VOLUME FOUR

HANDBOOK OF PHARMACEUTICAL MANUFACTURING FORMULATIONS

THIRD EDITION

SEMISOLID PRODUCTS

Sarfaraz K. Niazi

CRC Press
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Handbook of Pharmaceutical Manufacturing Formulations

Volume Four, Semisolid Products

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To the memory of Dr. Norman L. Farnsworth

Dr. Norman L. Farnsworth passed away in 2011; a leader in research, a fine and kind human, and my teacher and colleague, who taught me the value of persistence—he created remarkable changes in the science of pharmacognosy.

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Contents

PART II Manufacturing Formulations

PART III Commercial Pharmaceutical Formulations

Preface to the Series—Third Edition

I am humbled by the wide praise and acceptance of the last two editions of the *Handbook of Pharmaceutical Formulations*, a six-volume series that found home in the R&D laboratories of just about every pharmaceutical company, both generic and branded, and in the classrooms of pharmaceutical technology; and the regulatory agencies used this treatise to compare the quality of pharmaceutical products. In creating this work, back in 2004, my primary objective was to provide a ready source of safe and scalable generic and new pharmaceutical formulations that take a long time to develop and incur a substantial cost, to enable the availability of affordable medicines.

Each of the six volumes in the series has a structured content. Part I includes regulatory guidance, formulation steps, references to active ingredients and excipients, and a self-audit guidance for cGMP compliance. Chapters of common interest to all volumes are distributed across the six volumes, such as the formulations for coating solutions are presented in Volume 5 (OTC), though they are also pertinent to Volume 1 (Compressed Dosage Forms), and global bioequivalence testing guidelines are provided in Volume 4 (Semisolids), though they apply to all volumes. Part II includes scalable formulations and Part III, where applicable, other general formulations. The appendices include a listing of excipients used in FDA approved products and a cGMP compliance self-testing tool. Whereas the main focus of the guidance provided in the handbook pertains to compliance with FDA requirements, these apply equally to EU requirements, and, as a result, to any global agency.

The third edition also gets several significant additions; now each volume includes a self-audit template, several chapters advising how to stay cGMP compliant, including a listing of most common FDA citations to look out for in the audits, a global regulatory focus and an updated list of excipients and the level of their incorporation in the FDA-approved products. The number of formulations is also increased, and the OTC volume now contains several cosmetic formulations, and the semisolid product volume also includes details on chewing gum delivery systems.

The updating of formulations is always cumulative as there is little need to remove any formulation provided previously—if it was right then, it shall remain good now. However, a variety of new drug delivery systems have evolved since the second edition was published, so I have included more details on these formulations, although some of these may not be available to practice due to possible limitations on the intellectual property.

As always, I advise the formulators to be aware of any intellectual property infringements as I cannot provide a guarantee to this effect.

Finally, I wish to acknowledge the leaders of the pharmaceutical world, to whom each of the volumes is dedicated. I have made a few changes to those whom the volumes are dedicated, to recognize those who have since passed away; they provided a role model to me and thousands of leaders and students of pharmacy over the decades of their careers. They are gone, but not without leaving an indelible mark on the profession.

I also consider myself fortunate to have the sponsorship and assistance of the great folks at the CRC Press, more particularly Jessica Poile and Hilary LaFoe. The teams at the CRC Press were very kind to put up with my redundant changes to the manuscript and were extremely generous in their advice in balancing the scientific and practical knowledge and, above all, making sure that the book was framed and published in the highest professional presentation. As always, I take responsibility for any mistakes and errors in my writing, and I am always open to suggestions by the readers to make future editions. I can be contacted at niazi@niazi.com.

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Preface to the Series—Second Edition

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

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

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

the modification will not affect the safety and efficacy of the products can be made but require prior approval of the regulatory agencies and generally these approvals are granted.

11. Expanded discussion on critical factors in the manufacturing of formulations provided; from basic shortcuts to smart modifications now extend to all dosage forms. Pharmaceutical compounding is one of the oldest professions and whereas the art of formulations has been relegated to more objective parameters, the art nevertheless remains. An experienced formulator, like an artist, would know what goes with what and why; he avoids the pitfalls and stays with conservative choices. These sections of the book present advice that is time tested, although it may appear random at times; this is intended for experienced formulators.
12. Expanded details on critical steps in the manufacturing processes provided but to keep the size of the book manageable, and these are included for prototype formulations. The reader is advised to browse through similar formulations to gain more insight. Where multiple formulations are provided for the same drug, it intended to show the variety of possibilities in formulating a drug and whereas it pertains to a single drug, the basic formulation practices can be extended to many drugs of same class or even of diversified classes. Readers have often requested that more details be provided in the Manufacturing Direction sections. Whereas sufficient details are provided, this is restricted to prototype formulations to keep the size of the book manageable and to reduce redundancy.
13. Addition of a listing of approved excipients and the level allowed by regulatory authorities. This new section allows formulators a clear choice on which excipients to choose; the excipients are reported in each volume pertaining to the formulation type covered. The listing is drawn from the FDA-approved entities. For the developers of an ANDA, it is critical that the level of excipients be kept within the range generally approved to avoid large expense in justifying any unapproved level. The only category for which the listing is not provided separately is the OTC volume since it contains many dosage forms and the reader is referred to dosage form-specific title of the series. The choice of excipients forms keeps increasing with many new choices that can provide many special release characteristics to the dosage forms. Choosing correct excipients is thus a tedious exercise and requires sophisticated multivariate statistical analysis. Whereas the formulator may choose any number of novel or classical components, it is important to know the levels of excipients that are generally allowed in various formulations to reduce the cost of redundant exercises; I have therefore included, as an appendix to each volume, a list of all excipients that are currently approved by the U.S. FDA along their appropriate levels. I suggest that a formula- tor consult this table before deciding on which level of excipient to use; it does not mean that the excipient cannot be used outside this range but it obviates the need for a validation and lengthy justification studies in the submission of NDAs.
14. Expanded section on bioequivalence submission was required to highlight the recent changes in these requirements. New entries include a comprehensive listing of bioequivalence protocols in abbreviated form as approved by the U.S. FDA; these descriptions are provided in each volume where pertinent. To receive approval for an ANDA, an applicant must generally demonstrate, among other things, equivalence of the active ingredient, dosage form, strength, route of administration and conditions of use as the listed drug, and that the proposed drug product is bioequivalent to the reference listed drug [21 USC 355(j)(2)(A); 21 CFR 314.94(a)]. Bioequivalent drug products show no significant difference in the rate and extent of absorption of the therapeutic ingredient [21 U.S.C. 355(j)(8); 21 CFR 320.1(e)]. BE studies are undertaken in support of ANDA submissions with the goal of demonstrating BE between a proposed generic drug product and its reference listed drug. The regulations governing BE are provided at 21 CFR in part 320. The U.S. FDA has recently begun to promulgate individual bioequivalence requirements. To streamline the process for making guidance available to the public on how to design product-specific BE studies, the U.S. FDA will be issuing product-specific BE recommendations (www.fda.gov/cder/ogd/index.htm). To make this vital information available, an appendix to each volume includes a summary of all currently approved products by the U.S. FDA where a recommendation on conducting bioequivalence studies is made available by the U.S. FDA. When filing an NDA or an ANDA, the filer is faced with the choice of defending the methods used to justify the bioavailability or bioequivalence data. The U.S. FDA now allows application for waiver of bioequivalence requirement; a new chapter on this topic has been added along with details of the dissolution tests, where applicable, approved for various dosage forms.
15. Dissolution testing requirements are included for all dosage forms where this testing is required by the FDA. Surrogate testing to prove efficacy and compliance is getting more acceptance at regulatory agencies; in my experience, a well-designed dissolution test is the best measure of continuous compliance. Coupled with chapters on waivers of bioequivalence testing, this information on dissolution testing should be great value to all manufacturers; it is recommended that manufacturers develop their own in-house specifications, more stringent than those allowed in these listings and the USP.

16. Best-selling products (top 200 prescription products) are identified with an asterisk and a brand name where applicable; in all instances, composition of these products is provided and formulation of generic equivalents. Despite the vast expansion of pharmaceutical sales and shifting of categories of blockbuster drugs, basic drugs affecting gastrointestinal tract, vascular system, and brain remain most widely prescribed.
17. Updated list of approved coloring agents in the United States, Canada, European Union, and Japan is included to allow manufactures to design products for worldwide distribution.
18. Tablet-coating formulations that meet worldwide requirements of color selection are included in the Volume 1 (compressed solids) and Volume 5 (OTC) because these represent the products often coated.
19. Guidelines on preparing regulatory filings are now dispersed throughout the series depending on where these guidelines are more crucial. However, the reader would, as before, need access to all volumes to benefit from the advice and guidelines provided.

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

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

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

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Preface to the Series—First Edition

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

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

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

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

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

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

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

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Preface to the Volume—First Edition

The semisolid drugs category is composed of ointments, creams, gels, suppositories, and special topical dosage forms. They share many common attributes of consistency, presentation, preservation requirement, and the route of administration, mainly topical. As a result, grouping them together for the purpose of defining common formulation practices and problems is justified. The topical dosage forms present unique opportunities to design novel drug delivery systems such as patches and other transdermal systems. Some of these are described in the volume, but the reader is referred to specific patents issued, wherein greater details are readily obtainable. In selecting the formulations, I have tried to provide representative techniques and technologies involved in the preparation of semisolid products; for example, I have included a significant number of what is called "base" formulation, a formulation that can easily carry a drug, depending on the proportion involved. Obviously, considerations such as incompatability of the drug with the ingredients is of pivotal importance; these base formulations of stable emulsions provide a good starting point in the development of new products or even when a different topical consistency is desired. I have also made an effort to highlight those formulations that are currently approved in the United States and provide them as they appear in the Physicans Desk Reference, where possible. Obviously, where the formulations are straightforward, I have chosen to only give the composition or mere identification of ingredients to conserve space for those formulations that need more elaborate description.

The regulatory agencies impose certain specific requirements on the formulation and efficacy determination of drugs contained in these formulations. For example, the cGMP factors, scale-up and postapproval changes, and dermatological testing for irritation or photosensitivity are some of the specified elements.

In this volume, we present over 350 formulations and, in keeping with the tradition in other volumes, a chapter on formulation-related matters. In the regulatory section, we offer a difficult area of compliance, changes to approved new drug applications (NDAs), and abbreviated new drug applications (ANDAs), particularly with reference to semisolid drugs. The stability considerations, particularly the evolving guidelines of the International Conference on Harmonization (ICH), are detailed in this volume, with particular reference to stability-testing requirements in postapproval stages. Unique to this category is the dermal testing of products, including photosensitivity-testing requirements that are still evolving. It is noteworthy that much of the regulatory discussion presented here is drawn from the requirements of the U.S. Food and Drug Administration (FDA) and the harmonized guidelines with the ICH listings. Although it is likely that some of the requirements and recommendations made here might change, it is unlikely that the basic thrust in establishing these guidelines will change. As always, the applicants are highly encouraged to communicate with the FDA on the changes made to these guidelines and especially for any significant changes made to compliance requirements. The Web site of the FDA, http://www.fda.gov, is very comprehensive and continuously evolving; pay special attention to the withdrawal and finalization of guidelines provided. Of particular importance is the listing of new and withdrawn guidelines (http://www.fda.gov/cder/guidance/New-Revised-Withdrawn.PDF), which should be reviewed periodically.

Chapter 1 provides details on how to handle changes made to approved NDAs or ANDAs; this is a significant topic for continued compliance with the cGMP requirements but, unfortunately, the one that is most easily misunderstood or misconstrued. For example, at what level of change should the FDA be informed, either before making a change or after? What happens if a change is made inadvertently and later discovered; how to report this change? Years of experience teaches me that a manufacturer can never be too careful in avoiding a 483 issuance when it comes to changes made to NDAs or ANDAs. The situation gets extremely complex when there are multiple dosage forms, for which the requirements may be different.

Chapter 2 gets into details of changes made pursuant to discussion in chapter 1 when it comes to semisolid drugs. A more detailed description of level of changes is described here, and advice is provided on when to conduct a regulatory review.

Chapter 3 continues the themes developed in the first two chapters and applies to changes made to equipment. This is a topic of special interest to the FDA because in the processing of semisolid products, the equipment plays a pivotal role. The mixing of drugs within the base media is highly affected by the process and mechanism of mixing used. Also, because of the nature of product manufactured, often the cleaning and validation of equipment become serious issues.

Chapter 4 is a comprehensive review of the present thinking of the regulatory authorities on how the stability studies should be designed and conducted and how the data should be interpreted; the induction of ICH guidelines and an attempt to streamline the requirements of testing new drug products have resulted in much dispute when it comes to global marketing of products. Should the stability testing be done at all environmental regional standards, or is it possible to extrapolate these data based on accelerated stability testing? These are some of the questions answered in this chapter, wherein the FDA and ICH guidelines are merged.

Chapter 5 extends the discussion on stability-testing protocols to retest periods and elaborates on the procedures used for continued testing of products.

Chapter 6 introduces a topic of great importance in the development of semisolid, and particularly dermal, products: skin irritation and sensitization studies. Whereas the standard test protocols have almost become universal in their

nature, it is always advised that these should be agreed on, most appropriately in a pre-investigational new drug application (IND) filing. Established in 1988, the Office of Drug Evaluation IV (ODE IV) Pre-IND Consultation Program is designed to facilitate and foster informal early communications between the divisions of ODE IV and potential sponsors of new therapeutics for the treatment of bacterial infections, HIV, opportunistic infections, transplant rejection, and other diseases. The program is intended to serve sponsors of all drug products that may be submitted to any division within ODE IV, including but not limited to drugs for the treatment of life-threatening illnesses [21 CFR 312.82(a)]. Pre- IND advice may be requested for issues related to drug development plans; data needed to support the rationale for testing a drug in humans; the design of nonclinical pharmacology, toxicology, and drug activity studies; data requirements for an IND application; and regulatory requirements for demonstrating safety and efficacy. Included among the ODE IV Pre-IND Program activities are coordination of all Pre-IND interactions with the FDA Topical Microbicide Working Group.

Chapter 7 deals with the topic of photosensitivity caused by drugs; photosafety is a serious issue in the development of topical products. It is worth noting here that certain classes of drugs such as quinolone antibiotics are generally regarded unsafe without thorough testing for photosensitivity. Does photosensitivity correlate with carcinogenicity? These are questions of importance to the regulatory authorities. Chapter 8 includes a variety of topics related to formulation of semisolid drugs, from cGMP considerations to packaging and validation issues; these topics are collated for their particular importance, but the discussions provided are not comprehensive, and the reader is referred to standard texts on formulation theories, particularly where establishing a preservative system is required.

I am grateful to CRC Press for taking this lead in publishing what is possibly the largest such work in the field of pharmaceutical manufacturing. It has been a distinct privilege to have known Mr. Stephen Zollo, the Senior Editor at CRC Press, for years. Stephen has done more than any editor can to encourage me into completing this work on a timely basis. The editorial assistance provided by CRC Press staff was indeed exemplary, particularly the help given by Erika Dery, Naomi Lynch, and others. Although much care has gone into correcting errors, any errors remaining are altogether mine. I shall appreciate the readers bringing these to my attention for correction in future editions of this volume (niazi@pharmsci.com).

This volume is dedicated to John G. Wagner, the John G. Searle Professor Emeritus of Pharmaceutics in the College of Pharmacy and Professor Emeritus of Pharmacology in the Medical School, who passed away recently. Born in Weston, Ontario, Canada, in 1921, Wagner served in the Canada Air Force during World War II and then worked as a research scientist for the Upjohn Co. from 1953 to 1968, joining the University of Medicine in 1968. Wagner was the author of two books and coauthor of more than 340 articles. Throughout his life he received numerous awards, including the American Pharmaceutical Association (APhA) Ebert Prize, 1961; Academy Fellow of the AphA Academy of Pharmaceutical Sciences, 1969; the Centennial Achievement Award, Ohio State University, 1970; the Host-Madsen Medal, Federation Internationale Pharmaceutique, 1972; Outstanding Leadership and Research Award, Delta Chapter of Phi Lambda Epsilon, 1983; AAPS Fellow, American Association of Pharmaceutical Scientists, 1986; and Distinguished Professor, Michigan Association of Governing Boards, 1988. Following retirement, Wagner worked as a consultant to Upjohn, Schering Corp., Warner-Lambert/Parke-Davis, the Food and Drug Administration, and others. John Wagner became famous with the publication of his book, Biopharmaceutics and Relevant Pharmacokinetics; he then followed with other books on the subject of pharmacokinetics. This was the time, in the early 1970s, when the discipline of mathematical pharmacokinetics was in its infancy; its creation spearheaded by such giants as Sid Riegelman, Milo Gibaldi, and Gerhard Levy. John took the lead in infusing complex mathematics to the resolution of pharmacokinetic modeling approach; his savvy of introducing Laplace transforms to all kinetics problems bears well in my mind. I never found it difficult to get lost somewhere in the long chain of mathematical transformations; John could easily make any model mathematically awesome. I met John several times when I had invited him to speak at the institutions where I was working to frequent meetings at the Academy of Pharmaceutical Science. John was a slim, trim man who spoke with a comparably lean choice of words. He was indeed a leader, a remarkable educator, and someone who left many indelible impressions on the students in his era—including me.

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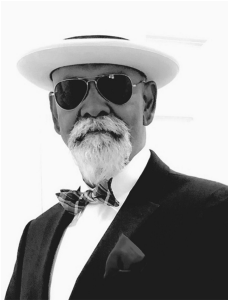
About the Author



Sarfaraz K. Niazi has been teaching and conducting research in the pharmaceutical industry for over 40 years. He has authored hundreds of scientific papers, scores of textbooks, handbooks and literary books on the topics of pharmaceutical formulation, biopharmaceutics, pharmacokinetics, bioprocessing, recombinant engineering, as well as poetry and philosophy. He is also an inventor with 100+ patents in the fields of bioprocessing, technology, drug and dosage form delivery systems; he is also licensed to practice law before the U.S. Patent and Trademark Office. He has formulated hundreds of products ranging from the most popular consumer products to complex generics and biotechnology-derived products. Dr. Niazi advises regulatory agencies and the pharmaceutical industry internationally on making safe and effective drugs affordable (www.pharmsci.com). He can be contacted at niazi@niazi.com.

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Part I

Regulatory and Manufacturing Guidance

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1 Waiver of In Vivo Bioequivalence Study

I. INTRODUCTION

Bioavailability (BA) and bioequivalence (BE) studies are expensive to conduct, and given the need for a multitude of these studies in the development of an NDA or ANDA, there had always existed a need to justify these needs on scientific grounds. This is particularly important for the generic drug industry since the generic competitors must keep their cost of regulatory approval to as low a level as possible. Recently, guidelines have emerged that would allow waiver of both BA and BE studies in some situations. There are also provisions available for the sponsor to challenge the requirement, and if the basic criteria set are met, there is a very good possibility of receiving waivers. These waivers are intended to apply to the following:

- Subsequent in vivo BA or BE studies of formulations after the initial establishment of the in vivo BA of immediate-release (IR) dosage forms during the IND period.
- In vivo BE studies of IR dosage forms in ANDAs. Regulations at 21 CFR part 320 address the requirements for BA and BE data for approval of drug applications and supplemental applications.

Provision for waivers of in vivo BA/BE studies (biowaivers) under certain conditions is provided at 21 CFR 320.22.

Waiver for bioequivalence testing therefore becomes a topic of great interest worldwide. Several consortiums have debated this topic for years, and a consensus has begun to develop on this topic. A large number of policy documents address this topic including the published FDA and ICH guidelines, Health Canada's Guideline on Preparation of DIN Submissions, WHO document (1999) entitled "Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products: a Manual for Drug Regulatory Authorities, Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability," Note for Guidance on the Investigation of Bioavailability and Bioequivalence, Committee for Proprietary Medicinal Products (CPMP), 26 July 2001 (CPMP/EWP/QWP/98), and Pan-American Network on Regulatory Harmonization: Bioavailability and Bioequivalence working group 2004.

The requirement for the in vivo bioequivalence study may be waived for certain generic products [21 USC 360 b (n) (1) (E)]. Categories of products which may be eligible for waivers include, but are not limited to, the following:

- Parenteral solutions intended for injection by the intravenous, subcutaneous, or intramuscular routes of administration
- Oral solutions or other solubilized forms
- Topically applied solutions intended for local therapeutic effects. Other topically applied dosage forms intended for local therapeutic effects for nonfood animals only
- Inhalant volatile anesthetic solutions

This guidance provides recommendations for sponsors of investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and supplements to these applications that wish to request a waiver of in vivo BA or BE studies for IR solid oral dosage forms. These waivers apply to

1. Subsequent in vivo BA or BE studies of formulations after the initial establishment of the in vivo BA of IR dosage forms during the IND period and
2. In vivo BE studies of IR dosage forms in ANDAs

Regulations at 21 CFR Part 320 address the requirements for BA and BE data for approval of drug applications and supplemental applications. Provision for waivers of in vivo BA/BE studies (biowaivers) under certain conditions is provided at 21 CFR 320.22. This guidance explains when biowaivers can be requested for IR solid oral dosage forms based on an approach termed the biopharmaceutics classification system (BCS).

II. THE BIOPHARMACEUTICALS CLASSIFICATION SYSTEM

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms: Dissolution, solubility, and intestinal permeability. According to the BCS, drug substances are classified as follows:

Class 1: High solubility—high permeability
Class 2: Low solubility—high permeability
Class 3: High solubility—low permeability
Class 4: Low solubility—low permeability

In addition, IR solid oral dosage forms are categorized as having rapid or slow dissolution. Within this framework, when certain criteria are met, the BCS can be used as a drug development tool to help sponsors justify requests for biowaivers. There are several factors that affect classification of drugs in different classes. Table 1.1 expands this classification to include a more detailed description including the effect of transporter efflux factors.

TABLE 1.1
The Biopharmaceutics Classification System (BCS) as Defined by the FDA and Modified by Recent Findings

	High Solubility (e.g., When the Highest dose Strength is Soluble in 250 mL or Less of Aqueous Media Over a pH Range of 1–7.5 at 37°C)	**Low Solubility**
High permeability (e.g., absorption >90% compared to intravenous dose) (drug + metabolite)	Class 1: (generally about 8% of new leads) • High solubility • High permeability • Rapid dissolution for biowaiver • Route of elimination: Metabolism, extensive • Transporter effects: Minimal Examples: Abacavir; Acetaminophen; Acyclovir[b]; Amiloride[S, I]; Amitryptyline[S, I]; Antipyrine; Atropine; Buspirone[C]; Caffeine; Captopril; Chloroquine[S, I]; Chlorpheniramine; Cyclophosphamide; Desipramine; Diazepam; Diltiazem[S, I]; diphenhydramine; Disopyramide; Doxepin; oxycycline; Enalapril; Ephedrine; Ergonovine; Ethambutol; Ethinyl estradiol; Fluoxetine[I]; Glucose; Imipramine[I]; Ketoprofen; Ketorolac; Labetalol; Levodopa[S]; Levofloxacin[S]; Lidocaine[I]; Lomefloxacin; Meperidine; Metoprolol; Metronidazole; Midazolam[S, I]; Minocycline; Misoprostol; Nifedipine[S]; Phenobarbital; Phenylalanine; Prednisolone; Primaquine[S]; Promazine; Propranolol[I]; Quinidine[S,I]; Rosiglitazone; Salicylic acid; Theophylline; Valproic acid; Verapamil[I]; Zidovudine	Class 2: • Low solubility • High permeability • Route of elimination: Metabolism, extensive. • Transporter: Efflux transporter effects predominant Examples: Amiodarone[I]; Atorvastatin[S, I]; Azithromycin[S, I]; Carbamazepine[S, I]; Carvedilol; Chlorpromazine[I]; Ciprofloxacin[S]; Cisapride[S]; Cyclosporine[S, I]; Danazol; Dapsone; Diclofenac; Diflunisal; Digoxin[S]; Erythromycin[S, I]; Flurbiprofen; Glipizide; Glyburide[S, I]; Griseofulvin; Ibuprofen; Indinavir[S]; Indomethacin; Itraconazole[S, I]; Ketoconazole[I]; Lansoprazole[I]; Lovastatin[S, I]; Mebendazole; Naproxen; Nelfinavir[S, I]; Ofloxacin; Oxaprozin; Phenazopyridine; Phenytoin[S]; Piroxicam; Raloxifene[S]; Ritonavir[S, I]; Saquinavir[S, I]; Saquinavir[S, I]; Sirolimus[S]; Spironolactone[I]; Tacrolimus[S, I]; Talinolol[S]; Tamoxifen[I]; Terfenadine[I]; Warfarin
Low permeability	Class 3: • High solubility • Low permeability • Route of elimination: Renal and/or biliary elimination of unchanged drug; metabolism poor • Transporter: Absorptive effects predominant Examples: Acyclovir; Amiloride[S, I]; Amoxicillin[S, I]; Atenolol; Atropine; Bidisomide; Bisphosphonates; Captopril; Cefazolin; Cetirizine; Cimetidine[S]; Ciprofloxacin[S]; Cloxacillin; Dicloxacillin[S]; Erythromycin[S, I]; Famotidine; Fexofenadine[S]; Folinic acid; Furosemide; Ganciclovir; Hydrochlorothiazide; Lisinopril; Metformin; Methotrexate; Nadolol; Penicillins; Pravastatin[S]; Ranitidine[S]; Tetracycline; Trimethoprim[S]; Valsartan; Zalcitabine	Class 4: • Low solubility • Low permeability • Route of elimination: Renal and/or biliary elimination of unchanged drug; metabolism poor • Transporter: Absorptive and efflux transporters can be predominant Examples: Amphotericin B; Chlorothiazide; Chlorthalidone; Ciprofloxacin[S]; Colistin; Furosemide; Hydrochlorothiazide; Mebendazole; Methotrexate; Neomycin

Note: The compounds listed in italic are those falling in more than one category by different authors, which could be a result of the definition of the experimental conditions. The compounds listed in bold are primarily CYP3A substrates where metabolism accounts for more than 70% of the elimination; superscript I and/or S indicate P-gp inhibitors and/or substrate, respectively. The Class 1 and Class 2 compounds are eliminated primarily via metabolism, whereas Class 3 and Class 4 compounds are primarily eliminated unchanged into the urine and bile.

Observed in vivo differences in the rate and extent of absorption of a drug from two pharmaceutically equivalent solid oral products may be due to differences in drug dissolution in vivo. However, when the in vivo dissolution of an IR solid oral dosage form is rapid in relation to gastric emptying and the drug has high permeability, the rate and extent of drug absorption is unlikely to be dependent on drug dissolution and/or gastrointestinal transit time. Under such circumstances, demonstration of in vivo BA or BE may not be necessary for drug products containing Class 1 drug substances, as long as the inactive ingredients used in the dosage form do not significantly affect absorption of the active ingredients. The BCS approach outlined in this guidance can be used to justify biowaivers for *highly soluble* and *highly permeable* drug substances (i.e., Class 1) in IR solid oral dosage forms that exhibit *rapid in vitro dissolution* using the recommended test methods [21 CFR 320.22(e)].

