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Aztreonam for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Quantity	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	Quantity	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		

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B-Complex Injection

1: Niacinamide, Pyridoxine, Riboflavin, and Thiamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min, cooled and bubbled with Item 14 for 20 min.
2. Dissolve Items 4 and 2 in sufficient Item 13 in a suitable container.
3. Dissolve Items 7, 1, and 3.
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 h) and using butyl coated with Teflon® rubber stoppers sterilized at 115°C for 30 min after washing. Provide pre- and postflush with Item 14.
10. Sample for complete testing.

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

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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, pyridoxin, 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-µm and 0.22-µm membrane filter. Check for integrity.
6. Autoclave vials at 121°C for 20 min.
7. Sample for assay, sterility, pyrogen/LAL, and stability.

2: Niacinamide, Pantothenate, Pyridoxine, Riboflavin, Thiamine Injection

This product is made up of two solutions prepared separately and mixed at the time of administration.

Bill of Materials for Solution 1 (Batch Size 1 L)

Scale/mL		Item	Material	Quantity	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

Bill of Materials for Solution 2 (Batch Size 1 L)

Scale/mL		Item	Material	Quantity	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 1-a.
   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.

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e. Check pH (range 2.5 to 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 h 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 over 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 to 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 1-b 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 insure 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 h 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.

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Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min, cooled and bubbled with Item 14 for 20 min.
2. Dissolve Items 4 and 2 in sufficient Item 13 in a suitable container.
3. Dissolve Items 7, 1, and 3.
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 h) and using butyl coated with Teflon or latex rubber stoppers sterilized at 115°C for 30 min after washing. Provide pre- and postflush with Item 14.
11. Sample for complete testing.

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

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MANUFACTURING DIRECTIONS

1. Use freshly distilled Item 8; autoclave at 121°C for 30 min, cooled and bubbled with Item 14 for 20 min.
2. Dissolve Items 4 and 2 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 min after washing. Provide pre- and postflush with Item 9 (purified by passing through 1% phenol solution).
11. Sample for complete testing.

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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	Quantity	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 D3 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 Quantity 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 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 two 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 h 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 D3 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 to 4.0).
   k. Sample for testing.

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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 over 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 min (–0, +360 min).

   Note: This cycle or an equivalent cycle that assures 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 min 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 min.
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 to 10.3 mL) for the 10-mL final reconstituted product.
      2. Alternatively, fill 1.13 mL (range 1.05 to 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 above 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

Bill of Materials (Batch Size 1 L)

Scale/mL		Item	Material	Quantity	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 (B12), 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

[a] Used only for pH adjustment if necessary.

[b] Bulk container should be flushed with N_2 and resealed after weighing.

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 Quantity 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

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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 Quantity column include both the manufacturing excess and any stability excess indicated in the Bill of Materials.

MANUFACTURING DIRECTIONS

1. *Preparation*.
   a. Dissolve sodium pantothenate and benzyl alcohol in 560 mL of water for injection.
   b. Add vitamin B12 and polyethylene glycol 400.
   c. Add water for injection and QS to 890 mL. Check pH. If pH is above 8.0, adjust down to 6.0 to 8.0 with 0.1 *N* hydrochloric acid.
   d. Allow solution to stand overnight. Check pH (range 6.0 to 8.0).
   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 over 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 min (–0, +360 min). Maintain oven temperature at 225°C (±10°C) for the duration of the cycle.
   Note: This cycle or an equivalent cycle that assures sterile, pyrogen-free ampoules may be used.
   c. Deliver to the sterile filling area.
4. *Filling*. Sterile 10-mL 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 to 9.3 mL) for the 10 mL final reconstituted product.
      2. Alternatively, fill 1.1 mL (range 1.05 to 1.15 mL) for the 1 mL final reconstituted product.
   b. Sample for testing.
5. *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.

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B-Complex Vitamin Veterinary

1:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

2:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

3:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

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4:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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% to 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	Quantity	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

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B-Complex Vitamins with Liver Extract Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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 (approx. 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	Quantity	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

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Beta-Carotene Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 8000 rpm) for 8 min. Homogenize the emulsion 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	Quantity	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 multi-dose vials; pH 6.8 to 7.2.

Bethanechol Chloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min without loss of potency.

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Biotin Injection

Bill of Materials (Batch Size 1.5 L)					
Scale/mL		Item	Material	Quantity	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 about 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 min); autoclave stoppers at 121°C for 60 min in 2% disodium edetate solution (final rinse stopper with RO water three times).

Biperiden Lactate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

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Bisantrene Emulsion Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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, 3, 4, and 5 until complete solution is obtained.
2. Make up the volume with Item 6. Shake and sonicate for 20 sec 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.

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Glycerine, USP	22.50	g
QS	mL	6	Water for Injection, USP, QS to	1.00	L

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Borax Sodium Lubricating Ophthalmic Drops

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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, 2, 3, 4, 5, and 6 with mixing, allowing each to disperse prior to addition of next ingredient. Rinse the inside tank walls and agitator shaft with 15 mL of Item 10.
   c. Continue mixing the solution for at least 20 min. 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.
   e. Discontinue heating and continue mixing for at least 20 min after last addition of Item 7.
   f. With mixing, continue to cool batch to below 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 min while batch is cooling to below 40°C. Check pH (range 6.7 to 6.9). Adjust, if necessary, with 1 *N* Item 8 or 1 *N* Item 9. Mix for 15 min. Sample.
2. *Sterilization and filling*. Initiate sterilization within 48 h of completion of bulk solution.
   a. Sterilize bulk solution at 121°C to 123°C for 30 to 35 min. As 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 below 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.

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Botulinum Toxin

Type A Purified Neurotoxin Complex

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Quantity	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.

Type B Injectable Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
1428	U	1	Clostridium Botulinum Type B Neurotoxin Complex	1,428,000	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	Quantity	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.

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Buflomedil Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 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 in-line 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 min.
   d. Sample for testing.

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Bupivacaine Hydrochloride Injection

1: 0.75% in Dextrose 8.25% Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 6.2). If necessary, adjust pH with Item 3 or 4 solution.
4. QS with Item 5 to final volume and mix.
5. Check the pH (range 5.8 to 6.2). If necessary, adjust pH with Item 3 or 4 solution. Sample.
6. Prior to filling, filter the solution through a 0.22-µm membrane with an approved prefilter, if needed.
7. Fill appropriate volume into ampoules. Sample.

2: Bupivacaine Hydrochloride Injection 0.25%

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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°C to 30°C). Add and dissolve Item 1. *Note:* Item 1 goes into solution very 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 min.
   e. Check pH. Adjust to 5.6 (range 5.6 to 5.8) with dilute Item 4 (1%) or dilute Item 5 (1%). Allow solution to mix for 10 min 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 min.

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g. Check pH (range 5.4 to 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 over seal.
   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.

3: Bupivacaine with Epinephrine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
2.50	mg	1	Bupivacaine Hydrochloride, use Bupivacaine HCl, USP, Monohydrate	2.64	g
0.005	mg	2	Epinephrine as Epinephrine Bitartarate	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	Quantity	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	Quantity	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.

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Calcitonin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 (SerGlnGluLeuHisLysLeuGlnThr-Tyr ProArgThrAspValGlyAlaGlyThrProNH_2)].

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Calcitriol Injection

1: 1 µg/mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
2.00[a]	mg	1	Calcitriol in Polysorbate 20 Concentrate, 575 µg/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 µg 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 min. 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°C to 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 a 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 5, 6, 3, 4, and 7 with mixing.
7. Mix until all ingredients are dissolved and solution is uniform. Switch to a N_2 gas blanket.
8. Check pH (range 7.0 to 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 a 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.

2: 2 µg /mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
4.00[a]	mg	1	Calcitriol in Polysorbate 20 Concentrate, 575 µg/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 µg of calcitriol and 4.00 mg Polysorbate 20.

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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 min. 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°C to 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 a 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 4, 5, 2, 3, and 6 with mixing.
7. Mix until all ingredients are dissolved and solution is uniform. Switch to a N_2 gas blanket.
8. Check pH (range 7.0 to 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.

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Calcium Glycerophosphate Injection

1: With Lactate

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min, and then combine into 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.

2: Calcium Glycerophosphate Injection (Human and Veterinary)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

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Calcium Injection

1: Calcium Gluconate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 h prior to start of filling.

1. Boil 0.8 L of water for injection, bubble filtered N_2 for 10 to 15 min and maintain a 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 h 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 min; 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.

2: Calcium Glycerophosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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

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Camptothecin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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	Quantity	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 below.
2. Bubble N_2 through Step 1 for at least 15 min 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 to 7.0); do not adjust pH.
5. Make up volume.
6. Check pH again (4.0 to 7.0); do not adjust.
7. Filter through 0.2-μm sterile filter and transferred 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.

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Carprofen Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min.
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 min.

Cefamandole Nafate for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Quantity	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	Quantity	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.

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Cefepime Hydrochloride for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 4.0 to 6.0.

Cefotaxime Injection

Bill of Materials (Batch Size 1 L)					
Scale/50 mL		Item	Material	Quantity	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	Quantity	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 Intravenous Solution

Bill of Materials (Batch Size 1 L)					
Scale/50 mL		Item	Material	Quantity	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 intravenous use only.