Several generalizations can be made about the interplay of transporters and the BCS classification.

a. Transporter effects are minimal for Class 1 compounds. The high permeability/high solubility of such compounds allows high concentrations in the gut to saturate any transporter, both efflux and absorptive. Class 1 compounds may be substrates for both uptake and efflux transporters in vitro in cellular systems under the right conditions [e.g., midazolam and nifedipine are substrates for P-glycoprotein (P-gp)], but transporter effects will not be important clinically. It is therefore possible that some compounds that should be considered Class 1 in terms of drug absorption and disposition are not Class 1 in BCS due to the requirement of good solubility and rapid dissolution at low pH values. Such pH effects would not be limiting in vivo where absorption takes place from the intestine. Examples of this include the NSAIDs diclofenac, diflunisal, flurbiprofen, indomethacin, naproxen, and piroxicam; warfarin is almost completely bioavailable. In contrast, ofloxacin is listed as Class 2 because of its low solubility at pH 7.5.
b. Efflux transporter effects will predominate for Class 2 compounds. The high permeability of these compounds will allow ready access into the gut membranes, and uptake transporters will have no effect on absorption, but the low solubility will limit the concentrations coming into the enterocytes, thereby preventing saturation of the efflux transporters. Consequently, efflux transporters will affect the extent of oral bioavailability and the rate of absorption of Class 2 compounds.
c. Transporter-enzyme interplay in the intestines will be important primarily for Class 2 compounds that are substrates for CYP3A and Phase 2 conjugation enzymes. For such compounds, intestinal uptake transporters will generally be unimportant due to the rapid permeation of the drug molecule into the enterocytes as a function of their high lipid solubility. That is, absorption of Class 2 compounds is primarily passive and a function of lipophilicity. However, because of the low solubility of these compounds, there will be little opportunity to saturate apical efflux transporters and intestinal enzymes such as cytochrome P450 3A4 (CYP3A4) and UDP-glucuronosyltransferases (UGTs). Thus, changes in transporter expression and inhibition or induction of efflux transporters will cause changes in intestinal metabolism of drugs that are substrates for the intestinal metabolic enzymes. Note the large number of Class 2 compounds in Table 1.1 that are primarily substrates for CYP3A (compounds listed in bold) as well as substrates or inhibitors of the efflux transporter P-gp (indicated by superscripts S and I, respectively). Work in our laboratory has characterized this interplay in the absorptive process for the investigational cysteine protease inhibitor K77 (28,32) and sirolimus (29), substrates for CYP3A and P-gp, and more recently for raloxifene (33), a substrate for UGTs and P-gp.
d. Absorptive transporter effects will predominate for Class 3 compounds. For Class 3 compounds, sufficient drug will be available in the gut lumen due to good solubility, but an absorptive transporter will be necessary to overcome the poor permeability characteristics of these compounds. However, intestinal apical efflux transporters may also be important for the absorption of such compounds when sufficient enterocyte penetration is achieved via an uptake transporter.

Table 1.2 lists model drugs suggested for use in establishing suitability of a permeability method. The permeability of these compounds was determined based on data available to the FDA. Potential *internal standards* (IS) and *efflux pump substrates* (ES) are also identified.

For application of the BCS, an apparent passive transport mechanism can be assumed when one of the following conditions is satisfied:

- A linear (pharmacokinetic) relationship between the dose (e.g., relevant clinical dose range) and measures of BA (area under the concentration–time curve) of a drug is demonstrated in humans.
- Lack of dependence of the measured in vivo or in situ permeability is demonstrated in an animal model on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest dose strength dissolved in 250 mL) in the perfusion fluid.
- Lack of dependence of the measured in vitro permeability on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest dose strength dissolved in 250 mL) is demonstrated in donor fluid and transport direction (e.g., no statistically significant difference in the rate of transport between the apical-to-basolateral and basolateral-to-apical direction for the drug concentrations selected) using a suitable in vitro cell culture method that has been shown to express known efflux transporters (e.g., P-gp).

TABLE 1.2
Model Drugs to Establish Permeability of Drugs

Drug	Permeability Class
Antipyrine	High (potential IS candidate)
Caffeine	High
Carbamazepine	High
Fluvastatin	High
Ketoprofen	High
Metoprolol	High (potential IS candidate)
Naproxen	High
Propranolol	High
Theophylline	High
Verapamil	High (potential ES candidate)
Amoxicillin	Low
Atenolol	Low
Furosemide	Low
Hydrochlorthiazide	Low
Mannitol	Low (potential IS candidate)
Methyldopa	Low
Polyethylene glycol (400)	Low
Polyethylene glycol (1000)	Low
Polyethylene glycol (4000)	Low (zero permeability marker)
Ranitidine	Low

To demonstrate suitability of a permeability method intended for application of the BCS, a rank-order relationship between test permeability values and the extent of drug absorption data in human subjects should be established using a sufficient number of model drugs. For in vivo intestinal perfusion studies in humans, six model drugs are recommended. For in vivo or in situ intestinal perfusion studies in animals and for in vitro cell culture methods, 20 model drugs are recommended. Depending on study variability, a sufficient number of subjects, animals, excised tissue samples, or cell monolayers should be used in a study to provide a reliable estimate of drug permeability. This relationship should allow precise differentiation between drug substances of low- and high-intestinal permeability attributes.

For demonstration of suitability of a method, model drugs should represent a range of low (e.g., <50%), moderate (e.g., 50–89%), and high (≥90%) absorption. Sponsors may select compounds from the list of drugs and/or chemicals provided in Attachment A, or they may choose to select other drugs for which there is information available on mechanism of absorption and reliable estimates of the extent of drug absorption in humans.

After demonstrating suitability of a method and maintaining the same study protocol, it is not necessary to retest all selected model drugs for subsequent studies intended to classify a drug substance. Instead, a low- and a high-permeability model drug should be used as IS (i.e., included in the perfusion fluid or donor fluid along with the test drug substance). These two IS are in addition to the fluid volume marker (or a zero-permeability compound such as Polyethylene glycol 4000) that is included in certain types of perfusion techniques (e.g., closed loop techniques). The choice of IS should be based on compatibility with the test drug substance (i.e., they should not exhibit any significant physical, chemical, or permeation interactions). When it is not feasible to follow this protocol, the permeability of IS should be determined in the same subjects, animals, tissues, or monolayers, following evaluation of the test drug substance. The permeability values of the two IS should not differ significantly between different tests, including those conducted to demonstrate suitability of the method. At the end of an in situ or in vitro test, the amount of drug in the membrane should be determined.

For a given test method with set conditions, selection of a high-permeability internal standard with permeability in close proximity to the low-/high-permeability class boundary may facilitate classification of a test drug substance. For instance, a test drug substance may be determined to be highly permeable when its permeability value is equal to or greater than that of the selected internal standard with high permeability.

The recommended methods for determining solubility, permeability, and in vitro dissolution are discussed below.

A. Solubility

The solubility class boundary is based on the highest dose strength of an IR product that is the subject of a biowaiver request. A drug substance is considered *highly soluble* when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1 to 7.5. The volume estimate of 250 mL is derived from typical BE study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water.

B. Permeability

The permeability class boundary is based indirectly on the extent of absorption (fraction of dose absorbed, not systemic BA) of a drug substance in humans and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, nonhuman systems capable of predicting the extent of drug absorption in humans can be used (e.g., in vitro epithelial cell culture methods). In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered *highly permeable* when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.

C. Dissolution

In this guidance, an IR drug product is considered *rapidly dissolving* when no less than 85% of the labeled amount of the drug substance dissolves within 30 min, using U.S. Pharmacopoeia (USP) Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 mL or less in each of the following media:

1. 0.1 N HCl or Simulated Gastric Fluid USP without enzymes
2. A pH 4.5 buffer
3. A pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes

III. METHODOLOGY FOR CLASSIFYING A DRUG SUBSTANCE AND FOR DETERMINING THE DISSOLUTION CHARACTERISTICS OF A DRUG PRODUCT

The following approaches are recommended for classifying a drug substance and determining the dissolution characteristics of an IR drug product according to the BCS.

A. Determining Drug Substance Solubility Class

An objective of the BCS approach is to determine the equilibrium solubility of a drug substance under physiological pH conditions. The pH-solubility profile of the test drug substance should be determined at $37 \pm 1°C$ in aqueous media with a pH in the range of 1 to 7.5. A sufficient number of pH conditions should be evaluated to accurately define the pH-solubility profile. The number of pH conditions for a solubility determination can be based on the ionization characteristics of the test drug substance. For example, when the pKa of a drug is in the range of 3 to 5, solubility should be determined at pH = pKa, pH = pKa + 1, pH = pKa −1, and at pH = 1 and 7.5. A minimum of three replicate determinations of solubility in each pH condition is recommended. Depending on study variability, additional replication may be necessary to provide a reliable estimate of solubility. Standard buffer solutions described in the USP are considered appropriate for use in solubility studies. If these buffers are not suitable for physical or chemical reasons, other buffer solutions can be used. Solution pH should be verified after addition of the drug substance to a buffer. Methods other than the traditional shake-flask method, such as acid or base titration methods, can also be used with justification to support the ability of such methods to predict equilibrium solubility of the test drug substance. Concentration of the drug substance in selected buffers (or pH conditions) should be determined using a validated stability-indicating assay that can distinguish the drug substance from its degradation products (www.fda.gov/cder/guidance/P147_9604#P147_9604). If degradation of the drug substance is observed as a function of buffer composition or pH, it should be reported along with other stability data recommended in Section III.B.3.

The solubility class should be determined by calculating the volume of an aqueous medium sufficient to dissolve the highest dose strength in the pH range of 1 to 7.5. A drug substance should be classified as highly soluble when the highest dose strength is soluble in ≤ 250 mL of aqueous media over the pH range of 1 to 7.5.

B. Determining Drug Substance Permeability Class

The permeability class of a drug substance can be determined in human subjects using mass balance, absolute BA, or intestinal perfusion approaches. Recommended methods not involving human subjects include in vivo or in situ intestinal perfusion in a suitable animal model (e.g., rats), in vitro permeability methods using excised intestinal tissues, or monolayers of suitable epithelial cells. In many cases, a single method may be sufficient (e.g., when the absolute BA is 90% or more, or when 90% or more of the administered drug is recovered in urine). When a single method fails to conclusively demonstrate a permeability classification, two different methods may be advisable. Chemical structure or certain physicochemical attributes of a drug substance (e.g., partition coefficient in suitable systems) can provide useful information about its permeability characteristics. Sponsors may wish to consider use of such information to further support a classification.

1. Pharmacokinetic Studies in Humans

a. Mass Balance Studies

Pharmacokinetic mass balance studies using unlabeled, stable isotopes or a radiolabeled drug substance can be used to document the extent of absorption of a drug. Depending on the variability of the studies, a sufficient number of subjects should be enrolled to provide a reliable estimate of extent of absorption. Because this method can provide highly variable estimates of drug absorption for many drugs, other methods described below may be preferable.

b. Absolute Bioavailability Studies

Oral BA determination using intravenous administration as a reference can be used. Depending on the variability of the studies, a sufficient number of subjects should be enrolled in a study to provide a reliable estimate of the extent of absorption. When the absolute BA of a drug is shown to be 90% or more, additional data to document drug stability in the gastrointestinal fluid is not necessary.

The following methods can be used to determine the permeability of a drug substance from the gastrointestinal tract: (1) in vivo intestinal perfusion studies in humans, (2) in vivo or in situ intestinal perfusion studies using suitable animal models, (3) in vitro permeation studies using excised human or animal intestinal tissues, or (4) in vitro permeation studies across a monolayer of cultured epithelial cells.

In vivo or in situ animal models and in vitro methods, such as those using cultured monolayers of animal or human epithelial cells, are considered appropriate for passively transported drugs. The observed low permeability of some drug substances in humans could be caused by efflux of drugs via membrane transporters such as P-gp. When the efflux transporters are absent in these models, or their degree of expression is low compared to that in humans, there may be a greater likelihood of misclassification of permeability class for a drug subject to efflux compared to a drug transported passively. Expression of known transporters in selected study systems

should be characterized. Functional expression of efflux systems (e.g., P-gp) can be demonstrated with techniques such as bidirectional transport studies, demonstrating a higher rate of transport in the basolateral-to-apical direction as compared to apical-to-basolateral direction using selected model drugs or chemicals at concentrations that do not saturate the efflux system (e.g., cyclosporin A, vinblastine, rhodamine 123). An acceptance criterion for intestinal efflux that should be present in a test system cannot be set at this time. Instead, this guidance recommends limiting the use of nonhuman permeability test methods for drug substances that are transported by passive mechanisms. Pharmacokinetic studies on dose linearity or proportionality may provide useful information for evaluating the relevance of observed in vitro efflux of a drug. For example, there may be fewer concerns associated with the use of in vitro methods for a drug that has a higher rate of transport in the basolateral-to-apical direction at low drug concentrations but exhibits linear pharmacokinetics in humans.

Poor absorption or permeation is more likely when there are more than five H-bond donors, ten H-bond acceptors, the molecular weight is greater than 500, and the calculated Log P is greater than 5. This is also often referred to as Rule of 5 of Lipinski. However, Lipinski specifically states that the Rule of 5 only holds for compounds that are *not* substrates for active transporters. Since almost all drugs are substrates for some transporter, much remains to be studied about Lipinski's rule. In addition, unless a drug molecule can passively gain intracellular access, it is not possible to simply investigate whether the molecule is a substrate for efflux transporters.

2. Intestinal Permeability Methods

The following methods can be used to determine the permeability of a drug substance from the gastrointestinal tract:

1. In vivo intestinal perfusion studies in humans
2. In vivo or in situ intestinal perfusion studies using suitable animal models
3. In vitro permeation studies using excised human or animal intestinal tissues
4. In vitro permeation studies across a monolayer of cultured epithelial cells

In vivo or in situ animal models and in vitro methods, such as those using cultured monolayers of animal or human epithelial cells, are considered appropriate for passively transported drugs. The observed low permeability of some drug substances in humans could be caused by efflux of drugs via membrane transporters such as P-gp. When the efflux transporters are absent in these models, or their degree of expression is low compared with that in humans, there may be a greater likelihood of misclassification of permeability class for a drug subject to efflux compared with a drug transported passively. Expression of known transporters in selected study systems should be characterized. Functional expression of efflux systems (e.g., P-gp) can be demonstrated with techniques such as bidirectional transport studies, demonstrating a higher rate of transport in the basolateral-to-apical direction as compared with apical-to-basolateral direction using selected model drugs or chemicals at concentrations that do not saturate the efflux system (e.g., cyclosporin A, vinblastine, rhodamine 123). An acceptance criterion for intestinal efflux that should be present in a test system cannot be set at this time. Instead, this guidance recommends limiting the use of nonhuman permeability test methods for drug substances that are transported by passive mechanisms. Pharmacokinetic studies on dose linearity or proportionality may provide useful information for evaluating the relevance of observed in vitro efflux of a drug. For example, there may be fewer concerns associated with the use of in vitro methods for a drug that has a higher rate of transport in the basolateral-to-apical direction at low drug concentrations but exhibits linear pharmacokinetics in humans.

For application of the BCS, an apparent passive transport mechanism can be assumed when one of the following conditions is satisfied:

- A linear (pharmacokinetic) relationship between the dose (e.g., relevant clinical dose range) and measures of BA (area under the concentration–time curve, AUC) of a drug is demonstrated in humans.
- Lack of dependence of the measured in vivo or in situ permeability is demonstrated in an animal model on initial drug concentration (e.g., 0.01, 0.1, and 1 H the highest dose strength dissolved in 250 mL) in the perfusion fluid.
- Lack of dependence of the measured in vitro permeability on initial drug concentration (e.g., 0.01, 0.1, and 1 H the highest dose strength dissolved in 250 mL) is demonstrated in donor fluid and transport direction (e.g., no statistically significant difference in the rate of transport between the apical-to-basolateral and basolateral-to-apical direction for the drug concentrations selected), using a suitable in vitro cell culture method that has been shown to express known efflux transporters (e.g., P-gp).

To demonstrate suitability of a permeability method intended for application of the BCS, a rank-order relationship between test permeability values and the extent of drug absorption data in human subjects should be established using a sufficient number of model drugs. For in vivo intestinal perfusion studies in humans, six model drugs are recommended. For in vivo or in situ intestinal perfusion studies in animals and for in vitro cell culture methods, 20 model drugs are recommended. Depending on study variability, a sufficient number of subjects, animals, excised tissue samples, or cell monolayers should be used in a study to provide a reliable estimate of drug permeability. This relationship should allow precise differentiation between drug substances of low- and high-intestinal permeability attributes.

Given below is a description of various approaches available to study permeability characteristics.

a. Surrogate Methods

As the U.S. FDA has begun accepting recommendations for waiver of bioequivalence requirement, protocols that prove extremely expensive in the drug development cycle, there is a greater need to develop surrogate models that one day may prove useful in securing waivers for all classes of drugs. Generally, the methods available currently show that the complexity of assay is directly proportional to its correlation with absorption of drugs in humans. Studies that correlated Log P with human absorption profile and the suitability or lead candidates are elaborated in Chapter 4. In this chapter, we will examine more complex assay systems. Data from both complex biological and artificial permeation assays can provide valuable information regarding the absorption of a drug.

Drug transport across epithelial cell barriers, especially the human small intestine, is difficult to predict. The intestinal epithelial cell barrier is a sophisticated organ that has evolved over hundreds of millions of years to become a "smart," effective, and selective xenobiotic screen. Nevertheless, there is large interindividual variability in the intestinal transport of drugs. Genetic variability in key proteins is believed to be causal. There is a pressing need to better understand the key processes and how the system components interact at the molecular, cellular, and tissue level to control drug transport and determine drug absorption in the small intestine.

Is it feasible to construct an in silico framework to represent the drug absorption in the small intestine at the cellular level in concert with the update molecular biochemical mechanism? This new generation of models and computational tools might integrate the available and emerging information at different levels to better account for and predict observed experimental results. Predicting aqueous solubility with in silico tools is a key drug property. It is, however, difficult to measure accurately, especially for poorly soluble compounds, and thus numerous in silico models have been developed for its prediction. Some in silico models can predict aqueous solubility of simple, uncharged organic chemicals reasonably well; however, solubility prediction for charged species and drug-like chemicals is not very accurate. However, extrapolating solubility data to intestinal absorption from pharmacokinetic and physicochemical data and elucidating crucial parameters for absorption and the potential for improvement of bioavailability are important at the pre-formulation stages.

The poor oral bioavailability of drugs is generally assumed to be due to physiochemical problems, which result in poor solubility in the gastrointestinal tract (GI tract) or difficulty in diffusion through the small intestine epithelial membrane. Furthermore, the biochemical process also contributes to oral bioavailability. The in vitro cell culture models of the intestinal epithelial cell barrier have evolved to become widely used experimental devices.

The permeability assay uses an artificial membrane composed of hexadecane. The automated systems comprise a multiwell system.

b. Parallel Artificial Membrane Permeability Analysis

Early drug discovery ADME assays, such as fast Caco-2 screens (see below), can help in rejecting test compounds that lack good pharmaceutical profiles. A cost-effective, high-throughput method—parallel artificial membrane permeability analysis (PAMPA)—that uses a phospholipid artificial membrane that models passive transport of epithelial cells is becoming increasingly popular. The PAMPA assay uses a range of lipid components that model a variety of different plasma membranes. The support membrane is 0.45 μm Hydrophobic Polyvinylidene Fluoride, 130 μm thick, and the artificial membrane is lecithin in dodecane; recommended incubation time is 16 to 24 hours. The permeability and PAMPA assays as described above are robust and reproducible assays for determining passive, transcellular compound permeability. Permeability and PAMPA are automation compatible, relatively fast (4–16 hours), inexpensive, and straightforward, and their results correlate with human drug absorption values from published methods. The PAMPA assay provides the benefits of a more biologically relevant system. It is also possible to tailor the lipophilic constituents so that they mimic specific membranes such as the blood–brain barrier. Optimization of incubation time, lipid mixture, and lipid concentration will also enhance the assay's ability to predict compound permeability.

Modifications of permeability and PAMPA systems have been reported, for example, using the pION PAMPA Evolution 96 System with double-sink and gut-box (www.pion-inc.com/products.htm) as a new surrogate assay that predicts the gastrointestinal tract absorption of candidate drug molecules at different pH conditions. Using Beckman Coulter's Biomek® FX Single Bridge Laboratory Automation Workstation PAMPA Assay System that features a 30-minute incubation time and an on-deck integrated Gut-Box™ and a SpectraMax® microplate spectrophotometer, the permeability coefficients of drug standards with diverse physiochemical properties can be compared from both PAMPA and Caco-2 assays automated using the Biomek FX Workstation.

These automated assays can be used for high-throughput ADME screening in early drug discovery. The Double-Sink PAMPA permeability assay mimics in vivo conditions by the use of a chemical sink in the acceptor wells and pH gradient in the donor wells. The use of the pION Gut-Box integrated on the deck has shortened the PAMPA assay incubation time to 30 min. The permeability coefficient and rank order correlate well with data obtained using the in vitro Caco-2 assay and in vivo permeability properties measured in rat intestinal perfusions.

c. Caco-2 Drug Transport Assays

Drug absorption generally occurs either through passive transcellular or paracellular diffusion, active carrier transport, or active efflux mechanisms. Several methods have been developed to aid in the understanding of the absorption of new lead compounds. The most common ones use an immortalized cell line (e.g., Caco-2, MDCK, etc.) to mimic the intestinal epithelium. These in vitro models provide more predictive

permeability information than artificial membrane systems (i.e., PAMPA and permeability assays, described above) based on the cells' ability to promote (active transport) or resist (efflux) transport. Various in vitro methods are listed in U.S. FDA guidelines, acceptable to evaluate the permeability of a drug substance, including monolayer of suitable epithelial cells, and one such epithelial cell line that has been widely used as a model system of intestinal permeability is the Caco-2 cell line.

The kinetics of intestinal drug absorption, permeation enhancement, chemical moiety structure–permeability relationships, dissolution testing, in vitro/in vivo correlation, bioequivalence, and the development of novel polymeric materials are closely associated with the concept of Caco-2. Since most drugs are known to absorb via intestines without using cellular pumps, passive permeability models came into the limelight. In a typical Caco-2 experiment, a monolayer of cells is grown on a filter separating two stacked micro well plates. The permeability of drugs through the cells is determined after the introduction of a drug on one side of the filter. The entire process is automated, and when used in conjunction with chromatography and/or mass spectroscopy detection, it enables any drug's permeability to be determined. The method requires careful sample analysis to calculate permeability correctly. Limitations of Caco-2 experiments are the 21 days to prepare a stable monolayer, as well as the stringent storage conditions; however, tight-junction formation prior to use is the better choice. The villus in the small intestine contains more than one cell type, the Caco-2 cell line does not produce the mucus as observed in the small intestine, and no P-450 metabolizing enzyme activity has been found in the Caco-2 cell line. Test compound solubility may pose a problem in Caco-2 assays because of the assay conditions. Finally, Caco-2 cells also contain endogenous transporter and efflux systems, the latter of which works against the permeability process and can complicate data interpretation for some drugs.

The Caco-2 cell line is heterogeneous and is derived from a human colorectal adenocarcinoma. Caco-2 cells are used as in vitro permeability models to predict human intestinal absorption because they exhibit many features of absorptive intestinal cells. This includes their ability to spontaneously differentiate into polarized enterocytes that express high levels of brush border hydrolases and form well-developed junctional complexes. Consequently, it becomes possible to determine whether passage is transcellular or paracellular based on a compound's transport rate. Caco-2 cells also express a variety of transport systems including dipeptide transporters and P-gp. Because of these features, drug permeability in Caco-2 cells correlates well with human oral absorption, making Caco-2 an ideal in vitro permeability model. Additional information can be gained on metabolism and potential drug–drug interactions as the drug undergoes transcellular diffusion through the Caco-2 transport model.

Although accurate and well researched, the Caco-2 cell model requires a high investment of time and resources. Depending on a number of factors, including initial seeding density, culturing conditions, and passage number, Caco-2 cells can take as many as 20 days to reach confluence and achieve full differentiation. During this 20-day period, they require manual or automated exchange of media as frequently as every other day. The transport assays consume valuable drug compounds and normally require expensive, post-transport sample analyses (e.g., LC/MS). Therefore, the use of the Caco-2 transport model in a high-throughput laboratory setting is only possible if the platform is robust, automation compatible, reproducible, and provides high-quality data that correlate well with established methodologies.

The Millipore MultiScreen® Caco-2 assay system is a reliable 96-well platform for predicting human oral absorption of drug compounds (using Caco-2 cells or other cell lines whose drug transport properties have been well characterized). The MultiScreen system format is automation compatible and is designed to offer more cost effective, higher-throughput screening of drugs than a 24-well system. The MultiScreen Caco-2 assay system exhibits good uniformity of cell growth and drug permeability across all 96 wells and low variability between production lots. The plate design supports the use of lower volumes of expensive media and reduced amounts of test compounds. Using the MultiScreen Caco-2 assay system, standard drug compounds are successfully categorized as either "high" or "low" permeable, as defined by FDA, and the permeability data correlate well with established human absorption values.

Historically, it has been shown that a sigmoidal relationship exists between drug absorption rates as measured with the in vitro Caco-2 model and human absorption. Caco-2 cells are heterogeneous, and their properties in final culture may differ based on the selection pressures of a particular laboratory. Direct comparison of compound permeability rates between laboratories is not possible unless the same Caco-2 cells and conditions are used. Therefore, transport rates and permeability classification ranges of specific drugs are expected to vary between reported studies. Most important is the ability to successfully classify compounds as low-, medium-, or high-permeable drugs and produce transport results that correlate to established human absorption values.

Several modifications of Caco-2 cell model have been tested; for example, CYP3A4-Transfected Caco-2 cells are also used to define the biochemical absorption barriers. Oral bioavailability and intestinal drug absorption can be significantly limited by metabolizing enzymes and efflux transporters in the gut. The most prevalent oxidative drug-metabolizing enzyme present in the intestine is CYP3A4. Currently, more than 50% of the drugs on the market metabolized by P450 enzymes are metabolized by CYP3A4. Oral absorption of CYP3A4 substrates can also be limited by the multidrug resistance transporter P-gp, because there is extensive substrate overlap between these two proteins. P-gp is an ATP-dependent transporter on the apical plasma membrane of enterocytes that functions to limit the entry of drugs into the cell. There is significant interaction between CYP3A4 and P-gp in the intestine. Although Caco-2 cells express a variety of uptake and efflux transporters found in the human intestine, a major drawback to the use of Caco-2 cells is that

they lack CYP3A4. As such, no data regarding the importance of intestinal metabolism on limiting drug absorption can be obtained from normal Caco-2 cells. Caco-2 cells pretreated with 1, 25-dihydroxyvitamin-D_3 (vitamin D_3) express higher levels of CYP3A4 compared with Caco-2 but still underestimate the amount of CYP3A4 in the human intestine. CYP3A4-transfected Caco-2 cells that P-gp can enhance drug metabolism and significantly decrease intestinal drug absorption.

d. Animal Model Testing

Whereas the quantity of substance available at the pre-formulation stages is generally small, in some instances, early animal testing for absorption potential is needed, particularly if the solid form of the new drug offers many options such as amorphous forms, solvates, and so forth. The absorption models used in animals are well described and will not be discussed here. Establishing good in vitro–in vivo correlation at this stage proves useful because of limited access to sufficient compound to run the entire absorption profiles. The "in vitroin vivo correlation" (IVIVC) analysis can be made extensive, or general conclusions drawn from limited studies; the choice depends on the amount of compound available and the nature or robustness of correlation observed.

e. In Vitro–In Vivo Correlation

The selection of a drug candidate marks the most crucial stage in the lifecycle of drug development. Such selection is primarily based on the drug "developability" criteria, which include physicochemical properties of the drug and the results obtained from preliminary studies involving several in vitro systems and in vivo animal models, which address efficacy and toxicity issues. During this stage, exploring the relationship between in vitro and in vivo properties of the drug in animal models provides an idea about the feasibility of the drug delivery system for a given drug. In such correlations, study designs including study of more than one formulation of the modified-release dosage forms and a rank order of release (fast/slow) of the formulations should be incorporated. Even though the formulations and methods used at this stage are not optimal, they prompt better design and development efforts in the future.

There are four levels of IVIVC that have been described in the FDA guidance, which include levels A, B, C, and multiple C.

- Level A Correlation: This correlation represents a point-to-point relationship between in vitro dissolution and in vivo dissolution (input/absorption rate). Level A IVIVC is also viewed as a predictive model for the relationship between the entire in vitro release time course and entire in vivo response time course. In general, correlations are linear at this level. Although a concern regarding acceptable nonlinear correlation has been addressed, no formal guidance on the nonlinear IVIVC has been established. Level A correlation is the most informative and very useful from a regulatory perspective.
- Level B Correlation: In level B correlation, the mean in vivo dissolution or mean residence time is compared to the mean in vitro dissolution time by using statistical moment analytical methods. This type of correlation uses all of the in vitro and in vivo data; thus, it is not considered as a point-to-point correlation. This is of limited interest and use because more than one kind of plasma curve produces similar mean residence time.
- Level C Correlation: This correlation describes a relationship between the amount of drug dissolved (e.g., % dissolved at 1 hour) at one time point and one pharmacokinetic parameter (e.g., either AUC or C_{max}). Level C correlation is considered the lowest correlation level as it does not reflect the complete shape of the plasma concentration time curve. Similarly, a multiple level C correlation relates one or more pharmacokinetic parameters to the percent drug dissolved at several time points of the dissolution profile and thus may be more useful. Level B and C correlations can be useful in early formulation development, including selecting the appropriate excipients, to optimize manufacturing processes, for quality control purposes, and to characterize the release patterns of newly formulated immediate-release and modified-release products relative to the reference.

The most basic IVIVC models are expressed as a simple linear equation between the in vivo drug absorption and in vitro drug dissolved (released).

Several commercial software programs are available to study IVIVC, for example, PDx-IVIVC (www.globomaxservice.com/pdxivivc.htm), which is a comprehensive IVIVC software program that performs deconvolution, calculating the fraction or percentage of drug absorbed and correlating it with in vitro fraction or percentage dissolved data. It also allows level C correlations (single or multiple) wherein a single-point relationship between a dissolution parameter, for example, percent dissolved in 4 hours, and a pharmacokinetic parameter (e.g., AUC, C_{max}, T_{max}) is determined. A successful IVIVC model can be developed if in vitro dissolution is the rate-limiting step in the sequence of events leading to appearance of the drug in the systemic circulation following oral or other routes of administration. Thus, the dissolution test can be used as a surrogate for bioequivalence studies (involving human subjects) if the developed IVIVC is predictive of in vivo performance of the product.

3. Instability in the Gastrointestinal Tract

Determining the extent of absorption in humans based on mass balance studies using total radioactivity in urine does not take into consideration the extent of degradation of a drug in the gastrointestinal fluid before intestinal membrane permeation. In addition, some methods for determining permeability could be based on loss or clearance of a drug from fluids perfused into the human or animal gastrointestinal tract either

in vivo or in situ. Documenting the fact that drug loss from the gastrointestinal tract arises from intestinal membrane permeation, instead of a degradation process, will help establish permeability. Stability in the gastrointestinal tract may be documented using gastric and intestinal fluids obtained from human subjects. Drug solutions in these fluids should be incubated at 37°C for a period that is representative of in vivo drug contact with these fluids (e.g., 1 hour in gastric fluid and 3 hours in intestinal fluid). Drug concentrations should then be determined using a validated stability-indicating assay method. Significant degradation (>5%) of a drug in this protocol could suggest potential instability. Obtaining gastrointestinal fluids from human subjects requires intubation and may be difficult in some cases. Use of gastrointestinal fluids from suitable animal models or simulated fluids such as Gastric and Intestinal Fluids USP can be substituted when properly justified.

C. Determining Drug Product Dissolution Characteristics and Dissolution Profile Similarity

Dissolution testing should be carried out in USP Apparatus I at 100 rpm or Apparatus II at 50 rpm using 900 mL of the following dissolution media (www.fda.gov/cder/guidance/P192_20127#P192_20127):

1. NHCl or Simulated Gastric Fluid USP without enzymes
2. A pH 4.5 buffer
3. A pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes

For capsules and tablets with gelatin coating, Simulated Gastric and Intestinal Fluids USP (with enzymes) can be used.

Dissolution testing apparatus used in this evaluation should conform to the requirements in USP (<711> Dissolution). Selection of the dissolution testing apparatus (USP Apparatus I or II) during drug development should be based on a comparison of in vitro dissolution and in vivo pharmacokinetic data available for the product. The USP Apparatus I (*basket method*) is generally preferred for capsules and products that tend to float, and USP Apparatus II (*paddle method*) is generally preferred for tablets. For some tablet dosage forms, in vitro (but not in vivo) dissolution may be slow due to the manner in which the disintegrated product settles at the bottom of a dissolution vessel. In such situations, USP Apparatus I may be preferred over Apparatus II. If the testing conditions need to be modified to better reflect rapid in vivo dissolution (e.g., use of a different rotating speed), such modifications can be justified by comparing in vitro dissolution with in vivo absorption data (e.g., a relative BA study using a simple aqueous solution as the reference product).

A minimum of 12 dosage units of a drug product should be evaluated to support a biowaiver request. Samples should be collected at a sufficient number of intervals to characterize the dissolution profile of the drug product (e.g., 10, 15, 20, and 30 min).

When comparing the test and reference products, dissolution profiles should be compared using a similarity factor (f_2). The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) of dissolution between the two curves.

$$f_2 = 50 \times \log\left\{\left[1 + (1/n)_{t=1^n}\left(R_t - T_t\right)^2\right] - 05 \times 100\right\}$$

Two dissolution profiles are considered similar when the f_2 value is >50. To allow the use of mean data, the coefficient of variation should not be more than 20% at the earlier time points (e.g., 10 min) and should not be more than 10% at other time points. Note that when both test and reference products dissolve 85% or more of the label amount of the drug in >15 min using all three dissolution media recommended previously, the profile comparison with an f_2 test is unnecessary.

IV. ADDITIONAL CONSIDERATIONS FOR REQUESTING A BIOWAIVER

When requesting a BCS-based waiver for in vivo BA/BE studies for IR solid oral dosage forms, applicants should note that the following factors could affect their request or the documentation of their request.

A. Excipients

Excipients can sometimes affect the rate and extent of drug absorption. In general, using excipients that are currently in FDA-approved IR solid oral dosage forms will not affect the rate or extent of absorption of a highly soluble and highly permeable drug substance that is formulated in a rapidly dissolving IR product. To support a biowaiver request, the quantity of excipients in the IR drug product should be consistent with the intended function (e.g., lubricant). When new excipients or atypically large amounts of commonly used excipients are included in an IR solid dosage form, additional information documenting the absence of an impact on the BA of the drug may be requested by the FDA. Such information can be provided with a relative BA study using a simple aqueous solution as the reference product. Large quantities of certain excipients, such as surfactants (e.g., polysorbate 80) and sweeteners (e.g., mannitol or sorbitol) may be problematic, and sponsors are encouraged to contact the review division when this is a factor.

B. Prodrugs

Permeability of prodrugs will depend on the mechanism and (anatomical) site of conversion to the drug substance. When it is demonstrated that the prodrug-to-drug conversion occurs predominantly after intestinal membrane permeation, the permeability of the prodrug should be measured. When this conversion occurs prior to intestinal permeation, the permeability of the drug should be determined. Dissolution and

pH-solubility data on both prodrugs and drugs can be relevant. Sponsors may wish to consult with appropriate review staff before applying the BCS approach to IR products containing prodrugs.

C. Exceptions

BCS-based biowaivers are not applicable for the following.

1. Narrow Therapeutic Range Drugs

This guidance defines narrow therapeutic range drug products (www.fda.gov/cder/guidance/P223_24901#P223_24901) as those containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring or where product labeling indicates a narrow therapeutic range designation. Examples include digoxin, lithium, phenytoin, theophylline, and warfarin. Because not all drugs subject to therapeutic drug concentration or pharmacodynamic monitoring are narrow therapeutic range drugs, sponsors should contact the appropriate review division to determine whether a drug should be considered as having a narrow therapeutic range.

2. Products Designed to Be Absorbed in the Oral Cavity

A request for a waiver of in vivo BA/BE studies based on the BCS is not appropriate for dosage forms intended for absorption in the oral cavity (e.g., sublingual or buccal tablets).

V. REGULATORY APPLICATIONS OF THE BCS

A. INDs/NDAs

Evidence demonstrating in vivo BA or information to permit the FDA to waive this evidence must be included in NDAs [21 CFR 320.21(a)]. A specific objective is to establish in vivo performance of the dosage form used in the clinical studies that provided primary evidence of efficacy and safety. The sponsor may wish to determine the relative BA of an IR solid oral dosage form by comparison with an oral solution, suspension, or intravenous injection [21 CFR 320.25 (d)(2) and 320.25 (d)(3)]. The BA of the clinical trial dosage form should be optimized during the IND period.

Once the in vivo BA of a formulation is established during the IND period, waivers of subsequent in vivo BE studies, following major changes in components, composition, or method of manufacture [e.g., similar to SUPAC-IR level 3 changes (www.fda.gov/cder/guidance/P239_26745#P239_26745)], may be possible using the BCS. BCS-based biowaivers are applicable to the to-be-marketed formulation when changes in components, composition, or method of manufacture occur to the clinical trial formulation, as long as the dosage forms have rapid and similar in vitro dissolution profiles (see Sections II and III). This approach is useful only when the drug substance is highly soluble and highly permeable (BCS Class 1), and the formulations pre- and post-change are *pharmaceutical equivalents* [under the definition at 21 CFR 320.1 (c)]. BCS-based biowaivers are intended only for BE studies. They do not apply to food effect BA studies or other pharmacokinetic studies.

B. aNDAs

BCS-based biowaivers can be requested for rapidly dissolving IR test products containing highly soluble and highly permeable drug substances, provided that the reference-listed drug product is also rapidly dissolving and the test product exhibits similar dissolution profiles to the reference-listed drug product (see Sections II and III). This approach is useful when the test and reference dosage forms are pharmaceutical equivalents. The choice of dissolution apparatus (USP Apparatus I or II) should be the same as that established for the reference-listed drug product.

C. Post-Approval Changes

BCS-based biowaivers can be requested for significant post-approval changes (e.g., level 3 changes in components and composition) to a rapidly dissolving IR product containing a highly soluble, highly permeable drug substance, provided that dissolution remains rapid for the post-change product and both pre- and post-change products exhibit similar dissolution profiles (see Sections II and III). This approach is useful only when the drug products pre- and post-change are pharmaceutical equivalents.

VI. DATA TO SUPPORT A REQUEST FOR BIOWAIVERS

The drug substance for which a waiver is being requested should be highly soluble and highly permeable. Sponsors requesting biowaivers based on the BCS should submit the following information to the FDA for review by the Office of Clinical Pharmacology and Biopharmaceutics (for NDAs) or Office of Generic Drugs, Division of Bioequivalence (for aNDAs).

A. Data Supporting High Solubility

Data supporting high solubility of the test drug substance should be developed (see Section III.A). The following information should be included in the application:

- A description of test methods, including information on analytical method and composition of the buffer solutions
- Information on chemical structure, molecular weight, nature of the drug substance (acid, base, amphoteric, or neutral), and dissociation constants [pKa(s)]
- Test results (mean, standard deviation, and coefficient of variation) summarized in a table under solution pH, drug solubility (e.g., mg/mL), and volume of media required to dissolve the highest dose strength
- A graphic representation of mean pH-solubility profile

B. Data Supporting High Permeability

Data supporting high permeability of the test drug substance should be developed (see Section III.B). The following information should be included in the application:

- For human pharmacokinetic studies, information on study design and methods used along with the pharmacokinetic data.
- For direct permeability methods, information supporting the suitability of a selected method that encompasses a description of the study method, criteria for selection of human subjects, animals, or epithelial cell line, drug concentrations in the donor fluid, description of the analytical method, method used to calculate extent of absorption or permeability, and, where appropriate, information on efflux potential (e.g., bidirectional transport data).
- A list of selected model drugs along with data on extent of absorption in humans (mean, standard deviation, and coefficient of variation) used to establish suitability of a method, permeability values for each model drug (mean, standard deviation, and coefficient of variation), permeability class of each model drug, and a plot of the extent of absorption as a function of permeability (mean, standard deviation, or 95% confidence interval) with identification of the low- and high-permeability class boundary and selected internal standard. Information to support high permeability of a test drug substance should include permeability data on the test drug substance, the IS (mean, standard deviation, and coefficient of variation), stability information, data supporting passive transport mechanism where appropriate, and methods used to establish high permeability of the test drug substance.

C. Data Supporting Rapid and Similar Dissolution

For submission of a biowaiver request, an IR product should be rapidly dissolving. Data supporting rapid dissolution attributes of the test and reference products should be developed (see Section III.C). The following information should be included in the application:

- A brief description of the IR products used for dissolution testing, including information on batch or lot number, expiration date, dimensions, strength, and weight.
- Dissolution data obtained with 12 individual units of the test and reference products using recommended test methods in Section III.C. The percentage of labeled claims dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent (%) dissolved, range (highest and lowest) of dissolution, and coefficient of variation (relative standard deviation) should be tabulated. A graphic representation of the mean dissolution profiles for the test and reference products in the three media should also be included.
- Data supporting similarity in dissolution profiles between the test and reference products in each of the three media, using the f_2 metric.

D. Additional Information

The manufacturing process used to make the test product should be described briefly to provide information on the method of manufacture (e.g., wet granulation vs. direct compression). A list of excipients used, the amount used, and their intended functions should be provided. Excipients used in the test product should have been used previously in FDA-approved IR solid oral dosage forms. When requesting a BCS-based waiver for in vivo BA/BE studies for IR solid oral dosage forms, applicants should note that the following factors can affect their request or the documentation of their request:

1. Excipients

Excipients can sometimes affect the rate and extent of drug absorption. In general, using excipients that are currently in FDA-approved IR solid oral dosage forms will not affect the rate or extent of absorption of a highly soluble and highly permeable drug substance that is formulated in a rapidly dissolving IR product. To support a biowaiver request, the quantity of excipients in the IR drug product should be consistent with the intended function (e.g., lubricant). When new excipients or atypically large amounts of commonly used excipients are included in an IR solid dosage form, additional information documenting the absence of an impact on BA of the drug may be requested by the agency. Such information can be provided with a relative BA study using a simple aqueous solution as the reference product. Large quantities of certain excipients, such as surfactants (e.g., polysorbate 80) and sweeteners (e.g., mannitol or sorbitol), may be problematic, and sponsors are encouraged to contact the review division when this is a factor.

2. Prodrugs

Permeability of prodrugs will depend on the mechanism and (anatomical) site of conversion to the drug substance. When the prodrug-to-drug conversion is shown to occur predominantly after intestinal membrane permeation, the permeability of the prodrug should be measured. When this conversion occurs prior to intestinal permeation, the permeability of the drug should be determined. Dissolution and pH-solubility data on both prodrug and drug can be relevant. Sponsors may wish to consult with appropriate review staff before applying the BCS approach to IR products containing prodrugs.

3. Exceptions

BCS-based biowaivers are not applicable for the following.

a. Narrow Therapeutic Range Drugs

The narrow therapeutic range drug products are defined as those containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation. Examples include digoxin, lithium, phenytoin, theophylline, and warfarin. Because not all drugs subject to therapeutic drug concentration or pharmacodynamic monitoring are narrow therapeutic range drugs, sponsors should contact the appropriate review division to determine whether a drug should be considered to have a narrow therapeutic range.

b. Products Designed to Be Absorbed in the Oral Cavity

A request for a waiver of in vivo BA/BE studies based on the BCS is not appropriate for dosage forms intended for absorption in the oral cavity (e.g., sublingual or buccal tablets).

Fast-dissolving/-disintegrating tablets (FDDTs) disintegrate and/or dissolve rapidly in the saliva without the need for water and are thus of importance for patients who cannot or will not swallow. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. These tablets, if absorbed through the buccal cavity, avoid the first pass liver metabolism, and claims have been made for improvement of bioavailability using these platforms. Some of the key formulation considerations for FDDTs include the need to mask the taste and the most obvious method to do so is to include sweeteners and flavors; however, these are not a sufficient means for taste-masking many bitter drugs. Thus, most of the FDDT technologies incorporate unique forms of taste masking including adsorption onto or complexation with carriers and spray coating of drug particles. Frequently, the active drug powder is coated, and the coating does not completely dissolve until the drug has been swallowed. Drugs that are particle coated are more appropriately termed fast disintegrating due to the delayed release of the active molecule until they are swallowed. Additionally, effervescence is a physical method of taste masking used in some of the FDDTs. Details about the technology are sketchy as they pertain mostly to proprietary methods.

Currently, four fast-dissolving/-disintegrating technologies have reached the U.S. market: Zydis® (R.P. Scherer, Inc., Basking Ridge, NJ), WOWTABtm (Yamanouchi Pharma Technologies, Inc., Palo Alto, CA), and OraSolv® and DuraSolv® (Cima Labs, Inc., Brooklyn Park, MN). Three others are available outside the United States: FlashDose® (Fuisz Technologies, Ltd., Chantilly, VA), Flashtab® (Prographarm Group, Saint Cloud, France), and OraQuick™ (KV Pharmaceutical Co., Inc., St. Louis, MO). Examples of products available in the United States include:

Zydis Products

- Claritin Reditab: Micronized loratadine (10 mg), citric acid, gelatin, mannitol, mint flavor
- Feldene Melt: Piroxicam (10 or 20 mg), gelatin, mannitol, aspartame, citric anhydrous
- Maxalt-MLT: Rizatriptan (5 or 10 mg), gelatin, mannitol, aspartame, peppermint flavor
- Pepcid RPD: Famotidine (20 or 40 mg), gelatin, mannitol, aspartame
- Zyprexa Zydis: Olanzapine (5, 10, 15, or 20 mg), gelatin, mannitol, aspartame, methylparaben sodium, propylparaben sodium
- Zofran ODT: Ondansetron (4 or 8 mg), aspartame, gelatin, mannitol, methlparaben sodium, propylparaben sodium, strawberry flavor
- Dimetapp Quick Dissolve Children's Cold and Allergy Tablets (OTC)

OraSolv Products

- Remeron Soltab: Mirtazepine (15, 30, or 45 mg), aspartame, citric acid, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, mannitol, microcrystalline cellulose, polymethacrylate, povidone, sodium bicarbonate, starch, sucrose, orange flavor
- Tempra FirstTabs: Acetaminophen (80 or 160 mg), inactive ingredients including mannitol (currently available in Canada)
- Triaminic Softchew (OTC)

DuraSolv Products

- NuLev: Hyoscyamine sulfate (0.125 mg), aspartame, colloidal silicon dioxide, crospovidone, mint flavoring, magnesium stearate, mannitol, microcrystalline cellulose
- Zomig ZMT: Zolmitriptan (2.5 mg), mannitol, microcrystalline cellulose, crospovidone, aspartame, sodium bicarbonate, citric acid, anhydrous, colloidal silicon dioxide, magnesium stearate, orange flavor

WOWTAB Products

- Benadryl Allergy & Sinus Fastmelt (OTC)
- Children's Benadryl Allergy & Cold Fastmelt (OTC)
- Most FDDTs lack the mechanical strength common to traditional tablets. Many products are very lightweight and fragile requiring them to be individually packaged. Because of the formulation of FDDTs, they are also more susceptible to degradation via temperature and humidity.

Animal Products In general, the generic product being considered for a waiver contains the same active and inactive ingredients in the same dosage form and concentration and has the same pH and physicochemical characteristics as an approved pioneer product. However, the CVM will consider bioequivalence waivers for nonfood animal topical products

with certain differences in the inactive ingredients of the pioneer and generic products.

If a waiver of the in vivo bioequivalence and/or the tissue residue study/studies is granted for a food animal drug product, then the withdrawal period established for the pioneer product will be assigned to the generic product. Sponsors may apply for waivers of in vivo bioequivalence studies prior to submission of the ANADAs (Abbreviated New Drug Applications).

Species Selection A bioequivalence study generally should be conducted for each species for which the pioneer product is approved on the label, with the exception of "minor" species [as defined in section 514.1 (d) (1) of Title 21 of the Code of Federal Regulations] on the label.

Subject Characteristics Ordinarily, studies should be conducted with healthy animals representative of the species, class, gender, and physiological maturity for which the drug is approved. The bioequivalence study may be conducted with a single gender for which the pioneer product is approved, unless there is a known interaction of formulation with gender. An attempt should be made to restrict the weight of the test animals to a narrow range in order to maintain the same total dose across study subjects. The animals should not receive any medication prior to testing for a period of 2 weeks or more, depending upon the biological half-life of the ancillary drug.

Human Food Safety Considerations The toxicology and tolerance developed for the pioneer animal drug are applied to generic copies of the drug. The CVM has concluded that in addition to a bioequivalence study, a tissue residue depletion study should be conducted for approval of a generic animal drug product in a food-producing species. Two drug products may have the same plasma disposition profile at the concentrations used to assess product bioequivalence but may have very different tissue disposition kinetics when followed out to the withdrawal time for the pioneer product. Therefore, to show the withdrawal period at which residues of the generic product will be consistent with the tolerance for the pioneer product, a tissue residue depletion study is necessary.

The results of a bioequivalence study or tissue residue depletion study in one animal species cannot generally be extrapolated to another species. Possible species differences in drug partitioning or binding in tissues could magnify a small difference in the rate or extent of drug absorbed into a large difference in marker residue concentrations in the target tissue. Therefore, for a pioneer product labeled for more than one food-producing species, a bioequivalence study and a tissue residue depletion study will generally be requested for each major food-producing species on the label.

A traditional withdrawal study, as described in CVM's guidance number 3, "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals," is considered the best design for collecting data useful for the calculation of a preslaughter withdrawal period for drugs used in food-producing animals. In the traditional withdrawal study, 20 animals are divided into four or five groups of four to five animals each. Groups of animals are slaughtered at carefully preselected time points following the last administration of the test product, and the edible tissues are collected for residue analysis. A statistical tolerance limit approach is used to determine when, with 95% confidence, 99% of treated animals would have tissue residues below the codified limits.

For purposes of calculating a withdrawal period for a generic animal drug, only the generic product would be tested (i.e., not the pioneer product), and only the marker residue in the target tissue would be analyzed. Other study designs will be considered on a case-by-case basis. Sponsors are encouraged to submit the proposed tissue residue depletion protocol for CVM concurrence before proceeding with the withdrawal study.

The generic animal drug will be assigned the withdrawal time supported by the residue depletion data or the withdrawal time currently assigned to the pioneer product, whichever is the longer.

The generic animal drug sponsor may request a shorter withdrawal period for the generic product by supplementing the ANADA and providing tissue residue data necessary to support the shorter withdrawal period request. Such a supplement will be reviewed under the agency's policy for Category II supplements. For a Category II supplement, a reevaluation of the safety (or effectiveness) data in the parent application (i.e., the pioneer NADA) may be required [21 CFR 514.106 (b) (2)]. The CVM will ordinarily approve a request for a shorter withdrawal period when the residue data are adequate and when no other human food safety concerns for the drug are evident.

Under 21 CFR 514.1(b)(7), applications are required to include a description of practicable methods for determining the quantity, if any, of the new animal drug in or on food, and any substance formed in or on food because of its use, and the proposed tolerance or withdrawal period or other use restrictions to ensure that the proposed use of the drug will be safe. For certain drug products, a tissue residue depletion study is not needed to ensure that residues of the test product will be consistent with the codified drug tolerance at the withdrawal time assigned to the reference product. These include but may not be limited to products for which a waiver of in vivo bioequivalence testing is granted and products for which the assay method used in the blood level bioequivalence study is sensitive enough to measure blood levels of the drug for the entire withdrawal period assigned to the reference product. Other requests for waiver of the tissue residue study will be considered on a case-by-case basis.

CVM will not request that the assay methodology used to determine the withdrawal period for the generic product be more rigorous than the approved methodology used to determine the existing withdrawal period for the pioneer product. If an analytical method other than the approved method of analysis is used, the generic sponsor should provide data comparing the alternate method to the approved method.

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2 Quality Risk Management

I. INTRODUCTION

Risk management principles are effectively used in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries. Although there are some examples of the use of *quality risk management* in the pharmaceutical industry today, they are limited and do not represent the full contributions that risk management has to offer. In addition, the importance of *quality systems* has been recognized in the pharmaceutical industry, and it is becoming evident that quality risk management is a valuable component of an effective quality system.

It is commonly understood that *risk* is defined as the combination of the probability of occurrence of *harm* and the *severity* of that harm. However, achieving a shared understanding of the application of risk management among diverse *stakeholders* is difficult because each stakeholder might perceive different potential harms, place a different probability on each harm occurring, and attribute different severities to each harm. In relation to pharmaceuticals, although there are a variety of stakeholders, including patients and medical practitioners as well as government and industry, the protection of the patient by managing the risk to quality should be considered of prime importance.

The manufacturing and use of a drug (medicinal) product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product *quality* should be maintained throughout the *product lifecycle* such that the attributes that are important to the quality of the drug (medicinal) product remain consistent with those used in the clinical studies. An effective quality risk management approach can further ensure the high quality of the drug (medicinal) product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. Additionally, use of quality risk management can improve the decision making if a quality problem arises. Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and can beneficially affect the extent and level of direct regulatory oversight.

The purpose of this document is to offer a systematic approach to quality risk management. It serves as a foundation or resource document that is independent of, yet supports, other ICH quality documents and complements existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and regulatory environment. It specifically provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk-based decisions, both by regulators and by industry, regarding the quality of drug substances and drug (medicinal) products across the product lifecycle. It is not intended to create any new expectations beyond the current regulatory requirements.

It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or internal procedures, e.g., standard operating procedures). The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable. Appropriate use of quality risk management can facilitate but does not obviate industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators.

II. SCOPE

This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug (medicinal) products, biological, and biotechnological products (including the use of raw materials, solvents, excipients, packaging, and labeling materials in drug (medicinal) products, biological, and biotechnological products).

III. PRINCIPLES OF QUALITY RISK MANAGEMENT

Two primary principles of quality risk management are as follows:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.
- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

IV. GENERAL QUALITY RISK MANAGEMENT PROCESS

Quality risk management is a systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle. A model for quality risk management is outlined in Figure 2.1. Other models could be used. The emphasis on each component of the framework might differ from case to case, but a robust process will incorporate consideration of all

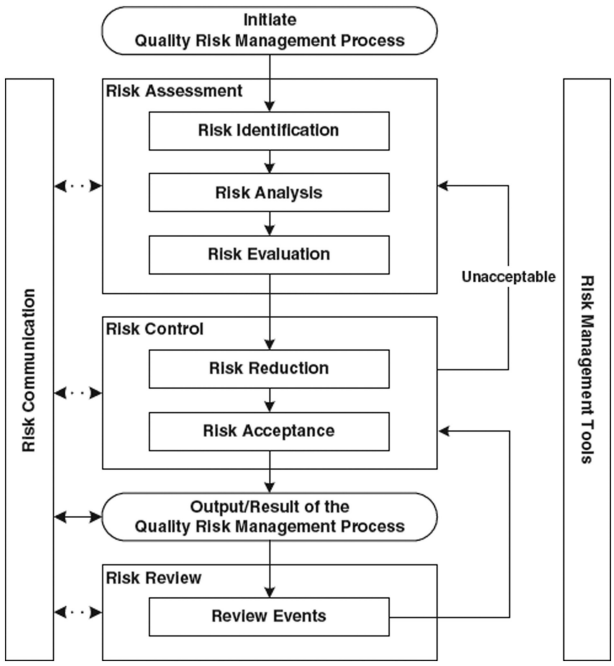

FIGURE 2.1 Overview of a typical quality risk management process.

the elements at a level of detail that is commensurate with the specific risk.

Decision nodes are not shown in Figure 2.1, because decisions can occur at any point in the process. These decisions might be to return to the previous step and seek further information, to adjust the risk models, or even to terminate the risk management process based upon information that supports such a decision. *Note*: "Unacceptable" in the flowchart does not only refer to statutory, legislative, or regulatory requirements but also to the need to revisit the risk assessment process.