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Ceftazidime for Injection — L-Arginine Formulation

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		**Item**	**Material**	**Quantity**	**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 per vial.

Ceftazidime Injection

Dry Powder

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		**Item**	**Material**	**Quantity**	**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.

Premix

Bill of Materials (Batch Size 1 L)					
Scale/50 mL		**Item**	**Material**	**Quantity**	**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.

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Ceftriaxone Injection

1: 500 mg Injection (IM and IV)

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Quantity	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.

2: 250-mg Injection (IM and IV)

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Quantity	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.

3: Premix

Bill of Materials (Batch Size 1 L)					
Scale/50 mL		Item	Material	Quantity	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 2.0-g strength, use 1.2 g of Item 2.

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Cefuroxime for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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**	**Quantity**	**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 Item 2. The pH of reconstituted solution is 5 to 8.

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Chloramphenicol and Phenylmercuric Nitrate Ophthalmic Drops

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Quantity	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 above 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 min.
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 below.
7. When the temperature is at 30°C or below, 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 min.
9. Check pH (range 5.4 to 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 min.

STERILE FILTRATION

1. Sterilize for 1 h (range 45 to 60 min) 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 min before filtration.
3. Connect the sterilized filter and sterile-filter with the aid of N_2 pressure (15 to 30 lb). Discard initial 10 L of filtrate, attach sterilized hose to

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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 in-line 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 h.

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 for Injection

Bill of Materials (Batch Size 1000 Vials)

Scale/Vial		Item	Material	Quantity	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 1.0-µm 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-µm filter and fill as required and lyophilize.
9. Cool the shelves in the lyophilizer to about –40°C; load the product and place thermocouples.
10. The product thermocouples should register –30°C or below for at least 4 h before starting the cycle.
11. Cool condenser until it attains –45°C or below; start vacuum pump to achieve a vacuum level of 300 microns or below 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 h.
13. Set temperature controller to +45°C; hold at this temperature for at least 12 h, 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 h.
14. Bleed chamber slowly to about 5 inHg 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.

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Chloramphenicol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 about 0.75 L of Item 6 and heat in a steam-jacketed kettle for 30 min.
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 to 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.

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Chloramphenicol Sodium Succinate for Injection

Bill of Materials (Batch Size 118 L)					
Scale/Vial		Item	Material	Quantity	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 1 suspension in a steady stream to pH 6.6 to 6.8.
5. Bring to final volume and check pH.
6. Prefilter through a 1.0-µm prefilter cartridge and through a Millipore® prefilter #CW03 012 02 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 about –40°C; load the product; place thermocouples.
9. The product thermocouples should register –30°C or below for at least 4 h before starting the cycle.
10. Cool condenser until it attains –45°C or below; start vacuum pump to achieve a vacuum level of 300 µm or below 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 h.
12. Set temperature controller to +45°C; hold at this temperature for at least 12 h, 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 h.
13. Bleed chamber slowly to about 5 inHg 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	Quantity	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.

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Chloroprocaine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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		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	Quantity	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 assure 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	Quantity	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.

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Chlorpheniramine Maleate Injection

1: 25 mg/mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 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 min.
8. Sample for clarity, sterility.

2: 10 mg/mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

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Chlorpromazine Hydrochloride Injection

1: 10 mg/mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 6.0); adjust with 10% Item 4 or 4% Item 5 if necessary.
5. Filter through 0.22-µm and 0.45-µm prefilters.
6. Flush presterilized ampoules with Item 6 and fill under cover of Item 8.
7. Fill 5.2 mL into flint Type I glass ampoules.
8. Autoclave at 116°C for 30 min.

2: 25 mg/mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 Alfa (Recombinant) for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
285.00	µg	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.

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Chorionic Gonadotropin for Injection

1: 20,000 units/10 mL Covial

Bill of Materials (Batch Size 24-L and 75-L Diluent)					
Scale/m		Item	Material	Quantity	UOM
5,000	U	1	Chorionic Gonadotropin, USP (potency units/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 5.0 to 7.0 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. two 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 below for at least 2 h before starting the cycle.
10. Start condenser and start vacuum only when condenser is below –40°C; start vacuum to chamber to at least 300 microns.
11. Bring up temperature controller to +25°C; set to low heat and switch on heat. Hold at +25°C for at least 36 h.
12. Bring up temperature controller to 45°C; hold at 45°C for 8 h.
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.

2: 10,000 units/10 mL

Bill of Materials (Batch Size 1 L)					
Scale/Vial		Item	Material	Quantity	UOM
10,000	U	1	Chorionic Gonadotropin	10MM	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.

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Chromium Chloride Additive Injection

5-m Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
102.50	µg	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	

10-mL Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
20.50	µg	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	

30-mL Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
20.50	µg	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	Quantity	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.

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Cimetidine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min.
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 µg to trace small impurities. Trace spots.

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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.

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Ciprofloxacin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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 μm.
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 h, and preferably 4 h.
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 h.

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Cisplatin with 2,2′-Dithio-*bis*-Ethane Sulfonate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 2500 rpm) at room temperature for 60 to 90 min.
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	Quantity	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.

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Clarithromycin Injection

Bill of Materials (Batch Size 10.4 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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 min. Sterilize the lyophilization stoppers in an autoclave at 121°C for 60 min, followed by vacuum drying for 90 min.
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 min.
   c. Add Item 4 solution cautiously so the pH does not fall below 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 to 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°C to 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 mmHg.
   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.

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Clindamycin Injection in 5% Dextrose

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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.

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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	Quantity	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 min. 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/L 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 min before proceeding.
   g. Slowly add the remaining volume of the sodium hydroxide slurry from Step 1-e to the solution.
   h. Slowly add the remaining Item 1 to the solution with mixing. Mix for not less than 30 min 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 to 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 to 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 min (–0, +360 min).
   c. Leach stoppers by boiling for 10 min 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 min.
   d. Fill. Sample.

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Clonidine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

Coagulation Factor VIIa (Recombinant) for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Quantity	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	Quantity	UOM
500	IU	1	Coagulation Factor IX	500,000	IU
10.00	m*M*	2	L-Histidine	10.00	m*M*
1.00	%	3	Sucrose	1.00	%
260.00	m*M*	4	Glycine	260.00	m*M*
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.

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Colistin Sulfate, Neomycin Sulfate, Thonzonium Bromide, and Hydrocortisone Acetate Otic Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	3	Hydrocortisone Acetate	10.00	g
0.50	mg	4	Polysorbate 80	0.50	g
QS	mg	5	Sodium Acetate for buffering	QS	
QS	mg	6	Acetic Acid for buffering	QS	
0.02	mg	7	Thimerosal	0.02	g
QS	mL		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	Quantity	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	5	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		Water for Injection, USP, QS to	1.00	L

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Copper Sulfate Additive Injection

5-mL Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	

10-mL Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	

30-mL Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to	1.00	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% to 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	Quantity	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

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Cortisone Acetate Injectable Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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	Quantity	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.

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Crude Liver Extract Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
2.00	µg	1	Crude Liver extract (concentrate 20 µg/mL) to give B12 activity of 2 µg (limit 1.8 to 4.0 µg/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	Quantity	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	Quantity	UOM
300.00	µg	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	

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Cyanocobalamin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min.
   b. Add and dissolve Items 4, 3, and 1 with mixing. Dissolve Item 6 in about 25 mL of Item 7 and add to other ingredients.
   c. Check and adjust pH to 5 (range 4.5 to 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 h and 25 min 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.

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Cyanocobalamin Injection for Veterinary Use

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 µg/mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

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Cyanocobalamin, Pyridoxine, and Thiamine Injection

1:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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] $\text{Quantity of thiamine HCl} = 40 \times \frac{(100)}{100 - \%\ \text{moisture}} \times \frac{(100)}{\%\ \text{Assay on dry basis}}\ \text{g}$

[b] $\text{Quantity of pyridoxine HCl} = 40 \times \frac{(100)}{100 - \%\ \text{moisture}} \times \frac{(100)}{\%\ \text{Assay on dry basis}}\ \text{g}$

[c] $\text{Quantity of cyanocobalamin} = 0.47 \times \frac{(100)}{100 - \%\ \text{moisture}} \times \frac{(100)}{\%\ \text{Assay on dry basis}}\ \text{g}$

[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 µS/cm) and pH (5.0 to 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 two or three times with Item 7, and transfer to the above solution. Mix well till it becomes clear solution.
6. Check pH (range 3.5 to 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 to 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.

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2:

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**UOM**
100.00	mg	1	Thiamine HCl, USP	100.00	g
100.00	mg	2	Pyridoxine HCl, USP	100.00	g
1000.00	µg	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	

3:

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**UOM**
33.00	mg	1	Thiamine Hydrochloride, USP (B1), 15% excess	38.00	g
33.00	mg	2	Pyridoxine (B6), 12% excess	36.97	g
0.333	mg	3	Cyanocobalamin (B12), 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 min) Item 10; bubble Item 11 for 20 min.
3. Add and dissolve Items 4 and 5 to 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 h) amber Type I glass ampoule using pre- and post-Item 11 flushing.
9. Sample for complete testing.