A. Responsibilities

Quality risk management activities are usually, but not always, undertaken by interdisciplinary teams. When teams are formed, they should include experts from the appropriate areas (e.g., quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics, and clinical) in addition to individuals who are knowledgeable about the quality risk management process.

Decision makers *should*

- Take responsibility for coordinating quality risk management across various functions and departments of their organization and
- Assure that a quality risk management process is defined, deployed, and reviewed and that adequate resources are available

B. Initiating a Quality Risk Management Process

Quality risk management should include systematic processes designed to coordinate, facilitate, and improve science-based decision making with respect to risk. Possible steps used to initiate and plan a quality risk management process might include the following:

- Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk.
- Assemble background information and/or data on the potential hazard, harm, or human health impact relevant to the risk assessment.
- Identify a leader and necessary resources.
- Specify a timeline, deliverables, and appropriate level of decision making for the risk management process.

C. Risk Assessment

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (as defined below). Quality risk assessments begin with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool (see examples in Section V) and the types of information needed to address the risk question will be more readily identifiable. As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Risk identification addresses the "What might go wrong?" question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process.

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.

Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions.

In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output. Revealing assumptions and reasonable sources of uncertainty will enhance confidence in this output and/or help identify its limitations. Uncertainty is due to combination of incomplete knowledge about a process and its expected or unexpected variability. Typical sources of uncertainty include gaps in knowledge, gaps in pharmaceutical science and process understanding, sources of harm (e.g., failure modes of a process, sources of variability), and probability of detection of problems.

The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of a range of risk. When risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as "high," "medium," or "low," which should be defined in as much detail as possible. Sometimes a "risk score" is used to further define descriptors in risk ranking. In quantitative risk assessments, a risk estimate provides the likelihood of a specific consequence, given a set of risk-generating circumstances. Thus, quantitative risk estimation is useful for one particular consequence at a time. Alternatively, some risk management tools use a relative risk measure to combine multiple levels of severity and probability into an overall estimate of relative risk. The intermediate steps within a scoring process can sometimes employ quantitative risk estimation.

D. Risk Control

Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. Decision makers might use different processes, including benefit–cost analysis, for understanding the optimal level of risk control.

Risk control might focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks, and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level (see Figure 2.1). Risk reduction might include actions taken to mitigate the severity and probability of harm. Processes that improve the detectability of hazards and quality risks might also be used as part of a risk control strategy. The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks. Hence, it might be appropriate to revisit the risk assessment to identify and evaluate any possible change in risk after implementing a risk reduction process.

Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk, or it can be a passive decision in which residual risks are not specified. For some types of harms, even the best quality risk management practices might not entirely eliminate risk. In these circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis.

E. Risk Communication

Risk communication is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process (see Figure 2.1: Dashed arrows). The output/result of the quality risk management process should be appropriately communicated and documented (see Figure 2.1: Solid arrows). Communications might include those among interested parties, for example, regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc. The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability, or other aspects of risks to quality. Communication need not be carried out for each and every risk acceptance. Between the industry and regulatory authorities, communication concerning quality risk management decisions might be effected through existing channels as specified in regulations and guidances.

F. Risk Review

Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented.

The output/results of the risk management process should be reviewed to take into account new knowledge and experience. Once a quality risk management process has been initiated, that process should continue to be used for events that might impact the original quality risk management decision, whether these events are planned (e.g., results of product review, inspections, audits, change control) or unplanned (e.g., root cause from failure investigations, recall). The frequency of any review should be based upon the level of risk. Risk review might include reconsideration of risk acceptance decisions (Section D).

V. RISK MANAGEMENT METHODOLOGY

Quality risk management supports a scientific and practical approach to decision making. It provides documented, transparent, and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity, and sometimes detectability of the risk.

Traditionally, risks to quality have been assessed and managed in a variety of informal ways (empirical and/or internal procedures) based on, for example, compilation of observations, trends, and other information. Such approaches continue to provide useful information that might support topics such as handling of complaints, quality defects, deviations, and allocation of resources.

Additionally, the pharmaceutical industry and regulators can assess and manage risk using recognized risk management tools and/or internal procedures (e.g., standard operating procedures). Below is a non-exhaustive list of some of these tools (further details in Annex I and Chapter 8):

- Basic risk management facilitation methods (flowcharts, check sheets, etc.)
- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects, and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering
- Supporting statistical tools

It might be appropriate to adapt these tools for use in specific areas pertaining to drug substance and drug (medicinal) product quality. Quality risk management methods and the supporting statistical tools can be used in combination (e.g., Probabilistic Risk Assessment). Combined use provides flexibility that can facilitate the application of quality risk management principles.

The degree of rigor and formality of quality risk management should reflect available knowledge and be commensurate with the complexity and/or criticality of the issue to be addressed.

VI. INTEGRATION OF QUALITY RISK MANAGEMENT INTO INDUSTRY AND REGULATORY OPERATIONS

Quality risk management is a process that supports science-based and practical decisions when integrated into quality systems (see Annex II). As outlined in the introduction, appropriate use of quality risk management does not obviate industry's obligation to comply with regulatory requirements. However, effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and might affect the extent and level of direct regulatory oversight. In addition, quality risk management can facilitate better use of resources by all parties.

Training of both industry and regulatory personnel in quality risk management processes provides for greater understanding of decision-making processes and builds confidence in quality risk management outcomes.

Quality risk management should be integrated into existing operations and documented appropriately. Annex II provides examples of situations in which the use of the quality risk management process might provide information that could then be used in a variety of pharmaceutical operations. These examples are provided for illustrative purposes only and should not be considered a definitive or exhaustive list. These examples are not intended to create any new expectations beyond the requirements laid out in the current regulations.

Examples for industry and regulatory operations (see Annex II):

- Quality management

  Examples for industry operations and activities (see Annex II):
- Development
- Facility, equipment, and utilities
- Materials management
- Production
- Laboratory control and stability testing
- Packaging and labeling

  Examples for regulatory operations (see Annex II):
- Inspection and assessment activities

While regulatory decisions will continue to be taken on a regional basis, a common understanding and application of quality risk management principles could facilitate mutual confidence and promote more consistent decisions among regulators on the basis of the same information. This collaboration could be important in the development of policies and guidelines that integrate and support quality risk management practices.

GLOSSARY

Decision Maker(s): Person(s) with the competence and authority to make appropriate and timely quality risk management decisions.

Detectability: The ability to discover or determine the existence, presence, or fact of a hazard.

Harm: Damage to health, including the damage that can occur from loss of product quality or availability.

Hazard: The potential source of harm (ISO/IEC Guide 51).

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

Quality: The degree to which a set of inherent properties of a product, system, or process fulfills requirements [see ICH Q6A definition specifically for "quality" of drug substance and drug (medicinal) products].

Quality Risk Management: A systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

Quality System: The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met.

Requirements: The explicit or implicit needs or expectations of the patients or their surrogates (e.g., healthcare professionals, regulators, and legislators). In this document, "requirements" refers not only to statutory, legislative, or regulatory requirements but also to such needs and expectations.

Risk: The combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51).

Risk Acceptance: The decision to accept risk (ISO Guide 73).

Risk Analysis: The estimation of the risk associated with the identified hazards.

Risk Assessment: A systematic process of organizing information to support a risk decision to be made

within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

Risk Communication: The sharing of information about risk and risk management between the decision maker and other stakeholders.

Risk Control: Actions implementing risk management decisions (ISO Guide 73).

Risk Evaluation: The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.

Risk Identification: The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description.

Risk Management: The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating, and reviewing risk.

Risk Reduction: Actions taken to lessen the probability of occurrence of harm and the severity of that harm.

Risk Review: Review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk.

Severity: A measure of the possible consequences of a hazard.

Stakeholder: Any individual, group, or organization that can affect, be affected by, or perceive itself to be affected by a risk. Decision makers might also be stakeholders. For the purposes of this guideline, the primary stakeholders are the patient, healthcare professional, regulatory authority, and industry.

Trend: A statistical term referring to the direction or rate of change of a variable(s).

ANNEX I: RISK MANAGEMENT METHODS AND TOOLS

The purpose of this annex is to provide a general overview of and references for some of the primary tools that might be used in quality risk management by industry and regulators. The references are included as an aid to gain more knowledge and detail about the particular tool. This is not an exhaustive list. It is important to note that no one tool or set of tools is applicable to every situation in which a quality risk management procedure is used.

I.1 Basic Risk Management Facilitation Methods

Some of the simple techniques that are commonly used to structure risk management by organizing data and facilitating decision making are as follows:

- Flowcharts
- Check Sheets
- Process Mapping
- Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram)

I.2 Failure Mode Effects Analysis

FMEA (see IEC 60812) provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce, or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures, and the likely effects of these failures.

Potential Areas of Use(s)

FMEA can be used to prioritize risks and monitor the effectiveness of risk control activities.

FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process. It identifies elements/operations within the system that render it vulnerable. The output/results of FMEA can be used as a basis for design or further analysis or to guide resource deployment.

I.3 Failure Mode, Effects, and Criticality Analysis

FMEA might be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their detectability, thereby becoming a Failure Mode Effect and Criticality Analysis (FMECA; see IEC 60812). In order for such an analysis to be performed, the product or process specifications should be established. FMECA can identify places where additional preventive actions might be appropriate to minimize risks.

Potential Areas of Use(s)

FMECA application in the pharmaceutical industry should mostly be used for failures and risks associated with manufacturing processes; however, it is not limited to this application. The output of an FMECA is a relative risk "score" for each failure mode, which is used to rank the modes on a relative risk basis.

I.4 Fault Tree Analysis

The FTA tool (see IEC 61025) is an approach that assumes failure of the functionality of a product or process. This tool evaluates system (or subsystem) failures one at a time but can combine multiple causes of failure by identifying causal chains. The results are represented pictorially in the form of a tree of fault modes. At each level in the tree, combinations of fault modes are described with logical operators (AND, OR, etc.). FTA relies on the experts' process understanding to identify causal factors.

Potential Areas of Use(s)

FTA can be used to establish the pathway to the root cause of the failure. FTA can be used to investigate complaints or deviations in order to fully understand their root cause and to

ensure that intended improvements will fully resolve the issue and not lead to other issues (i.e., solve one problem yet cause a different problem). FTA is an effective tool for evaluating how multiple factors affect a given issue. The output of an FTA includes a visual representation of failure modes. It is useful both for risk assessment and in developing monitoring programs.

I.5 Hazard Analysis and Critical Control Points

HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety (see WHO Technical Report Series No 908, 2003, Annex 7). It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products.

HACCP consists of the following seven steps:

(1) Conduct a hazard analysis, and identify preventive measures for each step of the process.
(2) Determine the critical control points.
(3) Establish critical limits.
(4) Establish a system to monitor the critical control points.
(5) Establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control.
(6) Establish system to verify that the HACCP system is working effectively.
(7) Establish a record-keeping system.

Potential Areas of Use(s)

HACCP might be used to identify and manage risks associated with physical, chemical, and biological hazards (including microbiological contamination). HACCP is most useful when product and process understanding is sufficiently comprehensive to support identification of critical control points. The output of a HACCP analysis is risk management information that facilitates monitoring of critical points not only in the manufacturing process but also in other lifecycle phases.

I.6 Hazard Operability Analysis

HAZOP (see IEC 61882) is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions. It is a systematic brainstorming technique for identifying hazards using so-called "guide-words." "Guide-words" (e.g., No, More, Other Than, Part of, etc.) are applied to relevant parameters (e.g., contamination, temperature) to help identify potential deviations from normal use or design intentions. It often uses a team of people with expertise covering the design of the process or product and its application.

Potential Areas of Use(s)

HAZOP can be applied to manufacturing processes, including outsourced production and formulation as well as the upstream suppliers, equipment, and facilities for drug substances and drug (medicinal) products. It has also been used primarily in the pharmaceutical industry for evaluating process safety hazards. As is the case with HACCP, the output of a HAZOP analysis is a list of critical operations for risk management. This facilitates regular monitoring of critical points in the manufacturing process.

I.7 Preliminary Hazard Analysis

PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations, and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product, or system. The tool consists of (1) the identification of the possibilities that the risk event happens, (2) the qualitative evaluation of the extent of possible injury or damage to health that could result, (3) a relative ranking of the hazard using a combination of severity and likelihood of occurrence, and (4) the identification of possible remedial measures.

Potential Areas of Use(s)

PHA might be useful when analyzing existing systems or prioritizing hazards where circumstances prevent a more extensive technique from being used. It can be used for product, process, and facility design as well as to evaluate the types of hazards for the general product type, then the product class, and finally the specific product. PHA is most commonly used early in the development of a project when there is little information on design details or operating procedures; thus, it will often be a precursor to further studies. Typically, hazards identified in the PHA are further assessed with other risk management tools such as those in this section.

I.8 Risk Ranking and Filtering

Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically requires evaluation of multiple diverse quantitative and qualitative factors for each risk. The tool involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks. "Filters," in the form of weighting factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.

Potential Areas of Use(s)

Risk ranking and filtering can be used to prioritize manufacturing sites for inspection/audit by regulators or industry. Risk ranking methods are particularly helpful in situations in which the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool. Risk ranking is useful when management needs to evaluate both quantitatively assessed and qualitatively assessed risks within the same organizational framework.

I.9 Supporting Statistical Tools

Statistical tools can support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision making. A listing of some of the principal statistical tools commonly used in the pharmaceutical industry is provided below:

- Control Charts, for example
  - Acceptance Control Charts (see ISO 7966)
  - Control Charts with Arithmetic Average and Warning Limits (see ISO 7873)
  - Cumulative Sum Charts (see ISO 7871)
  - Shewhart Control Charts (see ISO 8258)
  - Weighted Moving Average
- Design of Experiments
- Histograms
- Pareto Charts
- Process Capability Analysis

ANNEX II: POTENTIAL APPLICATIONS FOR QUALITY RISK MANAGEMENT

This annex is intended to identify potential uses of quality risk management principles and tools by industry and regulators. However, the selection of particular risk management tools is completely dependent upon specific facts and circumstances.

These examples are provided for illustrative purposes and only suggest potential uses of quality risk management. This annex is not intended to create any new expectations beyond the current regulatory requirements.

II.1 Quality Risk Management as Part of Integrated Quality Management

Documentation

To review current interpretations and application of regulatory expectations.

To determine the desirability of and/or develop the content for SOPs, guidelines, etc.

Training and Education

To determine the appropriateness of initial and/or ongoing training sessions based on education, experience, and working habits of staff, as well as on a periodic assessment of previous training (e.g., its effectiveness).

To identify the training, experience, qualifications, and physical abilities that allow personnel to perform an operation reliably and with no adverse impact on the quality of the product.

Quality Defects

To provide the basis for identifying, evaluating, and communicating the potential quality impact of a suspected quality defect, complaint, trend, deviation, investigation, out of specification result, etc.

To facilitate risk communications and determine appropriate action to address significant product defects, in conjunction with regulatory authorities (e.g., recall).

Auditing/Inspection

To define the frequency and scope of audits, both internal and external, taking into account factors such as

- Existing legal requirements
- Overall compliance status and history of the company or facility
- Robustness of a company's quality risk management activities
- Complexity of the site
- Complexity of the manufacturing process
- Complexity of the product and its therapeutic significance
- Number and significance of quality defects (e.g., recall)
- Results of previous audits/inspections
- Major changes of building, equipment, processes, key personnel
- Experience with manufacturing of a product (e.g., frequency, volume, number of batches)
- Test results of official control laboratories

Periodic Review

To select, evaluate, and interpret trend results of data within the product quality review.

To interpret monitoring data (e.g., to support an assessment of the appropriateness of revalidation or changes in sampling).

Change Management/Change Control

To manage changes based on knowledge and information accumulated in pharmaceutical development and during manufacturing.

To evaluate the impact of the changes on the availability of the final product.

To evaluate the impact on product quality of changes to the facility, equipment, material, manufacturing process, or technical transfers.

To determine appropriate actions preceding the implementation of a change, for example, additional testing, (re)qualification, (re)validation, or communication with regulators.

Continual Improvement

To facilitate continual improvement in processes throughout the product lifecycle.

II.2 Quality Risk Management as Part of Regulatory Operations

Inspection and Assessment Activities

To assist with resource allocation including, for example, inspection planning and frequency, and inspection and assessment intensity (see "Auditing" section in Annex II.1).

To evaluate the significance of, for example, quality defects, potential recalls, and inspectional findings.

To determine the appropriateness and type of post-inspection regulatory follow-up.

To evaluate information submitted by industry including pharmaceutical development information.

To evaluate impact of proposed variations or changes.

To identify risks which should be communicated between inspectors and assessors to facilitate better understanding of how risks can be or are controlled [e.g., parametric release, Process Analytical Technology (PAT)].

II.3 Quality Risk Management as Part of Development

To design a quality product and its manufacturing process to consistently deliver the intended performance of the product (see ICH Q8).

To enhance knowledge of product performance over a wide range of material attributes (e.g., particle size distribution, moisture content, flow properties), processing options, and process parameters.

To assess the critical attributes of raw materials, solvents, active pharmaceutical ingredient (API) starting materials, APIs, excipients, or packaging materials.

To establish appropriate specifications, identify critical process parameters, and establish manufacturing controls (e.g., using information from pharmaceutical development studies regarding the clinical significance of quality attributes and the ability to control them during processing).

To decrease variability of quality attributes:

- Reduce product and material defects and
- Reduce manufacturing defects

To assess the need for additional studies (e.g., bioequivalence, stability) relating to scale up and technology transfer.

To make use of the "design space" concept (see ICH Q8).

II.4 Quality Risk Management for Facilities, Equipment, and Utilities

Design of Facility/Equipment

To determine appropriate zones when designing buildings and facilities, for example,

- Flow of material and personnel
- Minimize contamination
- Pest control measures
- Prevention of mix-ups
- Open vs. closed equipment
- Clean rooms vs. isolator technologies
- Dedicated or segregated facilities/equipment

To determine appropriate product contact materials for equipment and containers (e.g., selection of stainless-steel grade, gaskets, lubricants).

To determine appropriate utilities [e.g., steam, gases, power source, compressed air, HVAC (heating, ventilation, and air conditioning), water].

To determine appropriate preventive maintenance for associated equipment (e.g., inventory of necessary spare parts).

Hygiene Aspects in Facilities

To protect the product from environmental hazards, including chemical, microbiological, and physical hazards (e.g., determining appropriate clothing and gowning, hygiene concerns).

To protect the environment (e.g., personnel, potential for cross-contamination) from hazards related to the product being manufactured.

Qualification of Facility/Equipment/Utilities

To determine the scope and extent of qualification of facilities, buildings, and production equipment and/or laboratory instruments (including proper calibration methods).

Cleaning of Equipment and Environmental Control

To differentiate efforts and decisions based on the intended use (e.g., multi- vs. single-purpose, batch vs. continuous production).

To determine acceptable (specified) cleaning validation limits.

Calibration/Preventive Maintenance

To set appropriate calibration and maintenance schedules.

Computer Systems and Computer-Controlled Equipment

To select the design of computer hardware and software (e.g., modular, structured, fault tolerance).

To determine the extent of validation, for example,

- Identification of critical performance parameters
- Selection of the requirements and design
- Code review
- The extent of testing and test methods and
- Reliability of electronic records and signatures

II.5. Quality Risk Management as Part of Materials Management

Assessment and Evaluation of Suppliers and Contract Manufacturers

To provide a comprehensive evaluation of suppliers and contract manufacturers (e.g., auditing, supplier quality agreements).

Starting Material

To assess differences and possible quality risks associated with variability in starting materials (e.g., age, route of synthesis).

Use of Materials

To determine whether it is appropriate to use material under quarantine (e.g., for further internal processing).

To determine appropriateness of reprocessing, reworking, use of returned goods.

Storage, Logistics, and Distribution Conditions

To assess the adequacy of arrangements to ensure maintenance of appropriate storage and transport conditions (e.g., temperature, humidity, container design).

To determine the effect on product quality of discrepancies in storage or transport conditions (e.g., cold chain management) in conjunction with other ICH guidelines.

To maintain infrastructure (e.g., capacity to ensure proper shipping conditions, interim storage, handling of hazardous materials and controlled substances, customs clearance).

To provide information for ensuring the availability of pharmaceuticals (e.g., ranking risks to the supply chain).

II.6. Quality Risk Management as Part of Production

Validation

To identify the scope and extent of verification, qualification, and validation activities (e.g., analytical methods, processes, equipment, and cleaning methods).

To determine the extent for follow-up activities (e.g., sampling, monitoring, and revalidation).

To distinguish between critical and noncritical process steps to facilitate design of a validation study.

In-Process Sampling and Testing

To evaluate the frequency and extent of in-process control testing (e.g., to justify reduced testing under conditions of proven control).

To evaluate and justify the use of PAT in conjunction with parametric and real-time release.

Production Planning

To determine appropriate production planning (e.g., dedicated, campaign, and concurrent production process sequences).

II.7. Quality Risk Management as Part of Laboratory Control and Stability Studies

Out of Specification Results

To identify potential root causes and corrective actions during the investigation of out of specification results.

Retest Period/Expiration Date

To evaluate adequacy of storage and testing of intermediates, excipients, and starting materials.

II.8. Quality Risk Management as Part of Packaging and Labeling

Design of Packages

To design the secondary package for the protection of primary packaged product (e.g., to ensure product authenticity, label legibility).

Selection of Container Closure System

To determine the critical parameters of the container closure system.

Label Controls

To design label control procedures based on the potential for mix-ups involving different product labels, including different versions of the same label.

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3 Pharmaceutical Quality System

I. PHARMACEUTICAL QUALITY SYSTEM

A. Introduction

This document establishes a new ICH tripartite guideline describing a model for an effective *quality* management system for the pharmaceutical industry, referred to as the *Pharmaceutical Quality System*. Throughout this guideline, the term "pharmaceutical quality system" refers to the ICH Q10 model.

ICH Q10 describes one comprehensive model for an effective pharmaceutical quality system that is based on International Standards Organization (ISO) quality concepts, includes applicable Good Manufacturing Practice (GMP) regulations, and complements ICH Q8 "Pharmaceutical Development" and ICH Q9 "Quality Risk Management." ICH Q10 is a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product lifecycle. Much of the content of ICH Q10 applicable to manufacturing sites is currently specified by regional GMP requirements. ICH Q10 is not intended to create any new expectations beyond current regulatory requirements. Consequently, the content of ICH Q10 that is additional to current regional GMP requirements is optional.

ICH Q10 demonstrates industry and regulatory authorities' support of an effective pharmaceutical quality system to enhance the quality and availability of medicines around the world in the interest of public health. Implementation of ICH Q10 throughout the product lifecycle should facilitate *innovation* and *continual improvement* and strengthen the link between pharmaceutical development and manufacturing activities.

B. Scope

This guideline applies to the systems supporting the development and manufacture of pharmaceutical drug substances (i.e., API) and drug products, including biotechnology and biological products, throughout the product lifecycle.

The elements of ICH Q10 should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognizing the differences among and the different goals of each stage (see Section 3).

For the purposes of this guideline, the product lifecycle includes the following technical activities for new and existing products:

- Pharmaceutical development:
  - Drug substance development
  - Formulation development (including container/closure system)
  - Manufacture of investigational products
  - Delivery system development (where relevant)
  - Manufacturing process development and scale-up
  - Analytical method development
- Technology transfer:
  - New product transfers during development through manufacturing
  - Transfers within or between manufacturing and testing sites for marketed products
- Commercial manufacturing:
  - Acquisition and control of materials
  - Provision of facilities, utilities, and equipment
  - Production (including packaging and labeling)
  - Quality control and assurance
  - Release
  - Storage
  - Distribution (excluding wholesaler activities)
- Product discontinuation:
  - Retention of documentation
  - Sample retention
  - Continued product assessment and reporting

C. Relationship of ICH Q10 to Regional GMP Requirements, ISO Standards, and ICH Q7

Regional GMP requirements, the ICH Q7 Guideline, "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients," and ISO quality management system guidelines form the foundation for ICH Q10. To meet the objectives described below, ICH Q10 augments GMPs by describing specific quality system elements and management responsibilities. ICH Q10 provides a harmonized model for a pharmaceutical quality system throughout the lifecycle of a product and is intended to be used together with regional GMP requirements.

The regional GMPs do not explicitly address all stages of the product lifecycle (e.g., development). The quality system elements and management responsibilities described in this guideline are intended to encourage the use of science- and risk-based approaches at each lifecycle stage, thereby promoting continual improvement across the entire product lifecycle.

D. Relationship of ICH Q10 to Regulatory Approaches

Regulatory approaches for a specific product or manufacturing facility should be commensurate with the level of product and process understanding, the results of *quality risk management*, and the effectiveness of the pharmaceutical quality system. When implemented, the effectiveness of the

pharmaceutical quality system can normally be evaluated during a regulatory inspection at the manufacturing site. Potential opportunities to enhance science- and risk-based regulatory approaches are identified in Annex 1. Regulatory processes will be determined by region.

E. ICH Q10 Objectives

Implementation of the Q10 model should result in achievement of three main objectives, which complement or enhance regional GMP requirements.

1. Achieve Product Realization

To establish, implement, and maintain a system that allows the delivery of products with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities (including compliance with approved regulatory filings), and other internal and external customers.

2. Establish and Maintain a State of Control

To develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and *capability of processes*. Quality risk management can be useful in identifying the monitoring and control systems.

3. Facilitate Continual Improvement

To identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations, and pharmaceutical quality system enhancements, thereby increasing the ability to fulfil quality needs consistently. Quality risk management can be useful for identifying and prioritizing areas for continual improvement.

F. Enablers: Knowledge Management and Quality Risk Management

Use of *knowledge management* and quality risk management will enable a company to implement ICH Q10 effectively and successfully. These enablers will facilitate achievement of the objectives described in section IE above by providing the means for science- and risk-based decisions related to product quality.

1. Knowledge Management

Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation. For example, development activities using scientific approaches provide knowledge for product and process understanding. Knowledge management is a systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes, and components. Sources of knowledge include, but are not limited to, prior knowledge (public domain or internally documented), pharmaceutical development studies, technology transfer activities, process validation studies over the product lifecycle, manufacturing experience, innovation, continual improvement, and *change management* activities.

2. Quality Risk Management

Quality risk management is integral to an effective pharmaceutical quality system. It can provide a proactive approach to identifying, scientifically evaluating, and controlling potential risks to quality. It facilitates continual improvement of process performance and product quality throughout the product lifecycle. ICH Q9 provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality.

G. Design and Content Considerations

(a) The design, organization, and documentation of the pharmaceutical quality system should be well structured and clear to facilitate common understanding and consistent application.

(b) The elements of ICH Q10 should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognizing the different goals and knowledge available for each stage.

(c) The size and complexity of the company's activities should be taken into consideration when developing a new pharmaceutical quality system or modifying an existing one. The design of the pharmaceutical quality system should incorporate appropriate risk management principles. While some aspects of the pharmaceutical quality system can be company-wide and others site-specific, the effectiveness of the pharmaceutical quality system is normally demonstrated at the site level.

(d) The pharmaceutical quality system should include appropriate processes, resources, and responsibilities to provide assurance of the quality of *outsourced activities* and purchased materials.

(e) Management responsibilities, as described in Section 2, should be identified within the pharmaceutical quality system.

(f) The pharmaceutical quality system should include the following elements, as described in Section 3: Process performance and product quality monitoring, *corrective* and *preventive action*, change management, and management review.

(g) *Performance indicators*, as described in Section 4, should be identified and used to monitor the effectiveness of processes within the pharmaceutical quality system.

H. Quality Manual

A *Quality Manual* or equivalent documentation approach should be established and should contain the description of the pharmaceutical quality system. The description should include

(a) The *quality policy* (see Section 2).
(b) The scope of the pharmaceutical quality system.
(c) Identification of the pharmaceutical quality system processes, as well as their sequences, linkages, and interdependencies. Process maps and flow charts can be useful tools to facilitate depicting pharmaceutical quality system processes in a visual manner.
(d) Management responsibilities within the pharmaceutical quality system (see Section 2).

II. MANAGEMENT RESPONSIBILITY

Leadership is essential to establish and maintain a company-wide commitment to quality and for the performance of the pharmaceutical quality system.

A. Management Commitment

(a) *Senior management* has the ultimate responsibility to ensure an effective pharmaceutical quality system is in place to achieve the *quality objectives* and that roles, responsibilities, and authorities are defined, communicated, and implemented throughout the company.
(b) Management should
    (1) Participate in the design, implementation, monitoring, and maintenance of an effective pharmaceutical quality system.
    (2) Demonstrate strong and visible support for the pharmaceutical quality system and ensure its implementation throughout their organization.
    (3) Ensure a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management.
    (4) Define individual and collective roles, responsibilities, authorities, and interrelationships of all organizational units related to the pharmaceutical quality system. Ensure these interactions are communicated and understood at all levels of the organization. An independent quality unit/structure with authority to fulfil certain pharmaceutical quality system responsibilities is required by regional regulations.
    (5) Conduct management reviews of process performance and product quality and of the pharmaceutical quality system.
    (6) Advocate continual improvement.
    (7) Commit appropriate resources.

B. Quality Policy

(a) Senior management should establish a quality policy that describes the overall intentions and direction of the company related to quality.
(b) The quality policy should include an expectation to comply with applicable regulatory requirements and should facilitate continual improvement of the pharmaceutical quality system.
(c) The quality policy should be communicated to and understood by personnel at all levels in the company.
(d) The quality policy should be reviewed periodically for continuing effectiveness.

C. Quality Planning

(a) Senior management should ensure the quality objectives needed to implement the quality policy are defined and communicated.
(b) Quality objectives should be supported by all relevant levels of the company.
(c) Quality objectives should align with the company's strategies and be consistent with the quality policy.
(d) Management should provide the appropriate resources and training to achieve the quality objectives.
(e) Performance indicators that measure progress against quality objectives should be established, monitored, communicated regularly, and acted upon as appropriate as described in Section 4.1 of this document.

D. Resource Management

(a) Management should determine and provide adequate and appropriate resources (human, financial, materials, facilities, and equipment) to implement and maintain the pharmaceutical quality system and continually improve its effectiveness.
(b) Management should ensure that resources are appropriately applied to a specific product, process, or site.

E. Internal Communication

(a) Management should ensure appropriate communication processes are established and implemented within the organization.
(b) Communications processes should ensure the flow of appropriate information between all levels of the company.
(c) Communication processes should ensure the appropriate and timely escalation of certain product quality and pharmaceutical quality system issues.

F. Management Review

(a) Senior management should be responsible for pharmaceutical quality system governance through management review to ensure its continuing suitability and effectiveness.
(b) Management should assess the conclusions of periodic reviews of process performance and product quality and of the pharmaceutical quality system, as described in Sections 3 and 4.

G. Management of Outsourced Activities and Purchased Materials

The pharmaceutical quality system, including the management responsibilities described in this section, extends to the control and review of any outsourced activities and quality of purchased materials. The pharmaceutical company is ultimately responsible to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials. These processes should incorporate quality risk management and include

(a) Assessing, prior to outsourcing operations or selecting material suppliers, the suitability and competence of the other party to carry out the activity or provide the material using a defined supply chain (e.g., audits, material evaluations, qualification).
(b) Defining the responsibilities and communication processes for quality-related activities of the involved parties. For outsourced activities, this should be included in a written agreement between the contract giver and contract acceptor.
(c) Monitoring and review of the performance of the contract acceptor or the quality of the material from the provider and the identification and implementation of any needed improvements.
(d) Monitoring incoming ingredients and materials to ensure they are from approved sources using the agreed supply chain.

H. Management of Change in Product Ownership

When product ownership changes (e.g., through acquisitions), management should consider the complexity of this and ensure:

(a) The ongoing responsibilities are defined for each company involved.
(b) The necessary information is transferred.

III. CONTINUAL IMPROVEMENT OF PROCESS PERFORMANCE AND PRODUCT QUALITY

This section describes the lifecycle stage goals and the four specific pharmaceutical quality system elements that augment regional requirements to achieve the ICH Q10 objectives, as defined in section IE. It does not restate all regional GMP requirements.

A. Lifecycle Stage Goals

The goals of each product lifecycle stage are described below.

1. Pharmaceutical Development

The goal of pharmaceutical development activities is to design a product and its manufacturing process to consistently deliver the intended performance and meet the needs of patients and health care professionals, and regulatory authorities' and internal customers' requirements. Approaches to pharmaceutical development are described in ICH Q8. The results of exploratory and clinical development studies, while outside the scope of this guidance, are inputs to pharmaceutical development.

2. Technology Transfer

The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing and within or between manufacturing sites to achieve product realization. This knowledge forms the basis for the manufacturing process, *control strategy*, process validation approach, and ongoing continual improvement.

3. Commercial Manufacturing

The goals of manufacturing activities include achieving product realization, establishing and maintaining a state of control, and facilitating continual improvement. The pharmaceutical quality system should assure that the desired product quality is routinely met, suitable process performance is achieved, the set of controls is appropriate, improvement opportunities are identified and evaluated, and the body of knowledge is continually expanded.

4. Product Discontinuation

The goal of product discontinuation activities is to manage the terminal stage of the product lifecycle effectively. For product discontinuation, a predefined approach should be used to manage activities such as retention of documentation and samples and continued product assessment (e.g., complaint handling and stability) and reporting in accordance with regulatory requirements.

B. Pharmaceutical Quality System Elements

The elements described below might be required in part under regional GMP regulations. However, the Q10 model's intent is to enhance these elements in order to promote the lifecycle approach to product quality. These four elements are:

- Process performance and product quality monitoring system
- Corrective action *and* preventive action *(CAPA) system*
- Change management system
- Management review of process performance and product quality

These elements should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognizing the differences among, and the different goals of, each stage. Throughout the product lifecycle, companies are encouraged to evaluate opportunities for innovative approaches to improve product quality.

Each element is followed by a table of example applications of the element to the stages of the pharmaceutical lifecycle.

1. Process Performance and Product Quality Monitoring System

Pharmaceutical companies should plan and execute a system for the monitoring of process performance and product quality to ensure a state of control is maintained. An effective monitoring system provides assurance of the continued capability of processes and controls to produce a product of desired quality and to identify areas for continual improvement. The process performance and product quality monitoring system should (Table 3.1):

(a) Use quality risk management to establish the control strategy. This can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. The control strategy should facilitate timely *feedback/feedforward* and appropriate corrective action and preventive action.
(b) Provide the tools for measurement and analysis of parameters and attributes identified in the control strategy (e.g., data management and statistical tools).
(c) Analyze parameters and attributes identified in the control strategy to verify continued operation within a state of control.
(d) Identify sources of variation affecting process performance and product quality for potential continual improvement activities to reduce or control variation.
(e) Include feedback on product quality from both internal and external sources, for example, complaints, product rejections, nonconformances, recalls, deviations, audits and regulatory inspections, and findings.
(f) Provide knowledge to enhance process understanding, enrich the *design space* (where established), and enable innovative approaches to process validation.

2. Corrective Action and Preventive Action System

The pharmaceutical company should have a system for implementing corrective actions and preventive actions resulting from the investigation of complaints, product rejections, nonconformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance, and product quality monitoring. A structured approach to the investigation process should be used with the objective of determining the root cause. The level of effort, formality, and documentation of the investigation should be commensurate with the level of risk, in line with ICH Q9. CAPA methodology should result in product and process improvements and enhanced product and process understanding (Table 3.2).

3. Change Management System

Innovation, continual improvement, the outputs of process performance, and product quality monitoring and CAPA drive change. In order to evaluate, approve, and implement these changes properly, a company should have an effective change management system. There is generally a difference in formality of change management processes prior to the initial regulatory submission and after submission, where changes to the regulatory filing might be required under regional requirements (Table 3.3).

The change management system ensures continual improvement is undertaken in a timely and effective manner.

TABLE 3.1
Application of Process Performance and Product Quality Monitoring System throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Process and product knowledge generated and process and product monitoring conducted throughout development can be used to establish a control strategy for manufacturing.	Monitoring during scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Knowledge obtained during transfer and scale-up activities can be useful in further developing the control strategy.	A well-defined system for process performance and product quality monitoring should be applied to assure performance within a state of control and to identify improvement areas.	Once manufacturing ceases, monitoring such as stability testing should continue to completion of the studies. Appropriate action on marketed product should continue to be executed according to regional regulations.

TABLE 3.2
Application of Corrective Action and Preventive Action System throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Product or process variability is explored. CAPA methodology is useful where corrective actions and preventive actions are incorporated into the iterative design and development process.	CAPA can be used as an effective system for feedback, feedforward, and continual improvement.	CAPA should be used, and the effectiveness of the actions should be evaluated.	CAPA should continue after the product is discontinued. The impact on product remaining on the market should be considered as well as other products, which might be impacted.

TABLE 3.3
Application of Change Management System throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Change is an inherent part of the development process and should be documented; the formality of the change management process should be consistent with the stage of pharmaceutical development.	The change management system should provide management and documentation of adjustments made to the process during technology transfer activities.	A formal change management system should be in place for commercial manufacturing. Oversight by the quality unit should provide assurance of appropriate science- and risk-based assessments.	Any changes after product discontinuation should go through an appropriate change management system.

It should provide a high degree of assurance that there are no unintended consequences of the change.

The change management system should include the following, as appropriate for the stage of the lifecycle:

(a) Quality risk management should be utilized to evaluate proposed changes. The level of effort and formality of the evaluation should be commensurate with the level of risk.
(b) Proposed changes should be evaluated relative to the marketing authorization, including design space, where established, and/or current product and process understanding. There should be an assessment to determine whether a change to the regulatory filing is required under regional requirements. As stated in ICH Q8, working within the design space is not considered a change (from a regulatory filing perspective). However, from a pharmaceutical quality system standpoint, all changes should be evaluated by a company's change management system.
(c) Proposed changes should be evaluated by expert teams contributing the appropriate expertise and knowledge from relevant areas (e.g., Pharmaceutical Development, Manufacturing, Quality, Regulatory Affairs, and Medical), to ensure the change is technically justified. Prospective evaluation criteria for a proposed change should be set.
(d) After implementation, an evaluation of the change should be undertaken to confirm the change objectives were achieved and that there was no deleterious impact on product quality.

4. Management Review of Process Performance and Product Quality

Management review should provide assurance that process performance and product quality are managed over the lifecycle. Depending on the size and complexity of the company, management review can be a series of reviews at various levels of management and should include a timely and effective communication and escalation process to raise appropriate quality issues to senior levels of management for review (Table 3.4).

(a) The management review system should include
  (1) The results of regulatory inspections and findings, audits and other assessments, and commitments made to regulatory authorities.
  (2) Periodic quality reviews, that can include
    (i) Measures of customer satisfaction such as product quality complaints and recalls
    (ii) Conclusions of process performance and product quality monitoring and
    (iii) The effectiveness of process and product changes including those arising from corrective action and preventive actions
  (3) Any follow-up actions from previous management reviews.
(b) The management review system should identify appropriate actions, such as:

TABLE 3.4
Application of Management Review of Process Performance and Product Quality throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Aspects of management review can be performed to ensure adequacy of the product and process design.	Aspects of management review should be performed to ensure the developed product and process can be manufactured at commercial scale.	Management review should be a structured system, as described above, and should support continual improvement.	Management review should include such items as product stability and product quality complaints.

(1) Improvements to manufacturing processes and products
(2) Provision, training, and/or realignment of resources
(3) Capture and dissemination of knowledge

IV. CONTINUAL IMPROVEMENT OF THE PHARMACEUTICAL QUALITY SYSTEM

This section describes activities that should be conducted to manage and continually improve the pharmaceutical quality system.

A. Management Review of the Pharmaceutical Quality System

Management should have a formal process for reviewing the pharmaceutical quality system on a periodic basis. The review should include

(a) Measurement of achievement of pharmaceutical quality system objectives
(b) Assessment of performance indicators that can be used to monitor the effectiveness of processes within the pharmaceutical quality system, such as:
  (1) Complaint, deviation, CAPA, and change management processes
  (2) Feedback on outsourced activities
  (3) Self-assessment processes including risk assessments, trending, and audits
  (4) External assessments such as regulatory inspections and findings and customer audits

B. Monitoring of Internal and External Factors Impacting the Pharmaceutical Quality System

Factors monitored by management can include

(a) Emerging regulations, guidance, and quality issues that can impact the pharmaceutical quality system
(b) Innovations that might enhance the pharmaceutical quality system
(c) Changes in business environment and objectives
(d) Changes in product ownership

C. Outcomes of Management Review and Monitoring

The outcome of management review of the pharmaceutical quality system and monitoring of internal and external factors can include

(a) Improvements to the pharmaceutical quality system and related processes
(b) Allocation or reallocation of resources and/or personnel training
(c) Revisions to quality policy and quality objectives
(d) Documentation and timely and effective communication of the results of the management review and actions, including escalation of appropriate issues to senior management

GLOSSARY

ICH and ISO definitions are used in ICH Q10 where they exist. For the purpose of ICH Q10, where the words "requirement," "requirements," or "necessary" appear in an ISO definition, they do not necessarily reflect a regulatory requirement. The source of the definition is identified in parentheses after the definition. Where no appropriate ICH or ISO definition was available, an ICH Q10 definition was developed.

Capability of a Process: Ability of a process to realize a product that will fulfil the requirements of that product. The concept of process capability can also be defined in statistical terms. (ISO 9000:2005)

Change Management: A systematic approach to proposing, evaluating, approving, implementing, and reviewing changes. (ICH Q10)

Continual Improvement: Recurring activity to increase the ability to fulfil requirements. (ISO 9000:2005)

Control Strategy: A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

Corrective Action: Action to eliminate the cause of a detected nonconformity or other undesirable situation. *Note*: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence. (ISO 9000:2005)

Design Space: The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. (ICH Q8)

Enabler: A tool or process which provides the means to achieve an objective. (ICH Q10)

Feedback: The modification or control of a process or system by its results or effects.

Feedforward: The modification or control of a process using its anticipated results or effects. (Oxford Dictionary of English. Oxford University Press; 2003)

Feedback/feedforward can be applied technically in process control strategies and conceptually in quality management. (ICH Q10)

Innovation: The introduction of new technologies or methodologies. (ICH Q10)

Knowledge Management: Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes, and components. (ICH Q10)

Outsourced Activities: Activities conducted by a contract acceptor under a written agreement with a contract giver. (ICH Q10)

Performance Indicators: Measurable values used to quantify quality objectives to reflect the performance of an organization, process, or system, also known as "performance metrics" in some regions. (ICH Q10)

Pharmaceutical Quality System (PQS): Management system to direct and control a pharmaceutical company with regard to quality. (ICH Q10 based upon ISO 9000:2005)

Preventive Action: Action to eliminate the cause of a potential nonconformity or other undesirable potential situation. *Note*: Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence. (ISO 9000:2005)

Product Realization: Achievement of a product with the quality attributes appropriate to meet the needs of patients, health care professionals, and regulatory authorities (including compliance with marketing authorization) and internal customers' requirements. (ICH Q10)

Quality: The degree to which a set of inherent properties of a product, system, or process fulfils requirements. (ICH Q9)

Quality Manual: Document specifying the quality management system of an organization. (ISO 9000:2005)

Quality Objectives: A means to translate the quality policy and strategies into measurable activities. (ICH Q10)

Quality Planning: Part of quality management focused on setting quality objectives and specifying necessary operational processes and related resources to fulfil the quality objectives. (ISO 9000:2005)

Quality Policy: Overall intentions and direction of an organization related to quality as formally expressed by senior management. (ISO 9000:2005)

Quality Risk Management: A systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle. (ICH Q9)

Senior Management: Person(s) who direct and control a company or site at the highest levels with the authority and responsibility to mobilize resources within the company or site. (ICH Q10 based in part on ISO 9000:2005)

State of Control: A condition in which the set of controls consistently provides assurance of continued process performance and product quality. (ICH Q10)

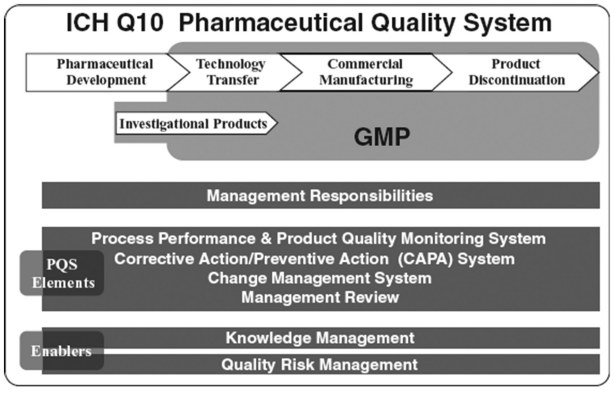
ANNEX 1

Potential Opportunities to Enhance Science- and Risk-Based Regulatory Approaches[a]

Scenario	Potential Opportunity
1. Comply with GMPs	Compliance-status quo
2. Demonstrate effective pharmaceutical quality system, including effective use of quality risk management principles (e.g., ICH Q9 and ICH Q10)	Opportunity to • Increase use of risk-based approaches for regulatory inspections Opportunity to • Facilitate science-based pharmaceutical quality assessment • Enable innovative approaches to process validation and • Establish real-time release mechanisms
3. Demonstrate product and process understanding, including effective use of quality risk management principles (e.g., ICH Q8 and ICH Q9)	
4. Demonstrate effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles (e.g., ICH Q8, ICH Q9, and ICH Q10)	Opportunity to • Increase use of risk-based approaches for regulatory inspections • Facilitate science-based pharmaceutical quality assessment • Optimize science- and risk-based post-approval change processes to maximize benefits from innovation and continual improvement • Enable innovative approaches to process validation and • Establish real-time release mechanisms

[a] Note*:* This annex reflects potential opportunities to enhance regulatory approaches. The actual regulatory process will be determined by region.

ANNEX 2



This diagram illustrates the major features of the ICH Q10 pharmaceutical quality system (PQS) model. The PQS covers the entire lifecycle of a product including pharmaceutical development, technology transfer, commercial manufacturing, and product discontinuation as illustrated by the upper portion of the diagram. The PQS augments regional GMPs

as illustrated in the diagram. The diagram also illustrates that regional GMPs apply to the manufacture of investigational products.

The next horizontal bar illustrates the importance of management responsibilities explained in Section 2 to all stages of the product lifecycle. The following horizontal bar lists the PQS elements, which serve as the major pillars under the PQS model. These elements should be applied appropriately and proportionally to each lifecycle stage recognizing opportunities to identify areas for continual improvement.

The bottom set of horizontal bars illustrates the enablers: Knowledge management and quality risk management, which are applicable throughout the lifecycle stages. These enablers support the PQS goals of achieving product realization, establishing and maintaining a state of control, and facilitating continual improvement.

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4 Pharmaceutical Development

I. INTRODUCTION

Where a company chooses to apply quality by design and quality risk management (ICH Q9, Quality Risk Management), linked to an appropriate pharmaceutical quality system, then opportunities arise to enhance science- and risk-based regulatory approaches, which is the subject of this chapter.

A. Approaches to Pharmaceutical Development

In all cases, the product should be designed to meet patients' needs and the intended product performance. Strategies for product development vary from company to company and from product to product. The approach to, and extent of, development can also vary and should be outlined in the submission. An applicant might choose either an empirical approach or a more systematic approach to product development. An illustration of the potential contrasts of these approaches is shown in Appendix 1. A more systematic approach to development (also defined as quality by design) can include, for example, incorporation of prior knowledge, results of studies using design of experiments, use of quality risk management, and use of knowledge management (see ICH Q10) throughout the lifecycle of the product. Such a systematic approach can enhance the process to achieve quality and help the regulators to better understand a company's strategy. Product and process understanding can be updated with the knowledge gained over the product lifecycle.

A greater understanding of the product and its manufacturing process can create a basis for more flexible regulatory approaches. The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided in the registration application. It is the knowledge gained and submitted to the authorities, and not the volume of data collected, that forms the basis for science- and risk-based submissions and regulatory evaluations. Nevertheless, appropriate data demonstrating that this knowledge is based on sound scientific principles should be presented with each application.

Pharmaceutical development should include, at a minimum, the following elements:

- Defining the target product profile as it relates to quality, safety, and efficacy, considering for example, the route of administration, dosage form, bioavailability, dosage, and stability
- Identifying critical quality attributes (CQAs) of the drug product, so that those product characteristics having an impact on product quality can be studied and controlled
- Determining the quality attributes of the drug substance, excipients etc., and selecting the type and amount of excipients to deliver drug product of the desired quality
- Selecting an appropriate manufacturing process
- Identifying a control strategy

An enhanced, quality by design approach to product development would additionally include the following elements:

- A systematic evaluation, understanding, and refining of the formulation and manufacturing process, including
  - Identifying, through, for example, prior knowledge, experimentation, and risk assessment, the material attributes and process parameters that can have an effect on product CQAs.
  - Determining the functional relationships that link material attributes and process parameters to product CQAs
- Using the enhanced process understanding in combination with quality risk management to establish an appropriate control strategy, which can, for example, include a proposal for design space(s) and/or real-time release.

As a result, this more systematic approach could facilitate continual improvement and innovation throughout the product lifecycle (see ICH Q10 Pharmaceutical Quality System).

II. ELEMENTS OF PHARMACEUTICAL DEVELOPMENT

The section that follows elaborates, by means of description and example, possible approaches to gaining a more systematic, enhanced understanding of the product and process under development. The examples given are purely illustrative and are not intended to create new regulatory requirements.

A. Target Product Profile

A target product profile is a prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, and hence the safety and efficacy, of a drug product is realized. The target product profile forms the basis of design for the development of the product.

Considerations for the target product profile should include

- Dosage form and route of administration
- Dosage form strength(s)
- Therapeutic moiety release or delivery and pharmacokinetic characteristics (e.g., dissolution; aerodynamic performance) appropriate to the drug product dosage form being developed
- Drug product quality criteria (e.g., sterility, purity) appropriate for the intended marketed product

B. Critical Quality Attributes

A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates, and drug product.

Drug product CQAs include the properties that impart the desired quality, safety, and efficacy. CQAs of solid oral dosage forms are typically those aspects affecting product purity, potency, stability, and drug release. CQAs for other delivery systems can additionally include more product-specific aspects, such as aerodynamic properties for inhaled products, sterility for parenterals, and adhesive force for transdermal patches. For drug substances or intermediates, the CQAs can additionally include those properties (e.g., particle size distribution, bulk density) that affect downstream processability.

Drug product CQAs are used to guide the product and process development. Potential drug product CQAs can be identified from the target product profile and/or prior knowledge. The list of potential CQAs can be modified when the formulation and manufacturing process are selected and as product knowledge and process understanding increase. Quality risk management can be used to prioritize the list of potential CQAs for subsequent evaluation. Relevant CQAs can be identified by an iterative process of quality risk management and experimentation that assesses the extent to which their variation can have an impact on the quality of the drug product.

C. Linking Material Attributes and Process Parameters to CQAs—Risk Assessment

Risk assessment is a valuable science-based process used in quality risk management (see ICH Q9) that can aid in identifying which material attributes and process parameters have an effect on product CQAs. While the risk assessment is typically performed early in the pharmaceutical development, it can be helpful to repeat the risk assessment as information and greater knowledge become available.

Risk assessment tools can be used to identify and rank parameters (e.g., operational, equipment, input material) with potential to have an impact on product quality based on prior knowledge and initial experimental data. For an illustrative example, see Appendix 2. The initial list of potential parameters can be quite extensive but is likely to be narrowed as process understanding is increased. The list can be refined further through experimentation to determine the significance of individual variables and potential interactions. Once the significant parameters are identified, they can be further studied (e.g., through a combination of design of experiments, mathematical models, or studies that lead to mechanistic understanding) to achieve a higher level of process understanding.

D. Design Space

The linkage between the process inputs (input variables and process parameters) and the critical quality attributes can be described in the design space.

1. Selection of Variables

The risk assessment and process development experiments described in Section 2.3 can not only lead to an understanding of the linkage and effect of process inputs on product CQAs but also help identify the variables and their ranges within which consistent quality can be achieved. These input variables can thus be selected for inclusion in the design space.

An explanation should be provided in the application to describe what variables were considered, how they affect the process and product quality, and which parameters were included or excluded in the design space. An input variable or process parameter need not be included in the design space if it has no effect on delivering CQAs when the input variable or parameter is varied over the full potential range of operation. The control of these variables would be under GMP. However, the knowledge gained from studies should be described in the submission.

2. Defining and Describing a Design Space in a Submission

A design space can be defined in terms of ranges of input variables or parameters or through more complex mathematical relationships. It is possible to define a design space as a time-dependent function (e.g., temperature and pressure cycle of a lyophilization cycle) or as a combination of variables such as principal components of a multivariate model. Scaling factors can also be included if the design space is intended to span multiple operational scales. Analysis of historical data can provide the basis for establishing a design space. Regardless of how a design space is developed, it is expected that operation within the design space will result in a product meeting the defined quality attributes.

Examples of different potential approaches to presentation of a design space are presented in Appendix 2.

3. Unit Operation Design Space(s)

The applicant can choose to establish independent design spaces for one or more unit operations or to establish a single design space that spans multiple operations. While a separate design space for each unit operation is often simpler to develop, a design space that spans the entire process can provide more operational flexibility. For example, in the case of a drug product that undergoes degradation in solution before lyophilization, the design space to control the extent of degradation (e.g., concentration, time, temperature) could be expressed for each unit operation or as a sum over all unit operations.

4. Relationship of Design Space to Scale and Equipment

When defining a design space, the applicant should keep in mind the type of operational flexibility desired. A design

space can be developed at small scale or pilot scale. The applicant should justify the relevance of a design space developed at small or pilot scale to the proposed production-scale manufacturing process and discuss the potential risks in the scale-up operation.

If the applicant wishes the design space to be applicable to multiple operational scales, the design space should be described in terms of relevant scale-independent parameters. For example, if a product was determined to be shear sensitive in a mixing operation, the design space could include shear rate, rather than agitation rate. Dimensionless numbers and/or models for scaling also can be included as part of the design space description.

The creation of a design space can be helpful for technology transfer or site changes. The subsequent regulatory processes will be region-specific.

5. Design Space vs. Proven Acceptable Ranges

A combination of proven acceptable ranges does not constitute a design space. However, proven acceptable ranges based on univariate experimentation can provide some knowledge about the process.

6. Design Space and Edge of Failure

It can be helpful to know where edges of failure could be or to determine potential failure modes. However, it is not an essential part of establishing a design space.

E. Control Strategy

A control strategy is designed to consistently ensure product quality.

The elements of the control strategy discussed in Section P.2 of the dossier should describe and justify how in-process controls and the controls of input materials (drug substance and excipients), container closure system, intermediates, and end products contribute to the final product quality. These controls should be based on product, formulation, and process understanding and should include, at a minimum, control of the critical parameters and attributes.

A comprehensive pharmaceutical development approach will generate process and formulation understanding that identifies sources of variability. Critical sources of variability that can lead to product failures should be identified, appropriately understood, and managed or controlled. Understanding sources of variability and their impact on downstream processes or processing, intermediate products, and finished product quality can provide flexibility for shifting of controls upstream and minimize the need for end product testing. This process understanding, in combination with quality risk management (see ICH Q9), will support the control of process parameters so that the variability of raw materials can be compensated for in an adaptable process to deliver consistent product quality.

This process understanding enables an alternative, manufacturing paradigm where the variability of input materials might not need to be tightly constrained. Instead, it can be possible to design an adaptive process step (a step that is responsive to the input materials) to ensure consistent product quality.