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4:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 B12 (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 min.
   d. Dissolve Vitamin B12 in a small quantity of N_2-saturated water for injection and add to the thiamine–pyridoxine solution from Step d.
   f. Make up to 1 L with N_2-saturated water for injection.
   g. Adjust pH to 3.8 to 4.2 with freshly prepared 10 *N* sodium hydroxide solution.
   h. Filter solution through a previously rinsed filter using an approved 0.45-µm membrane and an approved prefilter.
   i. Sample for testing.
   j. 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 min 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	Quantity	UOM
10.00	mg	1	Cyclosporine, USP	10.00	g
130.00	mg	2	Polyoxyethylated Castor Oil (Cremophot® 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 µm and a 0.22-µm filter.
5. Fill 5 mL into each ampoule and sterilize.

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Cytarabine Liposome Injection for Intrathecal Use, 50 mg/5 mL Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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, 3, 4, and 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 to 8.5).
6. Aseptically fill into 5-mL vial. For intrathecal use only.

Cytomegalovirus Immune Globulin Intravenous (Human)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 5 into a suitable vessel purged with Item 5 for at least 20 min.
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.

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Dacarbazine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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 about 0.8 L of Item 6 into a suitable vessel; purge with Item 9 for 20 min.
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 to 7.0)
7. Filter product and fill vials aseptically.

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Dactinomycin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	UOM
64.00	mg	1	Dalteprim Sodium (10,000 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 about 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 (95,000 IU) aseptically.

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Danaparoid Sodium Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
1,250	U	1	Danaparoid Sodium (anti-Xa units)	1,250,000	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 to 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	Quantity	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 min.
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 to 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	Quantity	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.

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Daunorubicin

1: Daunorubicin HCl Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

2: Daunorubicin Citrate Liposome Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min.
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.

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Desmopressin Acetate Injection-Intranasal

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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.

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Dexamethasone Acetate Suspension Injection

1: Dexamethasone Acetate 8 mg/mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

2: Dexamethasone Acetate/Sodium Phosphate Suspension 8/2 mg/mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

3: Dexamethasone Sodium Phosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

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4: Dexamethasone Sodium Phosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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, 2, 4, and 3 in Step c with continuous N_2 flushing.
   e. Check pH (range 7.0 to 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 min (–0, +360 min). This or 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.

5: Dexamethasone Injection, Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

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6: Dexamethasone Sodium Phosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min and use this throughout manufacture.
2. Heat 0.2 L of Item 9 to 80°C and dissolve Items 5 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 min.
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 1.0 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 min.
15. Fill under aseptic conditions.

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Dexpanthenol, Niacinamide, Pyridoxine, Riboflavin, and Thiamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 µS conductivity and pH 5.0 to 7.0.
2. Boil 1.5 L of Item 11 for 5 min in a jacketed pressure vessel. Cool to ambient temperature with continuous bubbling of CO_2 gas, and continue purging the head space 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 h.
10. Filter solution through a previously rinsed prefilter assembly and recirculate for at least 30 min 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 to 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 to 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 min (−0, +360 min). Maintain oven

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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	Quantity	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	Quantity	UOM
245.00	mg	1	Dextrose Anhydrous, USP, or	25.00	kg
269.31	mg		Dextrose, USP, Powder Hydrous or	27.47	kg
269.31	mg		Dextrose Monohydrate, BP, for parenteral use	27.47	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 to 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 to 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.

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Dextrose Injection 5% and 10% LVP

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 not more than 24 h at 80°C. Add Item 1 to Item 3 at 60°C and mix for 15 min.
2. Add Item 2 and mix vigorously for 15 min.
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 min; use triple aluminum seals and suitable plastic hangers.
6. Sterilize filled bottle by autoclaving at 121°C for 20 min; do not exceed temperature by 3°C or time by 2 min 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 to 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	Quantity	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 not more than 24 h at 80°C. Add Item 1 to Item 3 at 60°C and mix for 15 min.
2. Add Items 2 and 3 and mix vigorously for 15 min.
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 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 min; use triple aluminum seals and suitable plastic hangers.
6. Sterilize filled bottle by autoclaving at 121°C for 20 min; do not exceed temperature by 3°C or time by 2 min 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 to 4.3); before autoclaving, pH is 5.5 to 6.5.

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Diazepam Emulsion Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min.

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
5.00	mg	1	Diazepam	5.00	g
120.00	mg	2	Egg Lecithin	120.00	g
80.00	mg	3	Sodium Glycholate	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 min in a separate vessel. The micelles formed spontaneously at room temperature.
4. Add Item 7 and dissolve.
5. Filter the solution aseptically into ampoules.

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Diazepam Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min, 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 min.
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.

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Diazepam Rectal Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 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, 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	Quantity	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 min.

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Diclofenac Injection

1: Diclofenac Sodium Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 µS 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 min in a jacketed pressure vessel.
   b. Transfer 500 mL of the boiling Item 7 from Step 2-a to a suitable 316 stainless steel container.
   c. Allow the remaining Item 7 from Step 2-a 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 2-b.
   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 2-e to the solution of Step 2-d. Mix well with stirring while bubbling through filtered N_2 gas.
   g. Check pH (range 8.0 to 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 2-c.
   i. QC sample.
   j. Transfer the solution from Step 2-h 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 min (–0, +360 min). 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.
4. *Filling. Note:* Careful protection with sterile-filtered N_2 gas is essential for stability.
   a. Aseptically connect glass container containing the injection solution, sterile filtration setup, sterile surge bottle, N_2 gas filter, and filling unit.

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b. Filter the injection solution into the surge bottle and adjust flow rate through filter equal filling rate to prevent any surge on the filter.
c. Flush ampoules with sterile-filtered N_2 gas before filling.
d. 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.
e. Sample. Inspect ampoules.
f. Sample.

2: Diclofenac–Lecithin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

3: Diclofenac with Acetylcysteine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 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-µm membrane filter (nylon, polypropylene, or acrylic copolymer).
7. Fill ampoules.
8. Sterilize by autoclaving at 121°C for 15 min.

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4: Diclofenac Lyophilized Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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-μm filter membrane.
3. Transfer the solution to a sterilization vessel and sterilize in autoclave at 120°C for 20 min.
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.

5: Diclofenac Lyophilized Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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-μm membrane filter after transferring it to a sterilization vessel.
3. Autoclave the solution at 120°C for 15 min.
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	Quantity	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

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Digoxin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

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Dihydroergotamine Mesylate Drops

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
2.00	mg	1	Dihydroergotamine Mesylate, 10% excess	2.20	g
153.00	mg	2	Glycerine, 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 below 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 temp for 1 hour. Begin bubbling Item 7 and continue to heat for a further 1 h. Cool slowly to not more than 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 h.
   d. Check oxygen concentration in the Item 6 from Step 1-a. Continue Item 7 bubbling until concentration is below 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 1-d and begin bubbling with Item 7. From here on provide continuous Item 7 blanket.
   g. Add ca. 40 mL of water from Step 1-d to Item 2 in Step 1-b and bubble with Item 7 at a minimum pressure of 1 kg for at least 1 h. 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 1-f. Stir or mix by recirculation for at least 5 min.
   i. Dilute about 0.03 mL of acid Item 4 with Item 6 to make a 20% solution. Assure that oxygen level is less than 1 ppm.
   j. Measure pH and adjust to 3.25 with solution in Step 1-i.
   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 1-g to the batch and adjust the volume to 995 mL with water from Step 1-d. Stir or recirculate for at least 15 min.
   n. Dissolve 4 g of sodium hydroxide in 100 mL water from Step 1-d.
   o. Measure and adjust pH to 3.75 with solution in Step 1-n. Stir for at least 30 sec and recirculate for at least 5 min between each addition. Record final pH and amount used.
   p. Take testing samples.
   q. QS to 1 L with water.
   r. 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-µm pore-size filter previously sterilized by heating in an autoclave for 30 min at 121°C. Discard the first portion of filtrate. Record amount discarded.
   b. Carry out a bubble pressure leak test (21 to 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 min. 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.

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b. Wash stoppers with distilled water only and sterilize by heating at 121°C in an autoclave for 30 min.
c. Sterilize roll-on pilfer-proof caps by heating in an autoclave at 110°C for 1 h.
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	Quantity	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	Quantity	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.

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Diisopropylphenol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
0.028	m*M*	1	2,6-diisopropylphenol	28.00	m*M*
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 min 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	Quantity	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 about 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 mL 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. The Monovial® for continuous intravenous 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.

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Dimenhydrinate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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	Quantity	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.

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Diphenhydramine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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.

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Dipyrone Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 about 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 min.
5. Check pH (6.8 to 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 min.
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	Quantity	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 min.
3. Add Items 1 to 3 and bring volume.
4. Provide and keep Item 8 cover throughout.
5. Measure pH (3.8 to 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 h.
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 min.
10. Sample for final testing, clarity, and particle test.

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Disodium Edetate Injection

150 mg/mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 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	Quantity	UOM
121.30	mg	1	*S*-adenosyl-L-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 1.0 L.

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Dobutamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 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 to 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 over seals.
11. Sterilize product by using an approved autoclave cycle. QC samples.

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Dopamine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min, 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 3, 5, and 2. 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°C to 30°C).
   g. Check the pH (range 3.2 to 3.5). If above 3.5, adjust to pH 3.3 with Item 4. If below pH 3.2, adjust to pH 3.3 (range: 3.2 to 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.

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Doxapram Hydrochloride Injection, USP

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	UOM
2.00	µg	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.

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Doxorubicin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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 about 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 to 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.