Enhanced understanding of product performance can justify the use of surrogate tests or support real-time release in lieu of end-product testing. For example, disintegration could serve as a surrogate for dissolution for fast-disintegrating solid forms with highly soluble drug substances. Unit dose uniformity performed in-process [e.g., using weight variation coupled with near infrared (NIR) assay] can enable real-time release and provide an increased level of quality assurance compared to the traditional end-product testing using compendial content uniformity standards.

Elements of a control strategy can include, but are not limited to, the following:

- Control of input material attributes (e.g., drug substance, excipients, primary packaging materials) based on an understanding of their impact on processability or product quality
- Product specification(s)
- Controls for unit operations that have an impact on downstream processing or end-product quality (e.g., the impact of drying on degradation, particle size distribution of the granulate on dissolution)
- In-process or real-time release in lieu of end-product testing
- A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models

A control strategy can include redundant or alternative elements, if justified. For example, one element of the control strategy could rely on end-product testing, whereas an additional or alternative element could depend on real-time release using process analytical technology (PAT). The use of these alternative elements should be described in the submission.

Adoption of the principles in this guideline can support the justification of alternative approaches to the setting of specification attributes and acceptance criteria as described in Q6A and Q6B.

F. Product Lifecycle Management and Continual Improvement

Throughout the product lifecycle, companies have opportunities to evaluate innovative approaches to improve product quality (see ICH Q10).

For example, once approved, a design space provides the applicant flexibility to optimize and adjust a process as managed under their quality system. A design space is not necessarily static in nature and should be periodically reassessed to ensure that the process is working as anticipated to deliver product quality attributes. For certain design spaces using mathematical models (e.g., chemometrics models of NIR)

periodic maintenance could be essential to ensure the models' performance (e.g., checking calibration) or to update the model based upon additional data. Expansion, reduction, or redefinition of the design space could be desired upon gaining additional process information.

III. SUBMISSION OF PHARMACEUTICAL DEVELOPMENT AND RELATED INFORMATION IN CTD FORMATS

Pharmaceutical development information is submitted in Section P.2 of the Common Technical Document (CTD). Other information resulting from pharmaceutical development studies could be accommodated by the CTD format in a number of different ways, and some specific suggestions are provided below. Certain aspects (e.g., product lifecycle management, continual improvement) of this guidance are handled under the applicant's pharmaceutical quality system (see ICH Q10) and need not be submitted in the registration application.

A. Quality Risk Management and Product and Process Development

Quality risk management can be used at many different stages during product and process development and manufacturing implementation. The assessments used to guide and justify development decisions can be included in the relevant sections of P.2. For example, risk analyses and functional relationships linking material attributes to product CQAs can be included in P.2.1, P.2.2, and P.2.3. Risk analyses linking the design of the manufacturing process to product quality can be included in P.2.3.

B. Design Space

As an element of the proposed manufacturing process, the design space(s) can be described in the section of the application that includes the description of the manufacturing process and process controls (P.3.3). If appropriate, additional information can be provided in the section of the application that addresses the controls of critical steps and intermediates (P.3.4). The relationship of the design space(s) to the overall control strategy can be explained in the section of the application that includes the justification of the drug product specification (P.5.6). The product and manufacturing process development sections of the application (P.2.1, P.2.2, and P.2.3) are appropriate places to summarize and describe product and process development studies that provide the basis for the design space(s).

C. Control Strategy

The section of the application that includes the justification of the drug product specification (P.5.6) is a good place to summarize the control strategy. The summary should be clear about the various roles played by different components of the control strategy. However, detailed information about input material controls and process controls should still be provided in the appropriate CTD format sections [e.g., drug substance section (S), control of excipients (P.4), description of manufacturing process and process controls (P.3.3), controls of critical steps and intermediates (P.3.4)].

D. Drug Substance Related Information

If drug substance CQAs have the potential to affect the CQAs or manufacturing process of the drug product, some discussion of drug substance CQAs can be appropriate in the pharmaceutical development section of the application (e.g., P.2.1).

GLOSSARY

Control Strategy: A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (ICH Q10).

Critical Quality Attribute (CQA): A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

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

Edge of Failure: The boundary to a variable or parameter, beyond which the relevant quality attributes or specification cannot be met.

Proven Acceptable Range: A characterized range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria.

Quality by Design: A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Real-time release: The ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data, which typically include a valid combination of assessed material attributes and process controls.

APPENDIX 1: DIFFERING APPROACHES TO PHARMACEUTICAL DEVELOPMENT[A]

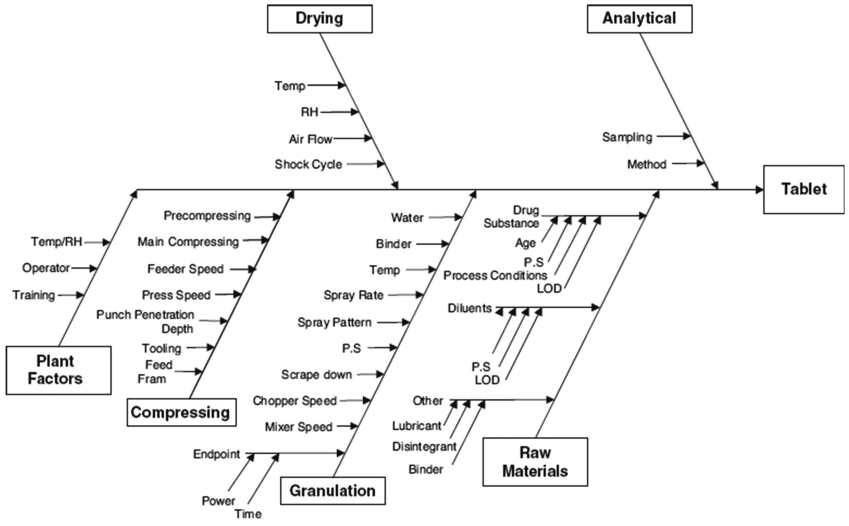
Aspect	Minimal Approach	Enhanced, Quality by Design Approach
Overall pharmaceutical development	• Mainly empirical • Developmental research often conducted one variable at a time	• Systematic, relating mechanistic understanding of input material attributes and process parameters to drug product CQAs • Multivariate experiments to understand product and process • Establishment of design space • PAT tools utilized
Manufacturing process	• Fixed • Validation primarily based on initial full-scale batches • Focus on optimization and reproducibility	• Adjustable within design space • Lifecycle approach to validation and, ideally, continuous process verification • Focus on control strategy and robustness • Use of statistical process control methods
Process controls	• In-process tests primarily for go/no-go decisions • Off-line analysis	• PAT tools utilized with appropriate feedforward and feedback controls • Process operations tracked and trended to support continual improvement efforts post-approval
Product specifications	• Primary means of control • Based on batch data available at time of registration	• Part of the overall quality control strategy • Based on desired product performance with relevant supportive data
Control strategy	• Drug product quality controlled primarily by intermediate and end-product testing	• Drug product quality ensured by risk-based control strategy for well-understood product and process • Quality controls shifted upstream, with the possibility of real-time release or reduced end-product testing
Lifecycle management	• Reactive (i.e., problem solving and corrective action)	• Preventive action • Continual improvement facilitated

[a] Note: This table is intended only to illustrate some potential contrasts between what might be considered a minimal approach and an enhanced approach regarding different aspects of pharmaceutical development and lifecycle management. It is not intended to specifically define the approach. Current practices in the pharmaceutical industry vary and typically lie between these approaches.

APPENDIX 2: ILLUSTRATIVE EXAMPLES

Example of Use of a Risk Assessment Tool

For example, a cross-functional team of experts could work together to develop an Ishikawa (fishbone) diagram that identifies all potential variables which can have an impact on the desired quality attribute. The team could then rank the variables based on probability, severity, and detectability using failure mode effect analysis (FMEA) or similar tools based on prior knowledge and initial experimental data. Design of experiments or other experimental approaches could then be used to evaluate the impact of the higher ranked variables, to gain greater understanding of the process, and to develop a proper control strategy.



Ishikawa Diagram

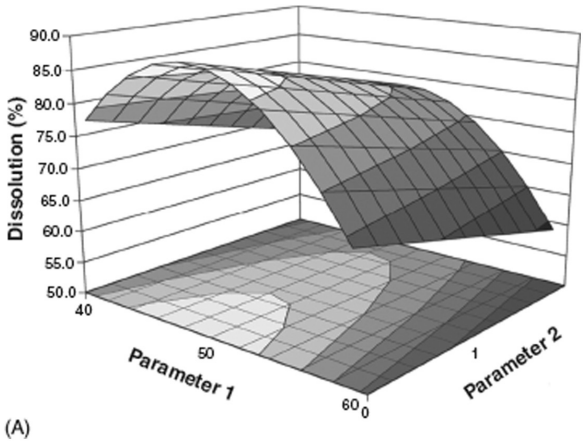
Example of Depiction of Interactions

Figure 4.1 depicts the effect of interactions, or lack thereof, between three process parameters on the level of degradation product Y. The figure shows a series of two-dimensional plots showing the effect of interactions among three process parameters (initial moisture content, temperature, mean particle size) of the drying operation of a granulate (drug product intermediate) on degradation product Y. The relative slopes of the lines or curves within a plot indicate if interaction is present. In this example, initial moisture content and temperature are interacting, but initial moisture content and mean particle size are not, nor are temperature and mean particle size.

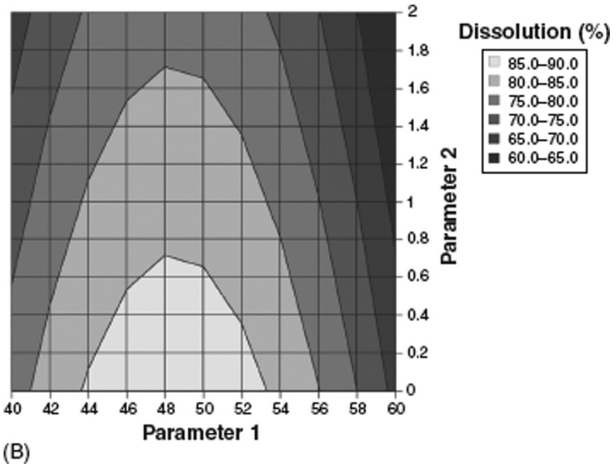
Illustrative Examples of Presentation of Design Space

Where multiple parameters are involved, the design space can be presented for two parameters, in a manner similar to the examples shown above, at different values (e.g., high, middle, low) within the range of the third parameter, the fourth parameter, and so on. A stacked plot of these design spaces can be considered, if appropriate (see Figures 4.1, 4.2 and 4.3).

- Parameter 1 has a range of 41 to 56.
- Parameter 2 has a lower limit of 0 and an upper limit that is a function of parameter.
- Parameter 1 has a range of 44 to 53.
- Parameter 2 has a range of 0 to 1.1.



(A)



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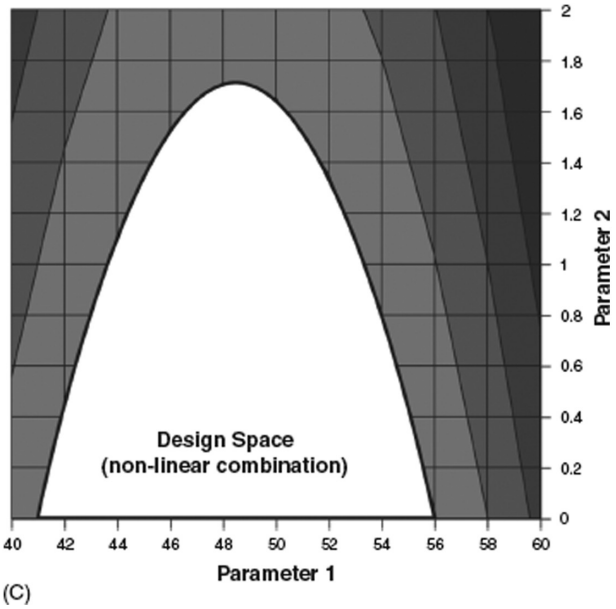
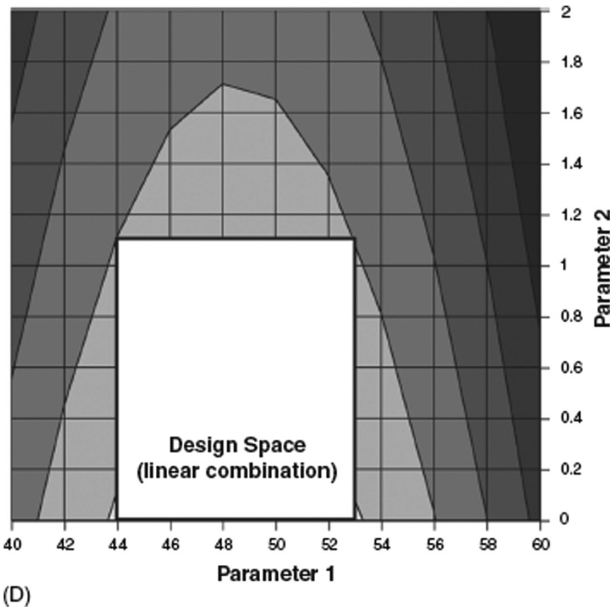


(C)



(D)

FIGURE 4.1 Design space described with the aid of response surface plot (A) or contour plot (B) and defined by nonlinear (C) or linear combination (D) of process parameter ranges. In this example, the effects of the two parameters are additive, but the two parameters do not interact. (A) Response surface plot of dissolution as a function of two parameters of a granulation operation. Dissolution above 80% is desired. (B) Contour plot of dissolution from Example 1A. (C) Design space for granulation parameters, defined by a nonlinear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%). In this example, the design space can be optionally expressed by equations that describe the boundaries, that is. (D) Design space for granulation parameters, defined by a linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%). This design space is a subset of the nonlinear design space from Example 1C and can be optionally expressed as shown in Figure 4.2.

FIGURE 4.1 (Continued)

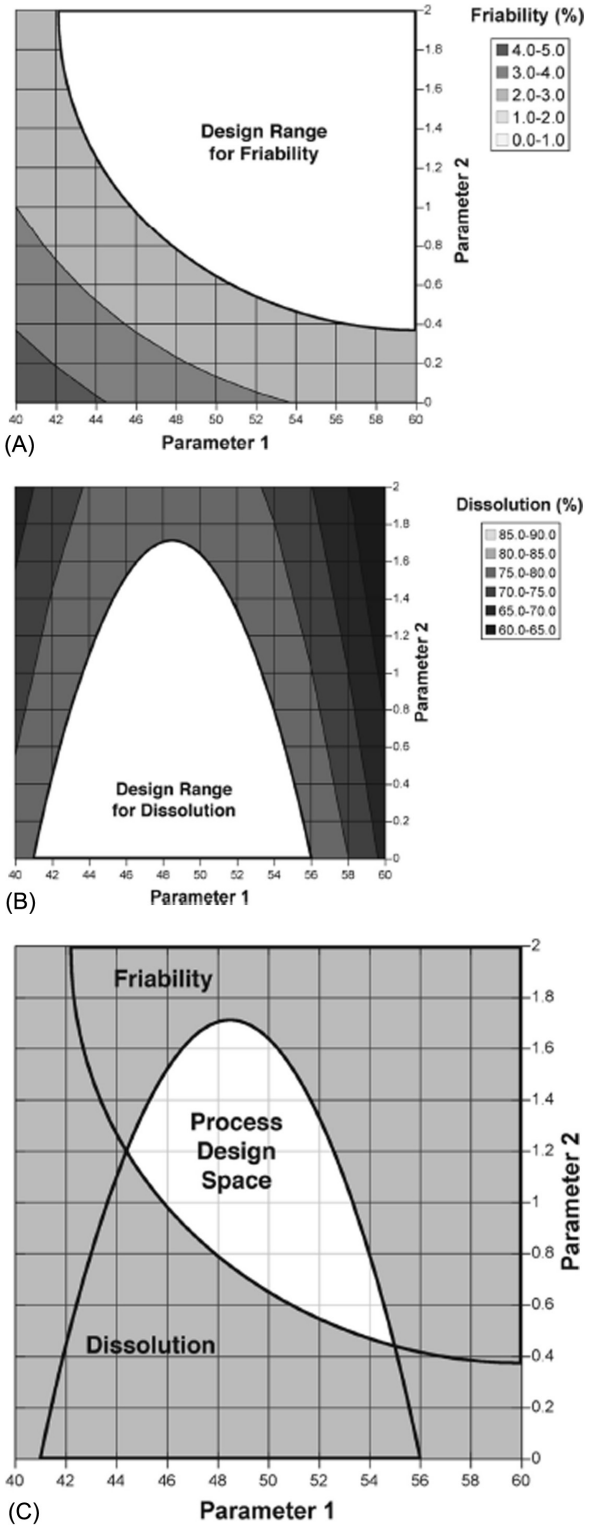


FIGURE 4.2 Design space determined from the common region of successful operating ranges for multiple CQAs. The relations of two CQAs, that is, friability and dissolution, to two process parameters of a granulation operation are shown in (A) and (B). (C) The overlap of these regions and the maximum ranges of the potential design space. (A) Contour plot of friability as a function of parameters 1 and 2. (B) Contour plot of dissolution as a function of parameters 1 and 2. (C) Potential process design space, comprised of the overlap region of design ranges for friability and or dissolution.

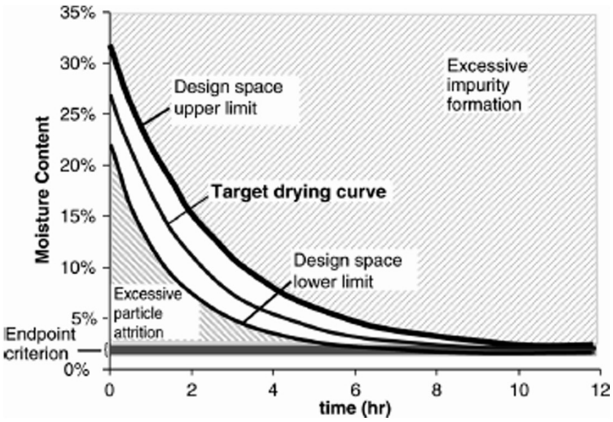


FIGURE 4.3 The design space for a drying operation that is dependent upon the path of temperature and/or pressure over time. The end point for moisture content is 1–2%. Operating above the upper limit of the design space can cause excessive impurity formation, while operating below the lower limit of the design space can result in excessive particle attrition.

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5 Scale-Up and Post-Approval Changes for Nonsterile Semisolid Dosage Forms: Manufacturing Equipment

To ensure continuing product quality and performance characteristics of the semisolid topical formulations, regulatory approvals are required for changes to

1. Components or composition
2. Manufacturing (process and equipment)
3. Scale-up/scale-down of manufacture and
4. Site of manufacture of a semisolid formulation during the post-approval period

It is important to define

1. The levels of change
2. Recommended chemistry, manufacturing, and controls tests to support each level of change
3. Recommended in vitro release tests or in vivo bioequivalence tests to support each level of change
4. Documentation to support the change

The effect that scale-up and post-approval changes may have on the stability of the drug product should be evaluated. For general guidance on conducting stability studies, see the FDA *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics.* For scale-up and post-approval changes submissions, the following points should also be considered:

A. In most cases, except those involving scale-up, stability data from pilot scale batches will be acceptable to support the proposed change.
B. Where stability data show a trend toward potency loss or degradant increase under accelerated conditions, it is recommended that historical accelerated stability data from a representative pre-change batch be submitted for comparison. It is also recommended that under these circumstances, all available long-term data on test batches from ongoing studies be provided in the supplement. Submission of historical accelerated and available long-term data would facilitate review and approval of the supplement.
C. A commitment should be included to conduct long-term stability studies through the expiration dating period, according to the approved protocol, on either the first or first three (see below for details) production batches and to report the results in subsequent annual reports.

Definition of level 1 changes are those that are unlikely to have any detectable effect on formulation quality and performance. Examples:

A. Deletion or partial deletion of an ingredient intended to affect the color, fragrance, or flavor of the drug product.
B. Any change in an excipient up to 5% of approved amount of that excipient. The total additive effect of all excipient changes should not be more than 5%. Changes in the composition should be based on the approved target composition and not on previous level 1 changes in the composition. A change in diluent (q.s. excipient) caused by component and composition changes in excipient may be made and is excluded from the 5% change limit.
C. Change in a supplier of a structure-forming excipient that is primarily a single chemical entity (purity 95%) or change in a supplier or technical grade of any other excipient.

Level 2 changes are defined as those that could have a significant effect on formulation quality and performance. Examples:

A. Changes of >5% and <10% of approved amount of an individual excipient; the total additive effect of all excipient changes should not be more than 10%.
B. Changes in the composition should be based on the approved target composition and not on previous level 1 or level 2 changes in the composition.
C. Changes in diluent (q.s. excipient) caused by component and composition changes in excipients are acceptable and are excluded from the 10% change limit.
D. Change in supplier of a structure-forming excipient not covered under level 1.
E. Change in the technical grade of structure-forming excipient.
F. Change in particle size distribution of the drug substance if the drug is in suspension.

Level 3 changes are defined as those that are likely to have a significant effect on formulation quality and performance. Examples:

A. Any qualitative and quantitative changes in an excipient beyond the ranges noted in level 2 change.
B. Change in crystalline form of the drug substance, if the drug is in suspension.

I. PRESERVATIVE

For semisolid products, any change in the preservative may affect the quality of the product. If any quantitative or qualitative changes are made in the formulation, additional testing should be performed. No in vitro release documentation or in vivo bioequivalence documentation is needed for preservative changes.

II. MANUFACTURING CHANGES

Manufacturing changes may affect both equipment used in the manufacturing process and the process itself. A level 1 change is a change from nonautomated or nonmechanical equipment to automated or mechanical equipment to transfer ingredients or a change to alternative equipment of the same design and operating principles. A level 2 change is a change in equipment to a different design or different operating principles or a change in type of mixing equipment, such as high shear to low shear and vice versa. No level 3 changes are anticipated in this category.

III. PROCESS

Level 1 changes include changes such as rate of mixing, mixing times, operating speeds, and holding times within approved application ranges, in addition to the order of addition of components (excluding actives) to either the oil or water phase. Level 2 changes include changes such as rate of mixing, mixing times, rate of cooling, operating speeds, and holding times outside approved application ranges for all dosage forms in addition to any changes in the process of combining the phases. No level 3 changes are anticipated in this category.

A. Batch Size (Scale-Up or Scale-Down)

The minimum batch size for the NDA pivotal clinical trial batch or the ANDA/AADA biobatch is at least 100 kg or 10% of a production batch, whichever is larger. All scale changes should be properly validated and may be inspected by appropriate agency personnel. Level 1 changes in batch size are those up to and including a factor of ten times the size of the pivotal clinical trial or biobatch, where the equipment used to produce the test batch or batches is of the same design and operating principles, the batch or batches are manufactured in full compliance with current good manufacturing practice (cGMPs), and the same standard operating procedures (SOPs) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch or batches and on the full-scale production batch or batches. Level 2 changes in batch size are those from beyond a factor of ten times the size of the pivotal clinical trial or biobatch, where the equipment used to produce the test batch or batches is of the same design and operating principles, the batch or batches is manufactured in full compliance with cGMPs, and the same SOPs and controls, as well as the same formulation and manufacturing procedures, are used on the test batch or batches and on the full-scale production batch or batches. No level 3 changes are anticipated in this category.

IV. MANUFACTURING SITE

Manufacturing site changes consist of changes in location in the site of manufacture, packaging and filling operations, or testing for both company-owned and contract manufacturing facilities, and they do not include any other level 2 or 3 changes, for example, changes in scale, manufacturing (including process or equipment), and components or composition. New manufacturing locations should have had a satisfactory cGMP inspection within the past 2 years. A stand-alone analytical testing laboratory site change may be submitted as a Changes Being Effected Supplement if the new facility has a current and satisfactory cGMP compliance profile with the FDA for the type of testing operation in question. The supplement should contain a commitment to use the same test methods employed in the approved application, written certification from the testing laboratory stating that they are in conformance with cGMPs, and a full description of the testing to be performed by the testing laboratory. If the facility has not received a satisfactory cGMP inspection for the type of testing involved, a prior approval supplement is recommended. No stability data are needed for a change in a stand-alone analytical facility. Level 1 changes consist of site changes within a single facility where the same equipment, SOPs, environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility. “Common” is defined as employees already working on the campus who have suitable experience with the manufacturing process.

Level 2 changes consist of site changes within a contiguous campus or between facilities in adjacent city blocks, where similar equipment, SOPs, environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility. Level 3 changes consist of a site change in manufacturing site to a different campus. A different campus is defined as one that is not on the same original contiguous site or where the facilities are not in adjacent city blocks. To qualify as a level 3 change, similar equipment, SOPs, environmental conditions, and controls should be used in the manufacturing process at the new site. Changes should not be made to the manufacturing batch records except when consistent with other level 1 changes. Administrative information, location, and language translation may be revised as needed. Any change to a new contract manufacturer also constitutes a level 3 change.

MANUFACTURING EQUIPMENT

I. INTRODUCTION

Any equipment changes should be validated in accordance with cGMPs. The resulting data will be subject to examination by field investigators during routine GMP inspections.

The information here is presented in broad categories of unit operation (particle size reduction or separation, mixing, emulsification, deaeration, transfer, and packaging).

Under scale-up and post-approval changes (semisolid) (SUPAC-SS), equipment within the same class and subclass are considered to have the same design and operating principle. For example, a change from a planetary mixer from manufacturer A to another planetary mixer from manufacturer B would not represent a change in design or operating principle and would be considered the same.

A change from equipment in one class to equipment in a different class would usually be considered a change in design and operating principle. For example, a change from a planetary mixer to a dispersator mixer demonstrates a change in operating principle from low-shear convection mixing to high-shear convection mixing. These types of equipment would be considered different under SUPAC-SS.

Applicants should carefully consider and evaluate on a case-by-case basis changes in equipment that are in the same class but different subclasses. In many situations, these changes in equipment would be considered similar. For example, in Section III, Mixing, under the convection mixers, low shear, a change from an impeller mixer (subclass) to a planetary mixer (subclass) represents a change within a class and between subclasses. Provided the manufacturing process with the new equipment is validated, this change would likely not need a Changes Being Effected Supplement. At the time of such a change the applicant should have available the scientific data and rationale used to make this determination. It is up to the applicant to determine the filing category.

II. PARTICLE SIZE REDUCTION AND SEPARATION

A. Definitions

1. Unit Operations

a. Particle Size Reduction

Particle size reduction is the mechanical process of breaking particles into smaller pieces via one or more size-reduction mechanisms. The mechanical process used is generally referred to as milling.

i. Particle A particle is either a discrete crystal or a grouping of crystals, generally known as an agglomerate.

ii. Particle Size Reduction Mechanisms

- Impact—particle size reduction caused by applying an instantaneous force perpendicular to the particle or agglomerate surface; the force can result from particle-to-particle or particle-to-mill surface collision.
- Attrition—particle size reduction by applying force parallel to the particle surface.
- Compression—particle size reduction by applying a force slowly (as compared with impact) to the particle surface toward the center of the particle.
- Cutting—particle size reduction by applying a shearing force to a material.

b. Particle Separation

Particle separation is particle size classification according to particle size alone.

2. Operating Principles

a. Fluid Energy Milling

Fluid energy milling is particle size reduction by high speed particle-to-particle impact or attrition (also known as micronizing).

b. Impact Milling

Particle size reduction by high-speed mechanical impact or impact with other particles (also known as milling, pulverizing, or comminuting) is known as impact milling.

c. Cutting

Cutting is particle size reduction by mechanical shearing.

d. Compression Milling

Particle size reduction by compression stress and shear between two surfaces is known as compression milling.

e. Screening

Particle size reduction by mechanically induced attrition through a screen (commonly referred to as milling or deagglomeration) is called screening.

f. Tumble Milling

Tumble milling is particle size reduction by attrition, using grinding media.

g. Separating

Particle segregation based on size alone, without any significant particle size reduction (commonly referred to as screening or bolting), is also known as separating.