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Doxycycline Hyclate Injection

Bill of Materials (Batch Size 50 L)					
Scale/mL		Item	Material	Quantity	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 about 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 below, 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 h. 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 h. 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 min. Drain solution, rinse three 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 min. Dry for not less than 8 h at 100°C; use additional time if necessary.

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

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Doxycycline Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 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	Quantity	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.

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Edetate Sodium, Polyvinyl Alcohol, Sodium Sulfacetamide, Sodium Thiosulfate Ophthalmic Drops

1: With Thimerosal

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Quantity	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 min until Item 2 is completely dissolved.
7. After mixing Item 2 for at least 90 min, 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, 6, 7, and 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 min.
4. Sample for pH (range 7.3 to 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.

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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 min.

Sterile Filtration

1. Sterilize for 1 h (range 45 to 60 min) 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 min before filtration.
4. Connect the sterilized Pall filter and sterile filter with the aid of N_2 pressure (15 to 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 h.

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 in-line gas filter before and after filtration at 18 psi. Sample.

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2: With Benzalkonium Chloride

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Quantity	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 min.
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 min.
4. Add Item 3 and mix thoroughly. Cool Part I to below 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, 6, 7, and 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 min. 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 min.
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.

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Edrophonium Injectable

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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.

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Electrolyte Maintenance Fluid

1: For Rehydration

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 micron 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 min; use triple aluminum seals and suitable plastic hangers.
7. Sterilized filled bottle by autoclaving at 121°C for 20 min; do not exceed temperature by 3°C or time by 2 min either side of the limit. The autoclaving cycle should be fully validated to prevent excess 5-hydroxy methyl furfural test limits of USP.

2: For Maintenance

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	4	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 prewashed and sterilized at 116°C for 30 min; use triple aluminum seals and suitable plastic hangers.
6. Sterilized filled bottle by autoclaving at 121°C for 20 min; do not exceed temperature by 3°C or time by 2 min either side of the limit. The autoclaving cycle should be fully validated to prevent excess 5-hydroxy methyl furfural test limits of USP.

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3: Maintenance, Pediatric

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	4	Water for Injection, USP, QS to	1.00	L

MANUFACTURING DIRECTIONS

1. Dissolve Items 2, 3, 4, and 5 in 0.9 L of Item 4.
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.
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 min; use triple aluminum seals and suitable plastic hangers.
7. Sterilized filled bottle by autoclaving at 121°C for 20 min; do not exceed temperature by 3°C or time by 2 min either side of the limit. The autoclaving cycle should be fully validated to prevent excess 5-hydroxy methyl furfural test limits of USP.

4: Maintenance (45 mEq)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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: Rehydration (75 mEq)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

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6: Rehydration (90 mEq)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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 min.
9. Inspect and finish.
10. Sample for testing.

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Emetine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 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	Quantity	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	Quantity	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

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Ephedrine Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 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 in-line filter, fill specified dose into each clean, dry ampoule, and seal and sterilize in a steam autoclave at 121°C for 15 min. Sample.

Epinephrine Auto Injector Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min, 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	Quantity	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	

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Epoetin Alfa for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
2000	U	1	Epoetin Alfa[a]	2,000,000	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 40,000 U require adjustment of ingredients; adjust pH to 6.9 (range 6.6 to 7.2).

Epoprostenol Sodium for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
0.50	mg	1	Epoprostenol Sodium equivalent to Espoprostenol	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	Quantity	UOM
400.00	IU	1	Ergocalciferol, USP = $8 \times 10^5/40 \times 10^6$ potency of raw material	800,000 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 about 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 about 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.

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Ergonovine Maleate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min. 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 to 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 h and 25 min 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	Quantity	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	

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Erythromycin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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] Quantity 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 h; All steps must be completed within a 12-h 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 below throughout processing.
   b. To this Item 1 slurry, slowly add 86 mL of Item 2 solution, the addition taking about 20 min. Mix for an additional 10 min. 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 to 7.5). If pH is above 7.5, adjust down to pH 7.4 very cautiously with Item 2. Add in small quantities with thorough mixing and check pH after each addition. If pH falls below 7.0, adjust up to 7.4 with small, careful additions of Item 1 base. Stir at least 30 min 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 below 18°C at all times. Mix for 1 h.
   h. Filter through a previously rinsed filter press or equivalent cellulose filters. Remove Item 3 by recirculation through press. Recirculate for at least 15 min 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 min 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°C to 6°C) until filled. Filling of this solution should be completed as soon as possible, but not more than 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 min (–0, +360 min). 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 min and vacuum dry at a temperature below 90°C.

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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 over 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 microns vacuum and set shelf temperature controller at 38°C. Set condenser temperature below −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 h.
   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	Quantity	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 to 5.5); package in nonlatex bags.

Concentrate

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

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Estradiol Cypionate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	UOM
0.50	mg	1	Estradiol, NF	0.50	g
1.00	mg	2	Carbodymethylcellulose 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 1.0 mg/mL strength.

Estradiol Valerate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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

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Estrone, Estradiol, and Cyanocobalamin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
2.00	mg	1	Estrone, NF	2.00	g
2.00	mg	2	Estradiol, NF	2.00	g
1000.00	µg	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	Quantity	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	Quantity	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

Lyophilized powder is reconstituted with 1.0 mL of water for injection containing 0.9% benzyl alcohol.

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Etorphine Hydrochloride Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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 min 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.

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Famotidine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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	Quantity	UOM
78.55	µg	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 to 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 in-line 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.

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Filgrastim Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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		Water for Injection, USP, QS to	1.00	L

Flosulide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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.

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Flumazenil Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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 to 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.

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Follitropin Beta for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

Furosemide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	

Note: $10.0 \times \left(\frac{100}{100 - \text{moisture}}\right) \times \left(\frac{100}{\%\ \text{assay on dry basis}}\right)$ g

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 µS/sec 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 min.
   c. Add and dissolve Items 2 and 3 into the Step 2-a preparation vessel.
   d. Add Item 1 into Step 2-c solution and stir until it is completely dissolved and the solution is clear.
   e. Check pH (range 8.5 to 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 2-b and mix it for 15 min, followed by bubbling Item 7 for 20 min.
   h. Check final pH (range 8.5 to 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 to 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 min.
8. *Ampoules leak test*. Perform the leak test.
9. *Optical checking*. Check the ampoules under the optical checking machine.

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Gentamicin and Prednisolone Ophthalmic Drops

Bill of Materials (Batch Size 42 L)					
Scale/mL		Item	Material	Quantity	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 × 1000 µg/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 × 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 below 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 h at 15°C or below until Item 2 is completely hydrated.

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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 min 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, 8, 9, 10, and 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 min. Avoid excess foam formation. Sample.
6. Mix the product for at least 10 min before filtration. Sterile-filter with the aid of N_2 pressure (15 to 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 min 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 h before mixing.
2. Aseptically receive 38.4 L of sterile-filtered base (combined Parts I, I, 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 h.
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 h. Sample.
7. Aseptically fill sterile solution through P2 sintered glass into sterilized container. Perform the bubble point test. Sample.

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Gentamicin Injection

20 mg/2 mL

Bill of Materials (Batch Size 10 L)					
Scale/mL		Item	Material	Quantity	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	

80 mg/2 mL

Bill of Materials (Batch Size 10 L)					
Scale/mL		Item	Material	Quantity	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: Quantity 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 1.0 pS/cm.
   b. Take the sample for pH (range 5.0 to 7.0)
2. *Preparation of solution.*
   a. Put 3.0 L of water for injection into the first 20-L preparation vessel and bubble N_2 gas to expel dissolved O_2 for 20 min.
   b. Put 9 L of water for injection (hot water, 82°C to 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 2-b with stirring until clear solution is obtained.
   d. Bubble N_2 gas through solution for 20 min and allow to cool to 30°C or below. Record temperature.
   e. Add and dissolve sodium EDTA into solution of Step 2-d. Mix until dissolved.
   f. Add and dissolve gentamicin sulfate into solution of Step 2-f and make a clear solution.
   g. Check and record pH (range 3.5 to 5.0).
   h. Adjust pH by 2 *N* H_2SO_4/2 *N* NaOH solution.
   i. Check pH after adjustment (range 3.5 to 5.0).
   j. Make volume up to 10 L by water for injection from Step 2-a and mix for 15 min.
   k. Take final pH (range 3.5 to 5.0).
   l. Bubble N_2 gas for 20 min.
   m. Request sample for assay.
   n. Transfer the preparation vessel to solution room.

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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 min. Set the parameters according to current validated cycle. Sterilize the gowns at 121°C for 30 min. 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 to 2.2 mL) solution from the bulk into each sterile, dry, clean ampoule and seal it.

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Gentamicin Ophthalmic Drops

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Quantity	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 µg/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 min 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, 5, 6, and 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 min.
5. Sample for pH (range 7.4 to 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 min.
7. Before filtration, mix the product for at least 10 min. Perform the bubble point test. Sample.
8. Aseptically fill sterile solution into sterilized containers. Perform the bubble point test.

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Glycine Antagonist Injection

Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
1.69	mg	1	Glycine Antagonist[a]	1.69	g
0.72	mg	2	Tris (Hydroxymethyl) Aminomethane	0.72	g
7.68	µg	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-→2-(phenylcarbamoyl) ethenyl-4,6-dichloroindole-2-carboxylic acid.