B. Equipment Classifications

1. Fluid Energy Mills

Fluid energy mill subclasses have no moving parts and primarily differ in the configuration or shape of their chambers, nozzles, and classifiers.

- Fixed target
- Fluidized bed
- Loop or oval
- Moving target
- Opposed jet
- Opposed jet with dynamic classifier
- Tangential jet

2. Impact Mills

Impact mill subclasses primarily differ in the configuration of the grinding heads, chamber grinding liners (if any), and classifiers.

- Cage
- Hammer air swept
- Hammer conventional
- Pin or disc

3. Cutting Mills

Although cutting mills can differ in whether the knives are movable or fixed, and in classifier configuration, no cutting mill subclasses have been identified.

4. Compression Mills

Although compression mills, also known as roller mills, can differ in whether one or both surfaces move, no compression mill subclasses have been identified.

5. Screening Mills

Screening mill subclasses primarily differ in the rotating element.

- Oscillating bar
- Rotating impeller
- Rotating screen

6. Tumbling Mills

Tumbling mill subclasses primarily differ in the grinding media used and whether the mill is vibrated.

- Ball media
- Rod media
- Vibrating

7. Separators

Separator subclasses primarily differ in the mechanical means used to induce particle movement.

- Centrifugal
- Vibratory or shaker

Note that if a single piece of equipment is capable of performing multiple discrete unit operations, it has been evaluated solely for its ability to affect particle size or separation.

III. MIXING

A. Definitions

1. Unit Operation

Mixing is the reorientation of particles relative to one another to achieve uniformity or randomness. This process can include wetting of solids by a liquid phase, dispersion of discrete particles, or deagglomeration into a continuous phase. Heating and cooling via indirect conduction may be used in this operation to facilitate phase mixing or stabilization.

2. Operating Principles

a. Convection Mixing, Low Shear

Convection mixing, low shear, is a mixing process with a repeated pattern of cycling material from top to bottom in which dispersion occurs under low power per unit mass through rotating low shear forces.

b. Convection Mixing, High Shear

Convection mixing, high shear, is a mixing process with a repeated pattern of cycling material from top to bottom in which dispersion occurs under high power per unit mass through rotating high shear forces.

c. Roller Mixing (Milling)

Also known as milling, roller mixing is a mixing process by high mechanical shearing action where compression stress is achieved by passing material between a series of rotating rolls. This is commonly referred to as compression or roller milling.

d. Static Mixing

In static mixing, material passes through a tube with stationary baffles. The mixer is generally used in conjunction with an in-line pump.

B. Equipment Classification

1. Convection Mixers, Low Shear

This group of mixers normally operates under low-shear conditions and is broken down by impeller design and movement. Design can also include a jacketed vessel to facilitate heat transfer.

- Anchor or sweepgate
- Impeller
- Planetary

2. Convection Mixers, High Shear

These mixers normally operate only under high-shear conditions. Subclasses are differentiated by how the high shear is introduced into the material, such as by a dispersator with serrated blades or homogenizer with rotor stator.

- Dispersator
- Rotor stator

3. Roller Mixers (Mills)

No roller mixer subclasses have been identified.

4. Static Mixers

No static mixer subclasses have been identified.

Note that if a single piece of equipment is capable of performing multiple discrete unit operations, it has been evaluated solely for its ability to mix materials.

5. Low-Shear Emulsifiers

Although low-shear emulsification equipment (mechanical stirrers or impellers) can differ in the type of fluid flow imparted to the mixture (axial-flow propeller or radial-flow turbines), no subclasses have been defined.

IV. TRANSFER

A. Definitions

1. Unit Operation

Transfer is the controlled movement or transfer of materials from one location to another.

2. Operating Principles

a. Passive

Passive transfer is the movement of materials across a non-mechanically induced pressure gradient, usually through a conduit or pipe.

b. Active

The movement of materials across a mechanically induced pressure gradient, usually through conduit or pipe, is known as active transfer.

B. Equipment Classification

1. Low Shear

Equipment used for active or passive material transfer, with a low degree of induced shear, is classified as "low-shear" equipment:

- Diaphragm
- Gravity
- Peristaltic
- Piston
- Pneumatic
- Rotating lobe
- Screw or helical screw

2. High Shear

Active or mechanical material transfer with a high degree of induced shear is performed by what is known as "high-shear" equipment:

- Centrifugal or turbine
- Piston
- Rotating gear

A single piece of equipment can be placed in either a low- or high-shear class, depending on its operating parameters. If a single piece of equipment is capable of performing multiple discrete unit operations, the unit has been evaluated solely for its ability to transfer materials.

V. PACKAGING

A. Definitions

1. Unit Operation

a. Holding

The process of storing product after completion of manufacturing process and before filling final primary packs is known as holding.

b. Transfer

Transfer is the process of relocating bulk finished product from holding to filling equipment using pipe, hose, pumps, or other associated components.

c. Filling

Filling is the delivery of target weight or volume of bulk finished product to primary pack containers.

d. Sealing

A device or process for closing or sealing primary pack containers, known collectively as sealing, follows the filling process.

2. Operating Principles

a. Holding

The storage of liquid, semisolids, or product materials in a vessel that may or may not have temperature control or agitation is called holding.

b. Transfer

The controlled movement or transfer of materials from one location to another is known as transfer.

c. Filling

Filling operating principles involve several associated subprinciples. The primary package can be precleaned to remove particulates or other materials by the use of ionized air, vacuum, or inversion. A holding vessel equipped with an auger, gravity, or pressure material feeding system should be used. The vessel may or may not be able to control temperature or agitation. Actual filling of the dosage form into primary containers can involve a metering system based on an auger, gear, orifice, peristaltic, or piston pump. A headspace blanketing system can also be used.

d. Sealing

Primary packages can be sealed using a variety of methods, including conducted heat and electromagnetic (induction or microwave) or mechanical manipulation (crimping or torqueing).

B. Equipment Classification

1. Holders

Although holding vessels can differ in their geometry and ability to control temperature or agitation, their primary differences are based on how materials are fed. Feeding devices include the following:

- Auger
- Gravity
- Pneumatic (nitrogen, air, etc.)

2. Fillers

The primary differences in filling equipment are based on how materials are metered. Different varieties of filling equipment include the following:

- Auger
- Gear pump

- Orifice
- Peristaltic pump
- Piston

3. Sealers

The differences in primary container sealing are based on how energy is transferred or applied. Energy transfer can be accomplished via the following:

- Heat
- Induction
- Microwave
- Mechanical or crimping
- Torque

6 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

1. INTRODUCTION

1.1. Objective

This document (Guide) is intended to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess.

In this Guide "manufacturing" is defined to include all operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control (QC), release, storage and distribution of APIs, and the related controls. In this Guide the term "should" indicates recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance (QA). For the purposes of this Guide, the terms "current good manufacturing practices" and "good manufacturing practices" are equivalent.

The Guide as a whole does not cover safety aspects for the personnel engaged in the manufacture, nor aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.

This Guide is not intended to define registration/filing requirements or modify pharmacopoeial requirements. This Guide does not affect the ability of the responsible regulatory agency to establish specific registration/filing requirements regarding APIs within the context of marketing/manufacturing authorizations or drug applications. All commitments in registration/filing documents must be met.

1.2. Regulatory Applicability

Within the world community, materials may vary as to the legal classification as an API. When a material is classified as an API in the region or country in which it is manufactured or used in a drug product, it should be manufactured according to this Guide.

1.3. Scope

This Guide applies to the manufacture of APIs for use in human drug (medicinal) products. It applies to the manufacture of sterile APIs only up to the point immediately prior to the APIs being rendered sterile. The sterilization and aseptic processing of sterile APIs are not covered by this guidance but should be performed in accordance with GMP guidelines for drug (medicinal) products as defined by local authorities.

This Guide covers APIs that are manufactured by chemical synthesis, extraction, cell culture/fermentation, by recovery from natural sources, or by any combination of these processes. Specific guidance for APIs manufactured by cell culture/fermentation is described in Section 18.

This Guide excludes all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs. However, it does include APIs that are produced using blood or plasma as raw materials. Note that cell substrates (mammalian, plant, insect or microbial cells, tissue or animal sources including transgenic animals) and early process steps may be subject to GMP but are not covered by this Guide. In addition, the Guide does not apply to medical gases, bulk-packaged drug (medicinal) products, and manufacturing/control aspects specific to radiopharmaceuticals.

Section 19 contains guidance that only applies to the manufacture of APIs used in the production of drug (medicinal) products specifically for clinical trials (investigational medicinal products).

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

The company should designate and document the rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which "API Starting Materials" are entered into the process. For other processes (e.g., fermentation, extraction, purification), this rationale should be established on a case-by-case basis. Table 6.1 gives guidance on the point at which the API Starting Material is normally introduced into the process.

From this point on, appropriate GMP as defined in this Guide should be applied to these intermediate and/or API manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the API. However, it should be noted that the fact that a company chooses to validate a process step does not necessarily define that step as critical.

The guidance in this document would normally be applied to the steps shown in gray in Table 6.1. It does not imply that all steps shown should be completed. The stringency of GMP in API manufacturing should increase as the process proceeds from early API steps to final steps, purification, and packaging. Physical processing of APIs, such as granulation, coating, or

TABLE 6.1
Application of This Guide to API Manufacturing

Type of Manufacturing	Application of This Guide to Steps (Shown in Gray) Used in This Type of Manufacturing				
Chemical manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of intermediate(s)	Isolation and purification	Physical processing and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API Starting Material into process	Isolation and purification	Physical processing and packaging
API extracted from plant sources	Collection of plants	Cutting and initial extraction(s)	Introduction of the API Starting Material into process	Isolation and purification	Physical processing and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/comminuting			Physical processing and packaging
Biotechnology: Fermentation/cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing and packaging
"Classical" fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing and packaging

physical manipulation of particle size (e.g., milling, micronizing), should be conducted at least to the standards of this Guide.

This GMP Guide does not apply to steps prior to the introduction of the defined "API Starting Material."

2. QUALITY MANAGEMENT

2.1. Principles

- 2.10 Quality should be the responsibility of all persons involved in manufacturing.
- 2.11 Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.
- 2.12 The system for managing quality should encompass the organizational structure, procedures, processes, and resources, as well as activities necessary to ensure confidence that the API will meet its intended specifications for quality and purity. All quality-related activities should be defined and documented.
- 2.13 There should be a quality unit(s) that is independent of production and that fulfills both QA and QC responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.
- 2.14 The persons authorized to release intermediates and APIs should be specified.
- 2.15 All quality-related activities should be recorded at the time they are performed.
- 2.16 Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.
- 2.17 No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g., release under quarantine as described in Section 10.20 or the use of raw materials or intermediates pending completion of evaluation).
- 2.18 Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects, and related actions (e.g., quality-related complaints, recalls, regulatory actions, etc.).

2.2. Responsibilities of the Quality Unit(s)

- 2.20 The quality unit(s) should be involved in all quality-related matters.
- 2.21 The quality unit(s) should review and approve all appropriate quality-related documents.

- 2.22 The main responsibilities of the independent quality unit(s) should not be delegated. These responsibilities should be described in writing and should include but not necessarily be limited to
  - 1. Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company.
  - 2. Establishing a system to release or reject raw materials, intermediates, packaging, and labeling materials.
  - 3. Reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution.
  - 4. Making sure that critical deviations are investigated and resolved.
  - 5. Approving all specifications and master production instructions.
  - 6. Approving all procedures impacting the quality of intermediates or APIs.
  - 7. Making sure that internal audits (self-inspections) are performed.
  - 8. Approving intermediate and API contract manufacturers.
  - 9. Approving changes that potentially impact intermediate or API quality.
  - 10. Reviewing and approving validation protocols and reports.
  - 11. Making sure that quality-related complaints are investigated and resolved.
  - 12. Making sure that effective systems are used for maintaining and calibrating critical equipment.
  - 13. Making sure that materials are appropriately tested and the results are reported.
  - 14. Making sure that there are stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates where appropriate.
  - 15. Performing product quality reviews (as defined in Section 2.5).

2.3. Responsibility for Production Activities

- The responsibility for production activities should be described in writing and should include but not necessarily be limited to
  - 1. Preparing, reviewing, approving, and distributing the instructions for the production of intermediates or APIs according to written procedures.
  - 2. Producing APIs and, when appropriate, intermediates according to preapproved instructions.
  - 3. Reviewing all production batch records and ensuring that these are completed and signed.
  - 4. Making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded.
  - 5. Making sure that production facilities are clean and when appropriate disinfected.
  - 6. Making sure that the necessary calibrations are performed and records kept.
  - 7. Making sure that the premises and equipment are maintained and records kept.
  - 8. Making sure that validation protocols and reports are reviewed and approved.
  - 9. Evaluating proposed changes in product, process, or equipment.
  - 10. Making sure that new and, when appropriate, modified facilities and equipment are qualified.

2.4. Internal Audits (Self-Inspection)

- 2.40 In order to verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.
- 2.41 Audit findings and corrective actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.

2.5. Product Quality Review

- 2.50 Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least
  - A review of critical in-process control and critical API test results
  - A review of all batches that failed to meet established specification(s)
  - A review of all critical deviations or nonconformances and related investigations
  - A review of any changes carried out to the processes or analytical methods
  - A review of results of the stability monitoring program
  - A review of all quality-related returns, complaints, and recalls and
  - A review of adequacy of corrective actions
- 2.51 The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.

3. PERSONNEL

3.1. Personnel Qualifications

- 3.10 There should be an adequate number of personnel qualified by appropriate education, training, and/or experience to perform and supervise the manufacture of intermediates and APIs.

- 3.11 The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.
- 3.12 Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

3.2. Personnel Hygiene

- 3.20 Personnel should practice good sanitation and health habits.
- 3.21 Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved, and this clothing should be changed when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn when necessary, to protect intermediates and APIs from contamination.
- 3.22 Personnel should avoid direct contact with intermediates or APIs.
- 3.23 Smoking, eating, drinking, chewing, and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.
- 3.24 Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

3.3. Consultants

- 3.30 Consultants advising on the manufacture and control of intermediates or APIs should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.
- 3.31 Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

4. BUILDINGS AND FACILITIES

4.1. Design and Construction

- 4.10 Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate.
- 4.11 Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.
- 4.12 Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.
- 4.13 The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.
- 4.14 There should be defined areas or other control systems for the following activities:
  - Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection
  - Quarantine before release or rejection of intermediates and APIs
  - Sampling of intermediates and APIs
  - Holding rejected materials before further disposition (e.g., return, reprocessing, or destruction)
  - Storage of released materials
  - Production operations
  - Packaging and labeling operations
  - Laboratory operations
- 4.15 Adequate, clean washing and toilet facilities should be provided for personnel. These washing facilities should be equipped with hot and cold water as appropriate, soap or detergent, air driers or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.
- 4.16 Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements and the laboratory and its operations do not adversely affect the production process or intermediate or API.

4.2. Utilities

- 4.20 All utilities that could impact on product quality (e.g., steam, gases, compressed air, and heating, ventilation and air conditioning) should be qualified and appropriately monitored, and action should be taken when limits are exceeded. Drawings for these utility systems should be available.
- 4.21 Adequate ventilation, air filtration, and exhaust systems should be provided, where appropriate.

These systems should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.

- 4.22 If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.
- 4.23 Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API.
- 4.24 Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.

4.3. Water

- 4.30 Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use.
- 4.31 Unless otherwise justified, process water should, at a minimum, meet World Health Organization (WHO) guidelines for drinking (potable) water quality.
- 4.32 If drinking (potable) water is insufficient to assure API quality, and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms, and/or endotoxins should be established.
- 4.33 Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.
- 4.34 Where the manufacturer of a nonsterile API either intends or claims that it is suitable for use in further processing to produce a sterile drug (medicinal) product, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.

4.4. Containment

- 4.40 Dedicated production areas, which can include facilities, air handling equipment, and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins.
- 4.41 Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anticancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.
- 4.42 Appropriate measures should be established and implemented to prevent cross-contamination from personnel, materials, etc. moving from one dedicated area to another.
- 4.43 Any production activities (including weighing, milling, or packaging) of highly toxic nonpharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic nonpharmaceutical materials should be separate from APIs.

4.5. Lighting

- 4.50 Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.

4.6. Sewage and Refuse

- 4.60 Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

4.7. Sanitation and Maintenance

- 4.70 Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.
- 4.71 Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.
- 4.72 When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labeling materials, intermediates, and APIs.

5. PROCESS EQUIPMENT

5.1. Design and Construction

- 5.10 Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance.

- 5.11 Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.
- 5.12 Production equipment should only be used within its qualified operating range.
- 5.13 Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.
- 5.14 Any substances associated with the operation of equipment, such as lubricants, heating fluids, or coolants, should not contact intermediates or APIs so as to alter their quality beyond the official or other established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the fitness for purpose of the material. Wherever possible, food-grade lubricants and oils should be used.
- 5.15 Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.
- 5.16 A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems).

5.2. Equipment Maintenance and Cleaning

- 5.20 Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.
- 5.21 Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include
  - Assignment of responsibility for cleaning of equipment
  - Cleaning schedules, including, where appropriate, sanitizing schedules
  - A complete description of the methods and materials, including dilution of cleaning agents used to clean equipment
  - When appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning
  - Instructions for the removal or obliteration of previous batch identification
  - Instructions for the protection of clean equipment from contamination prior to use
  - Inspection of equipment for cleanliness immediately before use, if practical and
  - Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate
- 5.22 Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carryover of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.
- 5.23 Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent buildup and carryover of contaminants (e.g., degradants or objectionable levels of microorganisms).
- 5.24 Nondedicated equipment should be cleaned between production of different materials to prevent cross-contamination.
- 5.25 Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.
- 5.26 Equipment should be identified as to its contents and its cleanliness status by appropriate means.

5.3. Calibration

- 5.30 Control, weighing, measuring, monitoring, and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.
- 5.31 Equipment calibrations should be performed using standards traceable to certified standards, if existing.
- 5.32 Records of these calibrations should be maintained.
- 5.33 The current calibration status of critical equipment should be known and verifiable.
- 5.34 Instruments that do not meet calibration criteria should not be used.
- 5.35 Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

5.4. Computerized Systems

- 5.40 GMP-related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity, and criticality of the computerized application.
- 5.41 Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks.

- 5.42 Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available.
- 5.43 Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g., system turned off and data not captured). There should be a record of any data change made, the previous entry, who made the change, and when the change was made.
- 5.44 Written procedures should be available for the operation and maintenance of computerized systems.
- 5.45 Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.
- 5.46 Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.
- 5.47 Changes to the computerized system should be made according to a change procedure and should be formally authorized, documented, and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software, and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.
- 5.48 If system breakdowns or failures would result in the permanent loss of records, a backup system should be provided. A means of ensuring data protection should be established for all computerized systems.
- 5.49 Data can be recorded by a second means in addition to the computer system.

6. DOCUMENTATION AND RECORDS

6.1. Documentation System and Specifications

- 6.10 All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved, and distributed according to written procedures. Such documents can be in paper or electronic form.
- 6.11 The issuance, revision, superseding, and withdrawal of all documents should be controlled with maintenance of revision histories.
- 6.12 A procedure should be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records). The retention periods for these documents should be specified.
- 6.13 All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed.
- 6.14 When entries are made in records, these should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed and leave the original entry still readable.
- 6.15 During the retention period, originals or copies of records should be readily available at the establishment where the activities described in such records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.
- 6.16 Specifications, instructions, procedures, and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.
- 6.17 Specifications should be established and documented for raw materials, intermediates where necessary, APIs, and labeling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets, or other materials used during the production of intermediates or APIs that could critically impact on quality. Acceptance criteria should be established and documented for in-process controls.
- 6.18 If electronic signatures are used on documents, they should be authenticated and secure.

6.2. Equipment Cleaning and Use Record

- 6.20 Records of major equipment use, cleaning, sanitization and/or sterilization, and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.
- 6.21 If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.

6.3. Records of Raw Materials, Intermediates, API Labeling and Packaging Materials

- 6.30 Records should be maintained including
  - The name of the manufacturer, identity, and quantity of each shipment of each batch of raw

materials, intermediates, or labeling and packaging materials for APIs; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt
    - The results of any test or examination performed and the conclusions derived from this
    - Records tracing the use of materials
    - Documentation of the examination and review of API labeling and packaging materials for conformity with established specifications and
    - The final decision regarding rejected raw materials, intermediates, or API labeling and packaging materials
- 6.31 Master (approved) labels should be maintained for comparison to issued labels.

6.4. Master Production Instructions (Master Production and Control Records)

- 6.40 To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s).
- 6.41 Master production instructions should include
    - The name of the intermediate or API being manufactured and an identifying document reference code, if applicable.
    - A complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics.
    - An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included. Variations to quantities should be included where they are justified.
    - The production location and major production equipment to be used.
    - Detailed production instructions, including the
        - Sequences to be followed
        - Ranges of process parameters to be used
        - Sampling instructions and in-process controls with their acceptance criteria, where appropriate
        - Time limits for completion of individual processing steps and/or the total process, where appropriate and
    - Expected yield ranges at appropriate phases of processing or time
    - Where appropriate, special notations and precautions to be followed or cross-references to these.
    - The instructions for storage of the intermediate or API to assure its suitability for use, including the labeling and packaging materials and special storage conditions with time limits, where appropriate.

6.5. Batch Production Records (Batch Production and Control Records)

- 6.50 Batch production records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to assure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.
- 6.51 These records should be numbered with a unique batch or identification number, dated, and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.
- 6.52 Documentation of completion of each significant step in the batch production records (batch production and control records) should include
    - Dates and, when appropriate, times
    - Identity of major equipment (e.g., reactors, driers, mills, etc.) used
    - Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing
    - Actual results recorded for critical process parameters
    - Any sampling performed
    - Signatures of the persons performing and directly supervising or checking each critical step in the operation
    - In-process and laboratory test results
    - Actual yield at appropriate phases or times
    - Description of packaging and label for intermediate or API
    - Representative label of API or intermediate if made commercially available
    - Any deviation noted, its evaluation, investigation conducted (if appropriate), or reference to that investigation if stored separately and
    - Results of release testing
- 6.53 Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

6.6. Laboratory Control Records

- 6.60 Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:
  - A description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing.
  - A statement of or reference to each test method used.
  - A statement of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents, and standard solutions.
  - A complete record of all raw data generated during each test, in addition to graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested.
  - A record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors.
  - A statement of the test results and how they compare with established acceptance criteria.
  - The signature of the person who performed each test and the date(s) the tests were performed.
  - The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.
- 6.61 Complete records should also be maintained for
  - Any modifications to an established analytical method
  - Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices
  - All stability testing performed on APIs and
  - Out-of-specification (OOS) investigations

6.7. Batch Production Record Review

- 6.70 Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labeling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.
- 6.71 Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of noncritical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).
- 6.72 All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.
- 6.73 The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

7. MATERIALS MANAGEMENT

7.1. General Controls

- 7.10 There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials.
- 7.11 Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials.
- 7.12 Materials should be purchased against an agreed specification, from a supplier or suppliers approved by the quality unit(s).
- 7.13 If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known by the intermediate and/or API manufacturer.
- 7.14 Changing the source of supply of critical raw materials should be treated according to Section 13, Change Control.

7.2. Receipt and Quarantine

- 7.20 Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labeling (including correlation between the name used by the supplier and the in-house name, if these are different), container damage, broken seals, and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined, or tested as appropriate and released for use.
- 7.21 Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.
- 7.22 If bulk deliveries are made in nondedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:
  - Certificate of cleaning
  - Testing for trace impurities
  - Audit of the supplier
- 7.23 Large storage containers, and their attendant manifolds, filling and discharge lines should be appropriately identified.

- 7.24 Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.

7.3. Sampling and Testing of Incoming Production Materials

- 7.30 At least one test to verify the identity of each batch of material should be conducted, with the exception of the materials described below in Section 7.32. A supplier's Certificate of Analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.
- 7.31 Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Full analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a full analysis should be performed at appropriate intervals and compared with the Certificates of Analysis. Reliability of Certificates of Analysis should be checked at regular intervals.
- 7.32 Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's Certificate of Analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.
- 7.33 Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based upon a sampling plan that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis.
- 7.34 Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.
- 7.35 Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

7.4. Storage

- 7.40 Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.
- 7.41 Materials stored in fiber drums, bags, or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.
- 7.42 Materials should be stored under conditions and for a period that have no adverse effect on their quality and should normally be controlled so that the oldest stock is used first.
- 7.43 Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.
- 7.44 Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorized use in manufacturing.

7.5. Reevaluation

- 7.50 Materials should be reevaluated as appropriate to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).

8. PRODUCTION AND IN-PROCESS CONTROLS

8.1. Production Operations

- 8.10 Raw materials for intermediate and API manufacturing should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.
- 8.11 If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:
  - Material name and/or item code
  - Receiving or control number
  - Weight or measure of material in the new container and
  - Reevaluation or retest date if appropriate
- 8.12 Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.
- 8.13 Other critical activities should be witnessed or subjected to an equivalent control.
- 8.14 Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale, or manufacturing data. Deviations in yield associated with critical process steps should be investigated to

determine their impact or potential impact on the resulting quality of affected batches.
- 8.15 Any deviation should be documented and explained. Any critical deviation should be investigated.
- 8.16 The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems, or alternative means.
- 8.17 Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.

8.2. Time Limits

- 8.20 If time limits are specified in the master production instruction (see Section 6.41), these time limits should be met to ensure the quality of intermediates and APIs. Deviations should be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g., pH adjustment, hydrogenation, drying to predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing.
- 8.21 Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.

8.3. In-Process Sampling and Controls

- 8.30 Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria should be defined based on the information gained during the development stage or historical data.
- 8.31 The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted, and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g., isolation and purification steps).
- 8.32 Critical in-process controls (and critical process monitoring), including the control points and methods, should be stated in writing and approved by the quality unit(s).
- 8.33 In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s) approval if the adjustments are made within preestablished limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.
- 8.34 Written procedures should describe the sampling methods for in-process materials, intermediates, and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.
- 8.35 In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or APIs. Procedures should be established to ensure the integrity of samples after collection.
- 8.36 OOS investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.

8.4. Blending Batches of Intermediates or APIs

- 8.40 For the purpose of this document, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API. In-process mixing of fractions from single batches (e.g., collecting several centrifuge loads from a single crystallization batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.
- 8.41 OOS batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.
- 8.42 Acceptable blending operations include but are not limited to
  - Blending of small batches to increase batch size and
  - Blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch
- 8.43 Blending processes should be adequately controlled and documented, and the blended batch should be tested for conformance to established specifications where appropriate.
- 8.44 The batch record of the blending process should allow traceability back to the individual batches that make up the blend.
- 8.45 Where physical attributes of the API are critical (e.g., APIs intended for use in solid oral dosage forms or suspensions), blending operations should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes (e.g., particle size distribution, bulk density, and tap density) that may be affected by the blending process.
- 8.46 If the blending could adversely affect stability, stability testing of the final blended batches should be performed.

- 8.47 The expiry or retest date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.

8.5. Contamination Control

- 8.50 Residual materials can be carried over into successive batches of the same intermediate or API if there is adequate control. Examples include residue adhering to the wall of a micronizer, residual layer of damp crystals remaining in a centrifuge bowl after discharge, and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carryover should not result in the carryover of degradants or microbial contamination that may adversely alter the established API impurity profile.
- 8.51 Production operations should be conducted in a manner that will prevent contamination of intermediates or APIs by other materials.
- 8.52 Precautions to avoid contamination should be taken when APIs are handled after purification.

9. PACKAGING AND IDENTIFICATION LABELING OF APIs AND INTERMEDIATES

9.1. General

- 9.10 There should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release, and handling of packaging and labeling materials.
- 9.11 Packaging and labeling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.
- 9.12 Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing, and whether accepted or rejected.

9.2. Packaging Materials

- 9.20 Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.
- 9.21 Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive, or absorptive so as to alter the quality of the intermediate or API beyond the specified limits.
- 9.22 If containers are reused, they should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced.