MANUFACTURING DIRECTIONS

1. In sufficient quantity of Item 6, add and dissolve Items 2, 3, 4, and 5.
2. Add and dissolve Item 1.
3. Add Item 5 and dissolve.
4. Make up volume with Item 6.
5. Filter aseptically and sterilize by autoclaving.

Bolus Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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)-3→2-(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 min.

Glycopyrrolate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

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Granisetron Hydrochloride Injection

Single Dose

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

Multiple Dose

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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	Quantity	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.

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Hemin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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.

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Heparin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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, 10,000, 15,000, or 20,000 USP units heparin sodium derived from porcine intestinal mucosa (standardized for use as an anticoagulant), in water for injection, and not more than 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 units heparin sodium derived from porcine intestinal mucosa (standardized for use as an anticoagulant), in normal saline solution, and not more than 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 to 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 h, 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 min (–0, +360 min) 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 min 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 min.

   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.

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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 route only.

Hexamethylmelamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 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 12,000 psi pressure three 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 min.
10. Measure particle size again.

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Hydrochloric Acid

Bill of Materials (Batch Size 3 L)					
Scale/mL		Item	Material	Quantity	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 about 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	Quantity	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		Water for Injection, USP, QS to	1.00	L

Note: Adjust pH to 7.5 to 8.5.

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Hydrocortisone Sodium Succinate for Injection

SINGLE-UNIT SYSTEM

1: Lyophilized

Bill of Materials (Batch Size 20 L)					
Scale/mL		Item	Material	Quantity	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 1-c. Mix the tank contents to homogeneous solution.
2. *Compounding*.
   a. Place about 10 L of Item 6 into a clear compounding tank. Cool to between 15°C and 18°C.
   b. Add Item 1 to Step 2-a. 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 1-a in small portions to the suspension. Monitor pH and temperature so that they do not rise above 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 below.
   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 below for at least 4 h.
   f. Start condenser and let it reach −55°C or below.
   g. Start vacuum and let chamber achieve vacuum level of 100 microns or below.
   h. Set the shelf temperature to +15°C; let it run for at least 12 h.
   i. Raise shelf temperature to +30°C, and run the cycle for an additional 36 h 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.

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2: Non-Lyophilized

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

Solution 1

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	6	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 not more than 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 min.
   g. Check and record pH (range 7.5 to 7.6). If above 7.6, adjust with 10% hydrochloric acid (if below, use 2 *N* sodium hydroxide).

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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 h.
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 min (or an equivalent cycle).
   c. Deliver bottles to the sterile filling area.
3. *Preparation of stoppers.* Use West Cpd #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 min 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 h before increasing shelf temperature.
   d. Cool condenser to −50°C or below.
   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 h (±0.5 h) 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	Quantity	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 min.
   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.

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b. Sterilize ampoules by using dry heat at 200°C glass temperature for 225 min (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	Quantity	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.

Multiple Dose

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

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Hydroxycobalamin Injection

Bill of Materials (Batch Size 308 L)					
Scale/mL		Item	Material	Quantity	UOM
1000.00	µg	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	Quantity	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

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Hydroxypropylmethylcellulose Ophthalmic Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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.

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Hyoscine Butylbromide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 1.0 µS/cm and pH range of 5.0 to 7.0.
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 to 5.2).
   d. Adjust pH if necessary with Item 3 (range 4.0 to 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 to 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 to 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 min.
9. *Optical checking*. Check the ampoules under optical checking machine.

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Ibuprofen Lysinate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 maintained 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 assures 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 min.

Ibutilide Fumarate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

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Imiglucerase for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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	5	Sodium Hydroxide for pH adjustment	QS	
QS	mL	6	Citric Acid for pH adjustment	QS	
QS	mL		Water for Injection, USP, QS to	1.00	L

Note: Fill 10 mL for 212 units and 20 mL for 424 units and lyophilize after adjusting pH.

Immune Globulin (Human) for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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 intravenous (human) is pasteurization at 60°C for 10 h 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**	**Quantity**	**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.

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Insulin Aspart Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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	µg	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**	**Quantity**	**UOM**
3.637[a]	mg	1	Insulin Glargine	3.673	g
30.00	µg	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.

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Insulin Human 70/30

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
1000	U	1	Insulin Human, USP, about 2% excess	1,000,000	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	5	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 to 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 to 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 h. Adjust the pH of the mixture aseptically to the proper pH range (7.35 to 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 assure 97% to 103% value).

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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 to 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 to 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 to 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 semi-automated Biuret method, endotoxins, zinc by atomic absorption, and pH determination.

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Insulin Human Isophane Suspension (NPH)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
100.00	U	1	Insulin Human, USP, about 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 483,091 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 units 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 to 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 to 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 to 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.

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10. Maintain the filled vials at controlled room temperature for at least 24 h 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 h 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	Quantity	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.

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Insulin Regular

Bill of Materials (Batch Size 2500 L to give 241,545 Vials)					
Scale/mL		Item	Material	Quantity	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 about 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.

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Interferon Injection

1: Interferon Alfa-2a

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
3MM	IU	1	Interferon Alfa-2a	3B	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 MM to 36 MM with no change in the quantity of other ingredients.

Prefilled Syringe

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
3MM	IU	1	Interferon Alfa-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 µg/0.5 mL.

2: Interferon Beta-1b

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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).

3: Interferon Beta-1a

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
33.00[a]	µg	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.

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4: Interferon Alfa-n3

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
5 MM	U	1	Interferon Alfa-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 Alfacon-1 Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
0.03	mg	1	Interferon Alfacon-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

6: Interferon Gamma-1b Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
200.00	µg	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] A 0.5-mL fill gives 100 µg or 2 million IU.

Interleukin for Injection (IL-2)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
0.25	mg	1	IL-2	0.25	g
0.70	mg	2	Sodium Laurate	0.70	g
10.00	m*M*	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 6, 2, 3, and 4. Mix well.
2. Check and adjust pH to 7.5 (7.3 to 7.6) with Item 5.
3. Filter and lyophilize.

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Iodine Intravenous Additive

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
118.00	µg	1	Sodium Iodide (equivalent to 100 µg 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	Quantity	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	Quantity	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	Quantity	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.

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Isometheptene Hydrochloride Veterinary Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	UOM
10.00	mg	1	Itraconazole, use Itraconazole solubilized by Hydroxypropyl (Beta) Cyclodextrin	400.00	mg
3.80	µL	2	Hydrochloric Acid	3.00	mL
25.00	µL	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	Quantity	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 min 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.

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Ketorolac Tromethamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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	Quantity	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.

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Lactobionic Acid Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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. pat. no. 4,486,354 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 methanesulfonic 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 precooled to 5°C prior to loading.
9. Freeze the solution to −24°C for 4 to 5 h. 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 h. 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.

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Lazaroid Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 about 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 to 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	Quantity	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.

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Leucovorin Calcium Injection

1: 50 mg/5 mL, 10-mL Vial Lyophilized

Bill of Materials (Batch Size 5 L)					
Scale/mL		Item	Material	Quantity	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 below for at least 4 h before starting the drying cycle.
10. Start condenser and do not start vacuum until 100 µm or below.
11. Start vacuum to the chamber to achieve at least 100 µm or below.
12. Set to low heat and bring up temperature controller to +15°C; hold at this temperature for at least 12 h.
13. Bring up the temperature controller to +28°C; hold at this temperature for at least 24 h.
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.

2: 3 mg/mL, 2-mL Vial

Bill of Materials (Batch Size 5 L)					
Scale/mL		Item	Material	Quantity	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).

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Leuprolide Acetate Injection

1: 5 mg/mL Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 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 QS 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 1-b.
   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 min (–0, +360 min). 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 min 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 min.
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.

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d. Aseptically stopper each vial with a clean sterile, siliconized stopper.
e. Apply overseal.
f. Inspect each vial for defects.
g. Sample for testing.

2: Depot Preparation

3.75 and 7.50 mg for Injecting Every Month

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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.

11.25 and 22.50 mg for Injecting Every 3 Months

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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.

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30 mg for Injecting Every 4 Months

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

3: 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 by 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	Quantity	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	Quantity	UOM
20.00	µg	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 µg label, use 1.75 mg Item 3. Fill 10 mL and lyophilize. Reconstitute with 5 mL of 0.9% sodium chloride injection.

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Lidocaine Hydrochloride and Epinephrine Injection

1:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

2:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

3:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

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Lidocaine Hydrochloride Injection

1% or 1.5% 20 mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 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 in-line filter for the filling line.
2. *Filling*. Use Type I 20-mL or other fill size glass ampoules, USP.
   a. Using the in-line 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.

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Lincomycin Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
300.00	mg	1	Lincomycin, use Lincomycin Hydrochloride Monohydrate for Injectables (at the rate of 790 µg/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 to 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 min (–0, +360 min). 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	Quantity	UOM
10.00	µg	1	Liothyronine Sodium	10.00	mg
68.00	µL	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

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Lipid Emulsion 20% for Parenteral Nutrition

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	UOM
30.00	µg	1	Cyanocobalamin, USP	30.00	mg
0.10	mg	2	Liver Injection (supplies 2 µg of Cyanocobalamin activity), 20 µg/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.

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Liver, Iron, and Vitamin B12 Injection Veterinary

1:

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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	µg	6	Cyanocobalamin, USP	15.00	mg
33.00	µg	7	Ferrous Gluconate, NF	33.00	mg
0.10	mL	8	Liver Injection (20 µg/mL concentrate), supplies 2 µg of B12 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

2:

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**UOM**
50.00	µg	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 µg/mL concentrate), supplies 2 µg of B12	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**	**Quantity**	**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.

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Magnesium Sulfate 50% Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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	

10-mL Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	

30-mL Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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.

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Medroxyprogesterone Acetate Sterile Aqueous Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min.
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.

2:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

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3:

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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**	**Quantity**	**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.

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Melphalan Hydrochloride for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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**	**Quantity**	**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

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Menadione Sodium Bisulfite Injection Veterinary

1: 50 mg/mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	

2: 5 mg/mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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.

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Meperidine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 h and 25 min (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 to 1.3 mL) into each clean, sterile ampoule.
   c. Immediately seal each ampoule.
4. *Sterilization.*
   a. Autoclave at 121°C for 20 min.
   b. Sample for testing.

Meperidine Hydrochloride and Promethazine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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-mL and 10-mL vials.

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Mepivacaine Hydrochloride Injection

Single-Dose Vials

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 a 1% solution; for 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 min. May be reautoclaved.

Multi-Dose Vials

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min. May be reautoclaved.

Meropenem for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

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Mesoridazine Besylate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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	Quantity	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	Quantity	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.

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Methohexital Sodium for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

1:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 mg or 80 mg as Item 1.

2:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

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Metoclopramide Injection

1: Preservative Formula

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	4	Sodium Metabisulfite, USP	1.50	g
20.00	mg	5	Benzyl Alcohol, NF	20.00	g
QS	mL	6	Water for Injection, USP, QS to	1.00	L
QS	mL	7	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 µS/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 2-a 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 2-b.
   d. Check pH (range 3.5 to 5.5).
   e. Adjust pH if necessary with 1 *N* HCl solution or 10% NaOH solution (range 3.5 to 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 to 5.5).
3. *Preparation of prefiltration assembly.* Clean and sterilize filtration assembly by autoclaving at 121.5°C for 30 min 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 min (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 to 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 min.

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2: Preservative-Free Formula

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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	Quantity	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 about 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 min starting from the moment temperature has reached 115°C inside the bag.
6. Individually seal bag into further PVC bag. Sample for complete testing.

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Metronidazole Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 μS/sec 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 to 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 to 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.

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Metronidazole and Dextrose Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 not more than 24 h at 80°C. Add Items 1 and 2 to Item 3 at 60°C and mix for 15 min.
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 min; use triple aluminum seals and suitable plastic hangers.
4. Sterilize filled bottle by autoclaving at 121°C for 20 min; do not exceed temperature by 3°C or time by 2 min 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 to 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	Quantity	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 5.0-mg strength.

Milrinone Lactate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

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Mineral Complex Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 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.

Mitoxantrone for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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.

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Morphine Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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°C to 75°C). Pass bubble-filtered sterile N_2 gas for 10 min. Cool the water to 25°C (range 22°C to 30°C).
   b. Add and dissolve morphine with mixing. Check and record pH (2.7 to 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 a 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 h and 45 min to 3 h and 30 min 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	Quantity	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 a 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.

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Multiple Electrolytes and Dextrose Injection (Elliott's B Solution)

Bill of Materials (Batch Size 10.5 L)					
Scale/mL		Item	Material	Quantity	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	µg	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 about 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 h; rinse at least three times with purified water.

Muromonab-CD3 Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

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Nalbuphine Hydrochloride

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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.

0.04 mg/mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

0.02 mg/mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

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Nandrolone Decanoate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 about 0.8 L of Item 3 to about 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 min) and 1888 gray stopper without coating and appropriate aluminum seal.

Nandrolone Phenylpropionate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 h; 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.

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Naphazoline Ophthalmic Drops

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	µL	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 tank or stainless steel tank (#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 min 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°C to 30°C); discontinue agitation and QS to 950 mL with deionized water. Start agitator and mix for at least 15 min 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 min, 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.

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Natamycin Ophthalmic Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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	Quantity	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.

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Neomycin and Prednisolone Acetate Ophthalmic Suspension

Bill of Materials (Batch Size 45 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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
3.85[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, ca.; 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 as per the following formula: 259.9 g neomycin base × 1000 µg/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 as per the following formula: 776,250,000 units Polymyxin B sulfate/manufacturer's assay value (units/mg × 1000 mg/g = _____ g of Polymyxin B sulfate required. (Assuming assay = 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 as per the following formula: 0.675 g × 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 1 into a 2-L grinding jar filled to about 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.

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3. Sterilize the jar by autoclaving for at least 2 h and 30 min 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 the two rubber bands.
5. Sterilize Item 4 by autoclaving for 30 min 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 min 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 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 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 with a propeller mixer.
3. Add Item 6 slowly to the vortex. Avoid formation of excessive foam. Mix for at least 90 min until it is completely dissolved (mixing time not less than 90 min).
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 suitably calibrated for a final QS of 60 L; 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; 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 min.
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 h (range 45 to 60 min) 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 min before filtration.
3. Connect the sterilized filter and sterile filter with the aid of N_2 pressure (15 to 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-µm 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 h.

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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; secure the aluminum foil and parchment paper with two rubber bands.
2. Sterilize Item 17 by autoclaving for at least 60 min 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 h 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 IV. 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, II, III, IV, and V.
8. Allow the product to mix with a 0.5-in.-deep vortex for at least 2 h. 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 in-line 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	Quantity	UOM
40.00	mg	1	Neomycin Base	40.00	g
200,000	U	2	Polymixin 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.

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Neostigmine Methylsulfate Injection

Single-Dose Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

Multi-Dose Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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.

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Netilmicin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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	Quantity	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	

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Nicardipine Hydrochloride for Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	UOM
1.00	mg	1	Nicardipine Hydrochloride	1.00	g
48.90	mg	2	Sorbital	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	Quantity	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 to 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 h) Type I flint ampoules.
5. Autoclave at 121°C for 30 min.
6. Sample for clarity and sterility.

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Nimesulide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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	Quantity	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.

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Octreotide Acetate Injection

Single-Dose Ampoule

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
50.00	µg	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.

Multi-Dose Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
50.00	µg	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.

Depot

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
10.00	mg	1	Octreotide Base as Octreotide Acetate[a]	11.20	mg
188.80	mg	2	D, L-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.

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Ofloxacin Otic Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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.

Multi-Dose Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	5	Water for Injection, USP, QS to	1.00	L

Note: Fill 20 mL into each vial. pH 3.3 to 4.0.

Premixed for Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

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Oprelvekin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 units/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	Quantity	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	Quantity	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 about 0.9 L of Item 4. Bubble with Item 3 for 20 min.
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 min.

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Oxazepine Injection

Bill of Materials (Batch Size 3 L)					
Scale/mL		Item	Material	Quantity	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).

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Oxendolone Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min (–0, +360 min) 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 h at 121°C and vacuum dry with heat for a minimum of 4 h 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.

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Oxymorphone Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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 min.
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-min period; assure 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 min.
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.

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Oxytocin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 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 min slow exhaust.
   b. Sterilize all Pyrex bottle fittings in an autoclave at 121°C for 30 to 35 min.
   c. Sterilize a sufficient number of Pyrex bottles with dry heat (oven) at 245°C to 330°C for 2 h and 445 min to 3 h and 30 min.
   d. Aseptically filter through a 0.2-µm membrane assembly with an approved filter in a N_2 atmosphere.
3. *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 h and 45 min to 3 h and 30 min. May use equivalent cycle to assure sterility, pyrogen-free ampoules. Deliver to sterile filling area.
4. *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 head space 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	Quantity	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

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Paclitaxel Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 mL, 16.7 mL, or 50 mL into each vial.

Palivizumab for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
100.00	mg	1	Palivizumab	100.00	g
47.00	m*M*	2	Histidine	47.00	m*M*
3.00	m*M*	3	Glycine	3.00	m*M*
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.

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Pancuronium Bromide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
1.20	mg	1	Sodium Acetate Anhydrous, USP	1.20	g
3.20	µl	2	Glacial Acetic Acid, USP, for pH adjustment	3.20	mL
QS	µl	3	Glacial Acetic Acid, USP, for tonicity adjustment	QS	
QS	mL	5	Sodium Hydroxide for pH adjustment	QS	
10.00	mg	6	Benzyl Alcohol, NF	10.00	g
2.00	mg	7	Pancuronium Bromide	10.00	g
QS	mg	8	Sodium Chloride, USP, for tonicity adjustment	QS	
QS	mL	9	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 to 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 to 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.

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Parenteral Nutrition Fat Emulsion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 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	Quantity	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

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Pegademase Bovine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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 Alfa-2b for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Quantity	UOM
74.00	μg	1	Peginterferon Alfa-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.

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Penicillin G Benzathine and Penicillin G Procaine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
150,000	U	1	Penicillin G as the Benzathine Salt	150MM	U
150,000	U	2	Penicillin G as the Procaine Salt	150MM	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	Quantity	UOM
600,000	U	1	Penicillin G as the Benzathine Salt	600MM	U
3.00	mg	2	Polyvinylpyrrolidone	3.00	g
6.00	mg	4	Sodium Citrate	6.00	g
0.01	mg	5	Lecithin	0.01	g
3.00	mg	6	Carboxymethylcellulose	3.00	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

Pentobarbital Sodium Solution Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 g and 2.5 g/vial in multi-dose vials. Do not use if any precipitate appears.

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Pentostatin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

Pentylenetetrazole Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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 h).
5. Autoclave filled ampoules at 116°C for 30 min.
6. Sample for assay, sterility, and clarity testing.

Phenol Saline Diluent

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

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Phenylbutazone and Dipyrone Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 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 h.
10. Autoclave at 121°C for 30 min.
11. Sample for testing assay, clarity, and sterility.

Phenylbutazone Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	

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Phenylephrine and Zinc Sulfate Ophthalmic Drops

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Quantity	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 min 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, 5, 6, 7, 8, and 9, in order, allowing each to dissolve completely before adding the next. Mix well.
3. Sample for pH (range 6.8 to 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 min.
5. Before filtration, mix the product for at least 10 min.
6. Sterile-filter with the aid of N_2 pressure (15 to 30 lb). Before sterile filtration, perform bubble point test at NLT 40 psi. Sample.
7. Aseptically fill sterile solution into sterilized containers. Sample.

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Phenylpropanolamine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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/mL		Item	Material	Quantity	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.

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Phytonadione (Vitamin K1) Injection

1:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 about 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 about 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 a 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.

2:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	5	Sodium Hydroxide for pH adjustment	QS	
70.00	mg	5	Polysorbate 80, NF	70.00	g
QS	mL	4	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 to 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.

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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 h and 25 min 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 0.65 mL (range 0.6 to 0.7 mL) into each clean, sterile ampoule.
   c. Immediately seal each ampoule.
   d. Sample for testing.
4. *Finishing*. Sample for testing.

3: Phytonadione Injection—Aqueous Colloidal Solution of Vitamin K_1

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 5.0 to 7.0; lower strength of 2.0 mg/mL.

Piperacillin Sodium and Tazobactam Sodium Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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/mL		Item	Material	Quantity	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.

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Polyvinyl Alcohol Ophthalmic Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min. Raise the temperature to 82°C to 85°C and hold at this temperature for 30 to 45 min. (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, 4, 5, 6, 7, 8, 9, and 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 (about 0.2 mL/min; if added too rapidly, Povidone may precipitate out). Continue mixing with rinsing tank for another 30 min.
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 to 7.5); adjust pH with 1% of Item 12 solution by slow addition.
9. While mixing, add Item 13 very slowly and mix for at least 30 min.
10. Make up volume to 1 L.
11. Check and record pH (7.3 to 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.

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Potassium Estrone Sulfate Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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/mL		**Item**	**Material**	**Quantity**	**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

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Potassium Phosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	4	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°C to 75°C). Add and dissolve potassium phosphate monobasic with mixing, add and dissolve potassium phosphate dibasic with mixing, and cool to 25°C (20°C to 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 min (–0, +360 min). 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 min 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 min.
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 to 15.8 mL) of solution into each clean, dry, sterile bottle. Stopper aseptically, apply seal, and inspect. Sample.

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Prednisolone and Neomycin Ophthalmic Suspension

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Quantity	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 × 1000 µg/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: 776,250,000 units Polymyxin B sulfate/manufacturer's assay value (units/mg × 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 × 100.0%/assay value (%) = g thimerosal required.

MANUFACTURING DIRECTIONS

PART I

1. Add Item 1 into a 2-L grinding jar filled about 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 h and 30 min 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.

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5. Sterilize Item 4 by autoclaving for 30 min 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 min 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 min until it is completely dissolved. (Mixing time is not less than 90 min.)
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 min. Sample.
6. Mix the product for at least 10 min before filtration.
7. Connect the sterilized filter and sterile filter with the aid of N_2 pressure (15 to 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 in-line 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 min 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 h 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 h. Continue mixing at this setting.

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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 h. 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 in-line gas filter before and after filtration at 18 psi.

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Prednisolone Injection

1: Acetate/Phosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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		

2: Acetate Suspension Injection 50 mg/mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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		

3: Acetate Suspension Injection 10 mg/mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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		

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4: Acetate Suspension with Niacinamide Injection 20 mg/mL

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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		

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Prednisolone Ophthalmic Drops

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Quantity	UOM
			Part I		
			Borosilicate Beads		
1.32	mg	1	Prednisolone Acetate, USP, 10% overage	59.40	g
		2	Water Purified (Distilled), USP	221.70	mL
		3	Hydroxypropylmethyl Cellulose Micronizing Diluent[a]	250.00	mL
0.000063	mL	4	Polysorbate 80, NF (use a 10% solution)	28.30	mL
			Part II		
		5	Water Purified (Distilled), USP	10.00	L
1.20[a]		6	Hydroxypropylmethyl Cellulose F-4M	74.40	g
			Part III		
		7	Water Purified (Distilled), USP	40.00	L
10.00		8	Boric Acid, NF	635.30	g
3.00		9	Sodium Citrate Dihydrate, USP	190.60	g
0.548		10	Sodium Metabisulfite	34.80	g
2.61[a]		11	Sodium Chloride, USP	162.60	g
0.127		12	Disodium Edetate, USP	8.07	g
0.04		13	Benzalkonium Chloride, NF (use a 10% solution)	25.40[b]	mL
		14	5 *N* Hydrochloric Acid, NF[c]	QS	mL
		15	1 *N* Sodium Hydroxide[c]	QS	mL
		16	Water Purified (Distilled), USP, QS add Part II and Part III	60.00	L
		17	Sterile Filtrate, QS Parts II and III	42.50	L
			Part IV		
		18	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 1 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 h at 121°C.
4. Remove the grinding jar from the autoclave and allow it to cool to room temperature.
5. Measure out and add the Items 2, 3, and 4 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 min 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 min at 121°C.
8. In the laminar flow hood, wearing sterile mask, gloves, and gown, aseptically transfer the sterilized solution of Items 2, 3, and 4 into the grinding jar containing the sterilized Item 1 and glass beads.

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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 5 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 5 into a 6 L container. Begin mixing with a propeller mixer.
3. Add Item 6 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 5. 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 5 to the bottle to bring the volume to 10 L.
5. Fill the water sink with cold industrial water. Cool the dispersion to below 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 h at 15°C or below until Item 6 is completely hydrated.

Part III

1. Measure out ca. 40 L of Item 7 into a mixing tank, and begin mixing. Add Items 8, 9, 10, 11, 12, and 13, 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 16. Add the rinsings to the mixing tank. Sample for pH (range 5.6 to 5.8). If necessary, adjust the pH with Item 14 or 15.
3. Allow any foam to dissipate and QS the combined solution of Parts II and III to 60 L with Item 16. Mix combined Parts II and III thoroughly for at least 15 min. 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.

Sterile Filtration

Sterilize for 1 h (range 45 to 60 min) 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.

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 min 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 h 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 h.

Homogenization

Homogenize the suspension in a sterilized homogenizer. Filter and aseptically fill sterile solution through P2 sintered glass into sterilized containers.

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Procaine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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	Quantity	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 1.0 L of Item 5 into a suitable container and heat to 150°C and maintain for 1 h; cool to 60°C to 70°C.
2. Dissolve Item 1 in about 0.6 L of oil from Step 1.
3. Dissolve Item 2 in about 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.

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Progesterone Injection Repository Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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 min.
   c. Add and dissolve sodium chloride, ascorbic acid, sodium metabisulfite, and promazine with mixing.
   d. Check and record pH (range 4.5 to 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 h and 25 min 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 to 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 min.
   b. Sample for testing.

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Promethazine Hydrochloride Injection

Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

Cartridge Unit

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

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Propofol Emulsion Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 1.0-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	Quantity	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	

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Pyridoxine Hydrochloride Injection

100 mg/mL 30-mL vial

Bill of Materials (Batch Size 30 L)					
Scale/mL		Item	Material	Quantity	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 min.
10. Sample for full testing.

100 mg/mL 1-mL Ampoule

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 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 h and 25 min 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 to 1.3 mL) into each clean, sterile ampoule.
   c. Immediately seal each ampoule.
4. *Sterilization*.
   a. Autoclave at 121°C for 20 min.
   b. Sample for testing.

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Pyrilamine Maleate and Ephedrine Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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 min.
   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 h and 25 min (or equivalent cycle that assures 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 to 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 h) of drying. Under vacuum, the temperature is elevated to 20°C and kept for 24 h, and further elevated to 40°C and kept for 6 h to give a freeze-dried preparation.

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Quinolone–Calcium Lactate Complex for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 intravenous 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 to 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.

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Ranitidine Injection

Ampoule

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 above 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 to 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.

50-mL Flexible Plastic Container

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

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Reteplase Recombinant for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Quantity	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	Quantity	UOM
5000	IU	1	Vitamin A (Retinol in Polysorbate 20)[a]	1,000,000	IU
500.00	mg	2	Glycerin, USP	1,000.00	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] =1,000,000 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 about 40°C but do not exceed 60°C. Keep a 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 about 500 mL Item 4 to the tank; stir to a complete solution.
5. Check pH (6.0 to 7.0); adjust if necessary with 10% Item 5. (Item 5 also contains .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 a N_2 postfill flush. Use Type I amber vials and 1109 red with Y-40 coating stoppers.

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Rh_o (D) Immune Globulin (Human) Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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 min. 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 min; use triple aluminum seals and suitable plastic hangers.
9. Sterilize filled bottle by autoclaving at 121°C for 20 min.

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Rituximab Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min.
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 to 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	Quantity	UOM
2000	TCID[a]	1	Rubella Virus Vaccine Live Wistar RA 27/3 Strain	2,000,000	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	µg	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.

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Salbutamol Aerosol for Inhalation

Bill of Materials (Batch Size 1000 Units)					
Scale/mL		Item	Material	Quantity	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 1-a and mix for about 15 min.
   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 1-b 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 min. Sample (to determine nonvolatile matter, range 0.49 to 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 nonmetering 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 2-b. 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 units. Sample.

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Sisomicin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 about 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.

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Sodium Bicarbonate and Disodium Edetate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min and until solution is uniform.
   e. Cool solution to 23°C (range 18°C to 23°C).
   f. Filter solution through a previously rinsed filter press and recirculate for at least 30 min 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 to 7.9). If pH is above 7.9, add more CO_2 gas until pH falls within the range. If pH is below 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 h. If held longer, store in refrigerator. *Note:* Must allow to warm to room temperature before filling (range 18°C to 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 min (–0, +360 min). 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 min 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 min.
   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.

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Sodium Bicarbonate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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°C to 38°C) and bubble CO_2 gas into the water for injection for 30 min.
   c. Add and dissolve the sodium bicarbonate with mixing.
   d. Cool solution to 25°C (range 20°C to 30°C).
   e. QS with water for injection to final volume and mix for not less than 15 min and until solution is uniform.
   f. Check and record pH (range 7.7 to 7.9). If pH is above 7.9, add more CO_2 gas until pH falls within the range. If pH is below 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 min (–0, +360 min). 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 min 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 min.
   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.

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Sodium Chloride Bacteriostatic Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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 not more than 24 h at 80°C. Add Item 1 to Item 3 at 60°C and mix for 15 min.
2. Add Item 2 and mix vigorously for 15 min.
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 min; use triple aluminum seals and suitable plastic hangers.
6. Sterilized filled bottle by autoclaving at 121°C for 20 min; do not exceed temperature by 3°C or time by 2 min either side of the limit.
7. Check pH of solution (range 4.0 to 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	Quantity	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.

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Sodium Hyaluronate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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 not more than 1.4 µS/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 mL or 1065 mL into 500-mL or 1-L blow-fill seal containers.
6. Sterilize the product by using recirculated hot water and air overpressure. Perform complete sterilization within 12 h of addition of first ingredient.

Sodium Thiosulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

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Somatropin (rDNA Origin) Injection

4 mg or 8 mg (ca. 12 or 24 IU) Vials

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Quantity	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 8.00-mg vial. Diluent is water for injection containing 1.5% benzyl alcohol.

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	Quantity	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.

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Sterile Water for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 h 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 1 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 to18. 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	Quantity	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.

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Succinylcholine Chloride Injection

1: Lyophilized

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 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 min (–0, +360 min). 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 min 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 min.
   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 h).
   f. Freeze at −50°C for 4.5 h and lyophilize for 60 h to less than 10% moisture. (Do not allow temperature to go above 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.

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2: Ampoule

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 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.

3: Veterinary Nonsterile

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	

Sumatriptan Succinate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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.

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Testosterone Injection

1: Testosterone Suspension Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

2: Testosterone Cypionate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

3: Testosterone Enanthate–Estradiol Valerate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

4: Testosterone Enanthate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

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5: Repository Veterinary Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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

6: Testosterone Propionate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

7: Testosterone Propionate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	3	Sesame Oil, USP, QS to	1.00	L

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Tetrahydrozoline Ophthalmic Drops

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	µl	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 (#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 min 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 min. 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.

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Theophylline and Dextrose Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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 intravenous 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 min.
10. Sample for final testing.

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Thiamine Hydrochloride Injection

1: Unbuffered

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min; use gray stoppers.

In the next four formulations, a 5% to 10% stability excess can be added.

2: With Citric Acid and Gelatin

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	

3: Buffered

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
25.00	mg	1	Thiamine HCl, USP	25.00	g
52.50	µg	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	

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4: With Sodium Formaldehyde Sulfoxylate

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	

5: Buffered and Gelatin

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
25.00	mg	1	Thiamine HCl	25.00	g
52.50	µg	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	Quantity	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 below 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, Type II, or Type 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 min (–0, +360 min). 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.

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Thiotepa for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Quantity	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	Quantity	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 Alfa for injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
1.10	mg	1	Thyrotropin Alfa	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	Quantity	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.

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Tinzaparin Sodium Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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 mL 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	Quantity	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.

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Tobramycin Sulfate Injection

1:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 3.0 µS/cm and pH range of 5.0 to 7.0.
   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 min. Alternatively, heat the water to not less than 70°C, and then cool to 25°C (range 20°C to 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 2-e. 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 min.
   d. Check and record pH. Adjust, if necessary, to pH 5.5 (range 5.5 to 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 2-b.
   f. Recheck and record pH. If necessary, readjust to pH 5.5 (range 5.3 to 6.0) as in Step 2-d.
   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.

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2:

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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**	**Quantity**	**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.

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Trace Element Concentrate Injection

1-mL or 10-mL Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	µg	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.

3-mL or 10-mL Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	µg	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	Quantity	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 about 0.9 L of Item 2 into a stainless steel vessel, boil it for 10 min, and cool to room temperature.
2. Add Item 1, stir to dissolve, and make up the volume.
3. Check pH (7.2 to 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 min.
8. Sample for leak test, optical check, and complete specification testing.

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Trastuzumab for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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		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	Quantity	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	

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Triflupromazine Hydrochloride Injection

1:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
10.00	mg	1	Triflupromazine 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 1.0 L of freshly boiled Item 6 and purge with Item 5 for 20 min.
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 h) with pre- and postflush of Item 5.
7. Autoclave filled ampoules at 121°C for 30 min.
8. Sample for testing.

2:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 min.
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 h) with pre- and postflush of Item 5.
8. Autoclave filled ampoules at 121°C for 30 min.
9. Sample for testing.

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3:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
1.00	mg	1	Trifluperazine as Trifluperazine 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		Water for Injection, USP, QS to	1.00	L

Note: Fill 10-mL multi-dose vial.

Tripelennamine Hydrochloride Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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 to 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.

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Typhoid Vi Polysaccharide Vaccine

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	UOM
25.00	µg	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, $UTPNa_3$dihydrate is kept frozen at –20°C. The UTP powder is allowed to warm to handling temperature for at least 1 h 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	Quantity	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 110,000 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 to 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 (not more than 5 days after the preparation).
8. Target fill to be with 17% excess, 292,500 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.

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Valproate Sodium Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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	Quantity	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.

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Vancomycin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 to 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 1-C.
   f. Filter solution through a previously rinsed filter press and recirculate for about 30 min.
   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-µm 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 h. Start vacuum and raise temperature to −20°C and keep at this temperature for 3 h. Raise temperature to −15°C and keep at this temperature for 24 h. Raise temperature to 15°C and keep at this temperature for 6 h. Raise temperature to 35°C and hold for 6 h.
   b. Stopper vials after lyophilization.
4. *Oversealing and inspection.*
   a. Apply aluminum overseals.
   b. Inspect each vial for defects.
   c. Sample for testing.

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Varicella Virus Vaccine Live

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**UOM**
1350	PFU[a]	1	Varicella Virus	2,700,000	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**	**Quantity**	**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 to 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.

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Vecuronium Bromide for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 mL 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	Quantity	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 to 5.0); adjust with Item 3, if necessary (approximate volume to be used, 0 to 6 mL).
4. Prepare pressurized vessel with N_2 for sterile filling. Sterilize filling unit, jars, etc. at 121°C for 1 h; sterilize type I glass ampoule at 210°C to 220°C for 2 h.
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 in-line sintered glass; flush head space with N_2.
7. Sterilize in autoclave at 121°C for 20 min.
8. Sample for leak test. Perform other testing.

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Vinblastine Sulfate for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 about 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 to 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 below for at least 4 h before starting the drying cycle.
12. Start condenser and let it cool to –50°C or below before pulling the vacuum.
13. Let the chamber achieve a level of 150 microns or below.
14. Set the temperature controller to +15°C and let it run for at least 18 h.
15. Raise the shelf temperature to +25°C and run for about 10 h till all the probes register +25°C (± 2°C) and hold for an additional 8 h.
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.

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Vincristine Sulfate Injection

1:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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 about 800 mL Item 5 into a suitable mixing tank. Heat the water to about 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 below 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 to 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.

2:

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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.

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Water for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Quantity	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/sec 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 min. 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 min.
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	Quantity	UOM
15.00	mg	1	Benzyl Alcohol, NF	15.00	g
QS	mL	2	Water for Injection, USP, QS to	1.00	L

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Zinc Sulfate Additive Injection

5-mL Vial

Scale/mL		Item	Material	Quantity	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	

10-mL Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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	

30-mL Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		**Item**	**Material**	**Quantity**	**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 about 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 to 4.0); adjust with 10% sulfuric acid (pH 4.0 to 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 1000 Vials)					
Scale/mL		**Item**	**Material**	**Quantity**	**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.

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