9.3. Label Issuance and Control

- 9.30 Access to the label storage areas should be limited to authorized personnel.
- 9.31 Procedures should be used to reconcile the quantities of labels issued, used, and returned and to evaluate discrepancies found between the number of containers labeled and the number of labels issued. Such discrepancies should be investigated, and the investigation should be approved by the quality unit(s).
- 9.32 All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels should be maintained and stored in a manner that prevents mix-ups and provides proper identification.
- 9.33 Obsolete and outdated labels should be destroyed.
- 9.34 Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.
- 9.35 Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.
- 9.36 A printed label representative of those used should be included in the batch production record.

9.4. Packaging and Labeling Operations

- 9.40 There should be documented procedures designed to ensure that correct packaging materials and labels are used.
- 9.41 Labeling operations should be designed to prevent mix-ups. There should be physical or spatial separation from operations involving other intermediates or APIs.
- 9.42 Labels used on containers of intermediates or APIs should indicate the name or identifying code, the batch number of the product, and storage conditions, when such information is critical to assure the quality of intermediate or API.
- 9.43 If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents, and special transport conditions and any special legal requirements should also be included on the label. For intermediates or APIs with an expiry date, the expiry date should be indicated on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.
- 9.44 Packaging and labeling facilities should be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination should

be documented in the batch production records, the facility log, or other documentation system.
- 9.45 Packaged and labeled intermediates or APIs should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.
- 9.46 Intermediate or API containers that are transported outside of the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

10. STORAGE AND DISTRIBUTION

10.1. Warehousing Procedures

- 10.10 Facilities should be available for the storage of all materials under appropriate conditions (e.g., controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.
- 10.11 Unless there is an alternative system to prevent the unintentional or unauthorized use of quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been taken.

10.2. Distribution Procedures

- 10.20 APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.
- 10.21 APIs and intermediates should be transported in a manner that does not adversely affect their quality.
- 10.22 Special transport or storage conditions for an API or intermediate should be stated on the label.
- 10.23 The manufacturer should ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.
- 10.24 A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall.

11. LABORATORY CONTROLS

11.1. General Controls

- 11.10 The independent quality unit(s) should have at its disposal adequate laboratory facilities.
- 11.11 There should be documented procedures describing sampling, testing, approval or rejection of materials, and recording and storage of laboratory data. Laboratory records should be maintained in accordance with Section 6.6.
- 11.12 All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, and labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans, and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).
- 11.13 Appropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process. The specifications should include a control of the impurities (e.g., organic impurities, inorganic impurities, and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the API has a specification for endotoxins, appropriate action limits should be established and met.
- 11.14 Laboratory controls should be followed and documented at the time of performance. Any departures from the above described procedures should be documented and explained.
- 11.15 Any OOS result obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any resampling and/or retesting after OOS results should be performed according to a documented procedure.
- 11.16 Reagents and standard solutions should be prepared and labeled following written procedures. "Use by" dates should be applied as appropriate for analytical reagents or standard solutions.
- 11.17 Primary reference standards should be obtained as appropriate for the manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognized source are normally used without testing if stored under conditions consistent with the supplier's recommendations.
- 11.18 Where a primary reference standard is not available from an officially recognized source, an

"in-house primary standard" should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.

- 11.19 Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.

11.2. Testing of Intermediates and APIs

- 11.20 For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine conformance to specifications.
- 11.21 An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. The impurity profile should include the identity or some qualitative analytical designation (e.g., retention time), the range of each impurity observed, and classification of each identified impurity (e.g., inorganic, organic, solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin. Biotechnology considerations are covered in ICH Guideline Q6B.
- 11.22 The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data in order to detect changes to the API resulting from modifications in raw materials, equipment operating parameters, or the production process.
- 11.23 Appropriate microbiological tests should be conducted on each batch of intermediate and API where microbial quality is specified.

11.3. Validation of Analytical Procedures (see Section 12)

11.4. Certificates of Analysis

- 11.40 Authentic Certificates of Analysis should be issued for each batch of intermediate or API on request.
- 11.41 Information on the name of the intermediate or API including where appropriate its grade, the batch number, and the date of release should be provided on the Certificate of Analysis. For intermediates or APIs with an expiry date, the expiry date should be provided on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.
- 11.42 The Certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits and the numerical results obtained (if test results are numerical).
- 11.43 Certificates should be dated and signed by authorized personnel of the quality unit(s) and should show the name, address, and telephone number of the original manufacturer. Where the analysis has been carried out by a repacker or reprocessor, the Certificate of Analysis should show the name, address, and telephone number of the repacker/reprocessor and a reference to the name of the original manufacturer.
- 11.44 If new Certificates are issued by or on behalf of repackers/reprocessors, agents, or brokers, these Certificates should show the name, address, and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch Certificate, a copy of which should be attached.

11.5. Stability Monitoring of APIs

- 11.50 A documented, ongoing testing program should be designed to monitor the stability characteristics of APIs, and the results should be used to confirm appropriate storage conditions and retest or expiry dates.
- 11.51 The test procedures used in stability testing should be validated and be stability indicating.
- 11.52 Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in bags within fiber drums, stability samples can be packaged in bags of the same material and in smaller-scale drums of similar or identical material composition to the market drums.
- 11.53 Normally the first three commercial production batches should be placed on the stability monitoring program to confirm the retest or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least 2 years, fewer than three batches can be used.
- 11.54 Thereafter, at least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring program and tested at least annually to confirm the stability.
- 11.55 For APIs with short shelf lives, testing should be done more frequently. For example, for those biotechnological/biological and other APIs with shelf lives of 1 year or less, stability samples should be

obtained and should be tested monthly for the first 3 months and at 3-month intervals after that. When data exist that confirm that the stability of the API is not compromised, elimination of specific test intervals (e.g., 9-month testing) can be considered.
- 11.56 Where appropriate, the stability storage conditions should be consistent with the ICH guidelines on stability.

11.6. Expiry and Retest Dating

- 11.60 When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g., published data, test results).
- 11.61 An API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.
- 11.62 Preliminary API expiry or retest dates can be based on pilot scale batches if the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale and the quality of the API represents the material to be made on a commercial scale.
- 11.63 A representative sample should be taken for the purpose of performing a retest.

11.7. Reserve/Retention Samples

- 11.70 The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing purposes.
- 11.71 Appropriately identified reserve samples of each API batch should be retained for 1 year after the expiry date of the batch assigned by the manufacturer, or for 3 years after distribution of the batch, whichever is the longer. For APIs with retest dates, similar reserve samples should be retained for 3 years after the batch is completely distributed by the manufacturer.
- 11.72 The reserve sample should be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.

12. VALIDATION

12.1. Validation Policy

- 12.10 The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems, and persons responsible for design, review, approval, and documentation of each validation phase, should be documented.
- 12.11 The critical parameters/attributes should normally be identified during the development stage or from historical data, and the ranges necessary for the reproducible operation should be defined. This should include:
  - Defining the API in terms of its critical product attributes
  - Identifying process parameters that could affect the critical quality attributes of the API and
  - Determining the range for each critical process parameter expected to be used during routine manufacturing and process control
- 12.12 Validation should extend to those operations determined to be critical to the quality and purity of the API.

12.2. Validation Documentation

- 12.20 A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units.
- 12.21 The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g., retrospective, prospective, concurrent) and the number of process runs.
- 12.22 A validation report that cross-references the validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the appropriate conclusions, including recommending changes to correct deficiencies.
- 12.23 Any variations from the validation protocol should be documented with appropriate justification.

12.3. Qualification

- 12.30 Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:
  - Design Qualification (DQ): Documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.
  - Installation Qualification (IQ): Documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations, and/or user requirements.

- Operational Qualification (OQ): Documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges.
- Performance Qualification (PQ): Documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.

12.4. Approaches to Process Validation

- 12.40 Process validation is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.
- 12.41 There are three approaches to validation. Prospective validation is the preferred approach, but there are exceptions where the other approaches can be used. These approaches and their applicability are listed below.
- 12.42 Prospective validation should normally be performed for all API processes as defined in Section 12.12. Prospective validation performed on an API process should be completed before the commercial distribution of the final drug product manufactured from that API.
- 12.43 Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of API batches have been produced, API batches are produced infrequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in final drug product for commercial distribution based on thorough monitoring and testing of the API batches.
- 12.44 An exception can be made for retrospective validation for well-established processes that have been used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities, or the production process. This validation approach may be used where
  (1) Critical quality attributes and critical process parameters have been identified.
  (2) Appropriate in-process acceptance criteria and controls have been established.
  (3) There have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability.
  (4) Impurity profiles have been established for the existing API.
- 12.45 Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.

12.5. Process Validation Program

- 12.50 The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g., complex API processes or API processes with prolonged completion times). For retrospective validation, generally data from 10 to 30 consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified.
- 12.51 Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.
- 12.52 Process validation should confirm that the impurity profile for each API is within the limits specified. The impurity profile should be comparable to or better than historical data and, where applicable, the profile determined during process development or for batches used for pivotal clinical and toxicological studies.

12.6. Periodic Review of Validated Systems

- 12.60 Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

12.7. Cleaning Validation

- 12.70 Cleaning procedures should normally be validated. In general, cleaning validation should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to API quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.
- 12.71 Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same

equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability.

- 12.72 The cleaning validation protocol should describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled, and analytical methods. The protocol should also indicate the type of samples to be obtained and how they are collected and labeled.
- 12.73 Sampling should include swabbing, rinsing, or alternative methods (e.g., direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations (e.g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports or handling toxic materials, and small intricate equipment such as micronizers and microfluidizers).
- 12.74 Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery level should be established. Residue limits should be practical, achievable, verifiable, and based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological, or physiological activity of the API or its most deleterious component.
- 12.75 Equipment cleaning/sanitization studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API or other processes where such contamination could be of concern (e.g., nonsterile APIs used to manufacture sterile products).
- 12.76 Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis.

12.8. Validation of Analytical Methods

- 12.80 Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognized standard reference. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.
- 12.81 Methods should be validated to include consideration of characteristics included within the ICH guidelines on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.
- 12.82 Appropriate qualification of analytical equipment should be considered before starting validation of analytical methods.
- 12.83 Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

13. CHANGE CONTROL

- 13.10 A formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or API.
- 13.11 Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labeling and packaging materials, and computer software.
- 13.12 Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality unit(s).
- 13.13 The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. Classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g., as minor or major) depending on the nature and extent of the changes and the effects these changes may impart on the process. Scientific judgment should determine what additional testing and validation studies are appropriate to justify a change in a validated process.
- 13.14 When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.
- 13.15 After the change has been implemented, there should be an evaluation of the first batches produced or tested under the change.
- 13.16 The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or

API produced by the modified process can be placed on an accelerated stability program and/or can be added to the stability monitoring program.
- 13.17 Current dosage form manufacturers should be notified of changes from established production and process control procedures that can impact the quality of the API.

14. REJECTION AND REUSE OF MATERIALS

14.1. Rejection

- 14.10 Intermediates and APIs failing to meet established specifications should be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked as described below. The final disposition of rejected materials should be recorded.

14.2. Reprocessing

- 14.20 Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches, such reprocessing should be included as part of the standard manufacturing process.
- 14.21 Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. This is not considered to be reprocessing.
- 14.22 Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely impacted due to the potential formation of byproducts and overreacted materials.

14.3. Reworking

- 14.30 Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for nonconformance should be performed.
- 14.31 Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out, and the expected results. If there is only one batch to be reworked, then a report can be written and the batch released once it is found to be acceptable.
- 14.32 Procedures should provide for comparing the impurity profile of each reworked batch against batches manufactured by the established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used.

14.4. Recovery of Materials and Solvents

- 14.40 Recovery (e.g., from mother liquor or filtrates) of reactants, intermediates, or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.
- 14.41 Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or comingling with other approved materials.
- 14.42 Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.
- 14.43 The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented.

14.5. Returns

- 14.50 Returned intermediates or APIs should be identified as such and quarantined.
- 14.51 If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, the returned intermediates or APIs should be reprocessed, reworked, or destroyed, as appropriate.
- 14.52 Records of returned intermediates or APIs should be maintained. For each return, documentation should include the following:
  - Name and address of the consignee
  - Intermediate or API, batch number, and quantity returned
  - Reason for return
  - Use or disposal of the returned intermediate or API

15. COMPLAINTS AND RECALLS

- 15.10 All quality-related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.
- 15.11 Complaint records should include

- Name and address of complainant
- Name (and, where appropriate, title) and phone number of person submitting the complaint
- Complaint nature (including name and batch number of the API)
- Date complaint is received
- Action initially taken (including dates and identity of person taking the action)
- Any follow-up action taken
- Response provided to the originator of complaint (including date response sent) and
- Final decision on intermediate or API batch or lot

- 15.12 Records of complaints should be retained in order to evaluate trends, product-related frequencies, and severity with a view to taking additional and, if appropriate, immediate corrective action.
- 15.13 There should be a written procedure that defines the circumstances under which a recall of an intermediate or API should be considered.
- 15.14 The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated.
- 15.15 In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed and their advice sought.

16. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

- 16.10 All contract manufacturers (including laboratories) should comply with the GMP defined in this Guide. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.
- 16.11 Contract manufacturers (including laboratories) should be evaluated by the contract giver to ensure GMP compliance of the specific operations occurring at the contract sites.
- 16.12 There should be a written and approved contract or formal agreement between the contract giver and the contract acceptor that defines in detail the GMP responsibilities, including the quality measures, of each party.
- 16.13 The contract should permit the contract giver to audit the contract acceptor's facilities for compliance with GMP.
- 16.14 Where subcontracting is allowed, the contract acceptor should not pass to a third party any of the work entrusted to him under the contract without the contract giver's prior evaluation and approval of the arrangements.
- 16.15 Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available.
- 16.16 Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELERS

17.1. Applicability

- 17.10 This section applies to any party other than the original manufacturer who may trade and/or take possession, repack, relabel, manipulate, distribute, or store an API or intermediate.
- 17.11 All agents, brokers, traders, distributors, repackers, and relabelers should comply with GMP as defined in this Guide.

17.2. Traceability of Distributed APIs and Intermediates

- 17.20 Agents, brokers, traders, distributors, repackers, or relabelers should maintain complete traceability of APIs and intermediates that they distribute. Documents that should be retained and available include the following:
  - Identity of original manufacturer
  - Address of original manufacturer
  - Purchase orders
  - Bills of lading (transportation documentation)
  - Receipt documents
  - Name or designation of API or intermediate
  - Manufacturer's batch number
  - Transportation and distribution records
  - All authentic Certificates of Analysis, including those of the original manufacturer
  - Retest or expiry date

17.3. Quality Management

- 17.30 Agents, brokers, traders, distributors, repackers, or relabelers should establish, document, and implement an effective system of managing quality, as specified in Section 2.

17.4. Repackaging, Relabeling, and Holding of APIs and Intermediates

- 17.40 Repackaging, relabeling, and holding of APIs and intermediates should be performed under appropriate GMP controls, as stipulated in this Guide, to avoid mix-ups and loss of API or intermediate identity or purity.
- 17.41 Repackaging should be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.

17.5. Stability

- 17.50 Stability studies to justify assigned expiration or retest dates should be conducted if the API or intermediate is repackaged in a different type of container than that used by the API or intermediate manufacturer.

17.6. Transfer of Information

- 17.60 Agents, brokers, distributors, repackers, or relabelers should transfer all quality or regulatory information received from an API or intermediate manufacturer to the customer and from the customer to the API or intermediate manufacturer.
- 17.61 The agent, broker, trader, distributor, repacker, or relabeler who supplies the API or intermediate to the customer should provide the name of the original API or intermediate manufacturer and the batch number(s) supplied.
- 17.62 The agent should also provide the identity of the original API or intermediate manufacturer to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorized agents, depending on the legal relationship between the authorized agents and the original API or intermediate manufacturer. (In this context "authorized" refers to authorized by the manufacturer.)
- 17.63 The specific guidance for Certificates of Analysis included in Section 11.4 should be met.

17.7. Handling of Complaints and Recalls

- 17.70 Agents, brokers, traders, distributors, repackers, or relabelers should maintain records of complaints and recalls, as specified in Section 15, for all complaints and recalls that come to their attention.
- 17.71 If the situation warrants, the agents, brokers, traders, distributors, repackers, or relabelers should review the complaint with the original API or intermediate manufacturer in order to determine whether any further action, either with other customers who may have received this API or intermediate or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.
- 17.72 Where a complaint is referred to the original API or intermediate manufacturer, the record maintained by the agents, brokers, traders, distributors, repackers, or relabelers should include any response received from the original API or intermediate manufacturer (including date and information provided).

17.8. Handling of Returns

- 17.80 Returns should be handled as specified in Section 14.52. The agents, brokers, traders, distributors, repackers, or relabelers should maintain documentation of returned APIs and intermediates.

18. SPECIFIC GUIDANCE FOR APIS MANUFACTURED BY CELL CULTURE/FERMENTATION

18.1. General

- 18.10 Section 18 is intended to address specific controls for APIs or intermediates manufactured by cell culture or fermentation using natural or recombinant organisms and that have not been covered adequately in the previous sections. It is not intended to be a stand-alone section. In general, the GMP principles in the other sections of this document apply. Note that the principles of fermentation for "classical" processes for production of small molecules and for processes using recombinant and nonrecombinant organisms for production of proteins and/or polypeptides are the same, although the degree of control will differ. Where practical, this section will address these differences. In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.
- 18.11 The term "biotechnological process" (biotech) refers to the use of cells or organisms that have been generated or modified by recombinant DNA, hybridoma, or other technology to produce APIs. The APIs produced by biotechnological processes normally consist of high molecular weight substances, such as proteins and polypeptides, for which specific guidance is given in this section. Certain APIs of low molecular weight, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be produced by recombinant DNA technology. The level of control for these types of APIs is similar to that employed for classical fermentation.
- 18.12 The term "classical fermentation" refers to processes that use microorganisms existing in nature and/or modified by conventional methods (e.g., irradiation or chemical mutagenesis) to produce APIs. APIs produced by "classical fermentation" are normally low molecular weight products such as antibiotics, amino acids, vitamins, and carbohydrates.
- 18.13 Production of APIs or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of material from living organisms. Note that there may be additional process steps, such as physicochemical modification, that are part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, method of preparation, and the intended use of the API or intermediate, control of bioburden, viral contamination, and/or endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.

- 18.14 Appropriate controls should be established at all stages of manufacturing to assure intermediate and/or API quality. While this Guide starts at the cell culture/fermentation step, prior steps (e.g., cell banking) should be performed under appropriate process controls. This Guide covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing.
- 18.15 Appropriate equipment and environmental controls should be used to minimize the risk of contamination. The acceptance criteria for quality of the environment and the frequency of monitoring should depend on the step in production and the production conditions (open, closed, or contained systems).
- 18.16 In general, process controls should take into account:
  - Maintenance of the working cell bank (where appropriate)
  - Proper inoculation and expansion of the culture
  - Control of the critical operating parameters during fermentation/cell culture
  - Monitoring of the process for cell growth, viability (for most cell culture processes), and productivity where appropriate
  - Harvest and purification procedures that remove cells, cellular debris, and media components while protecting the intermediate or API from contamination (particularly of a microbiological nature) and from loss of quality
  - Monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production and
  - *Viral safety concerns as described in ICH Guideline Q5A* Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
- 18.17 Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities, and contaminants should be demonstrated.

18.2. Cell Bank Maintenance and Record Keeping

- 18.20 Access to cell banks should be limited to authorized personnel.
- 18.21 Cell banks should be maintained under storage conditions designed to maintain viability and prevent contamination.
- 18.22 Records of the use of the vials from the cell banks and storage conditions should be maintained.
- 18.23 Where appropriate, cell banks should be periodically monitored to determine suitability for use.
- *18.24 See ICH Guideline Q5D* Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products *for a more complete discussion of cell banking.*

18.3. Cell Culture/Fermentation

- 18.30 Where aseptic addition of cell substrates, media, buffers, and gases is needed, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.
- 18.31 Where the quality of the API can be affected by microbial contamination, manipulations using open vessels should be performed in a biosafety cabinet or similarly controlled environment.
- 18.32 Personnel should be appropriately gowned and take special precautions handling the cultures.
- 18.33 Critical operating parameters (e.g., temperature, pH, agitation rates, addition of gases, pressure) should be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability, for example) may not need to be monitored.
- 18.34 Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned, and sanitized or sterilized.
- 18.35 Culture media should be sterilized before use when appropriate to protect the quality of the API.
- 18.36 There should be appropriate procedures in place to detect contamination and determine the course of action to be taken. This should include procedures to determine the impact of the contamination on the product and those to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes should be identified as appropriate, and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.
- 18.37 Records of contamination events should be maintained.
- 18.38 Shared (multiproduct) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.

18.4. Harvesting, Isolation, and Purification

- 18.40 Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption, should be performed in equipment and areas designed to minimize the risk of contamination.
- 18.41 Harvest and purification procedures that remove or inactivate the producing organism, cellular debris,

and media components (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with consistent quality.
- 18.42 All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.
- 18.43 If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.
- 18.44 Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products.

18.5. Viral Removal/Inactivation Steps

- *18.50 See the ICH Guideline Q5A* Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin *for more specific information*.
- 18.51 Viral removal and viral inactivation steps are critical processing steps for some processes and should be performed within their validated parameters.
- 18.52 Appropriate precautions should be taken to prevent potential viral contamination from previral to post-viral removal/inactivation steps. Therefore, open processing should be performed in areas that are separate from other processing activities and have separate air handling units.
- 18.53 The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse. Appropriate precautions should be taken to prevent potential virus carryover (e.g., through equipment or environment) from previous steps.

19. APIs FOR USE IN CLINICAL TRIALS

19.1. General

- 19.10 Not all the controls in the previous sections of this Guide are appropriate for the manufacture of a new API for investigational use during its development. Section 19 provides specific guidance unique to these circumstances.
- 19.11 The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the drug product incorporating the API. Process and test procedures should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from preclinical stages through clinical stages. Once drug development reaches the stage where the API is produced for use in drug products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

19.2. Quality

- 19.20 Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism of approval of each batch.
- 19.21 A quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.
- 19.22 Some of the testing functions commonly performed by the quality unit(s) can be performed within other organizational units.
- 19.23 Quality measures should include a system for testing of raw materials, packaging materials, intermediates, and APIs.
- 19.24 Process and quality problems should be evaluated.
- 19.25 Labeling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.

19.3. Equipment and Facilities

- 19.30 During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean, and suitable for its intended use.
- 19.31 Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.

19.4. Control of Raw Materials

- 19.40 Raw materials used in production of APIs for use in clinical trials should be evaluated by testing or received with a supplier's analysis and subjected to identity testing. When a material is considered hazardous, a supplier's analysis should suffice.
- 19.41 In some instances, the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e., use testing) rather than on analytical testing alone.

19.5. Production

- 19.50 The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records, or by other appropriate means. These

documents should include information on the use of production materials, equipment, processing, and scientific observations.

- 19.51 Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.

19.6. Validation

- 19.60 Process validation for the production of APIs for use in clinical trials is normally inappropriate, where a single API batch is produced or where process changes during API development make batch replication difficult or inexact. The combination of controls, calibration, and, where appropriate, equipment qualification assures API quality during this development phase.
- 19.61 Process validation should be conducted in accordance with Section 12 when batches are produced for commercial use, even when such batches are produced on a pilot or small scale.

19.7. Changes

- 19.70 Changes are expected during development, as knowledge is gained and the production is scaled up. Every change in the production, specifications, or test procedures should be adequately recorded.

19.8. Laboratory Controls

- 19.80 While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated, they should be scientifically sound.
- 19.81 A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination, or discontinuation of an application.
- 19.82 Expiry and retest dating as defined in Section 11.6 applies to existing APIs used in clinical trials. For new APIs, Section 11.6 does not normally apply in early stages of clinical trials.

19.9. Documentation

- 19.90 A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.
- 19.91 The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriately documented.
- 19.92 A system for retaining production and control records and documents should be used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination, or discontinuation of an application.

GLOSSARY

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

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

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

Batch (or Lot): A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Batch Number (or Lot Number): A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.

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

Calibration: The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.

Computer System: A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions.

Computerized System: A process or operation integrated with a computer system.

Contamination: The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport.

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

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

Cross-Contamination: Contamination of a material or product with another material or product.

Deviation: Departure from an approved instruction or established standard.

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

Drug Substance: See Active Pharmaceutical Ingredient.

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

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

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

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

Intermediate: A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. (*Note*: This Guide only addresses those intermediates produced after the point that the company has defined as the point at which the production of the API begins.)

Lot: See Batch.

Lot Number: See Batch Number.

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

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

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

Packaging Material: Any material intended to protect an intermediate or API during storage and transport.

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

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

Process Control: See In-Process Control.

Production: All operations involved in the preparation of an API from receipt of materials through processing and packaging of the API.

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

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

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

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

Quarantine: The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

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

Reference Standard, Primary: A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be (1) obtained from an officially recognized source, (2) prepared by independent synthesis, (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material.

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

Reprocessing: Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process. Continuation of a process

step after an in-process control test has shown that the step is incomplete if considered to be part of the normal process and not reprocessing.

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

Reworking: Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g., recrystallizing with a different solvent).

Signature (signed): See definition for signed.

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

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

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. "Conformance to specification" means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

Validation: A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria.

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

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

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

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7 Validation of Analytical Procedures

I. INTRODUCTION

The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose. A tabular summation of the characteristics applicable to identification, control of impurities, and assay procedures is included. Other analytical procedures may be considered in future additions to this document.

II. TYPES OF ANALYTICAL PROCEDURES TO BE VALIDATED

The four most common types of analytical procedures are as follows:

- Identification tests
- Quantitative tests for impurities' content
- Limit tests for the control of impurities
- Quantitative tests of the active moiety in samples of drug substance or drug product or other selected component(s) in the drug product

Although there are many other analytical procedures, such as dissolution testing for drug products or particle size determination for drug substance, these have not been addressed in the initial text on validation of analytical procedures. Validation of these additional analytical procedures is equally important to those listed herein and may be addressed in subsequent documents.

A brief description of the types of tests considered in this document is provided below.

- Identification tests are intended to ensure the identity of an analyte in a sample. This is normally achieved by comparison of a property of the sample (e.g., spectrum, chromatographic behavior, chemical reactivity, etc.) to that of a reference standard.
- Testing for impurities can be either a quantitative test or a limit test for the impurity in a sample. Either test is intended to accurately reflect the purity characteristics of the sample. Different validation characteristics are required for a quantitative test than for a limit test.
- Assay procedures are intended to measure the analyte present in a given sample. In the context of this document, the assay represents a quantitative measurement of the major component(s) in the drug substance. For the drug product, similar validation characteristics also apply when assaying for the active or other selected component(s). The same validation characteristics may also apply to assays associated with other analytical procedures (e.g., dissolution).

The objective of the analytical procedure should be clearly understood since this will govern the validation characteristics which need to be evaluated. Typical validation characteristics which should be considered are listed below:

Accuracy
Precision
Repeatability
Intermediate Precision
Specificity
Detection Limit
Quantitation Limit
Linearity
Range

Each of these validation characteristics is defined in the attached Glossary. The table lists those validation characteristics regarded as the most important for the validation of different types of analytical procedures. This list should be considered typical for the analytical procedures cited, but occasional exceptions should be dealt with on a case-by-case basis. It should be noted that robustness is not listed in the table but should be considered at an appropriate stage in the development of the analytical procedure.

Furthermore revalidation may be necessary in the following circumstances:

- Changes in the synthesis of the drug substance
- Changes in the composition of the finished product and
- Changes in the analytical procedure

The degree of revalidation required depends on the nature of the changes. Certain other changes may require validation as well.

Type of Analytical Procedure Characteristics	Identification	Testing for Impurities Quantitation	Limit	Assay-Dissolution (Measurement Only)—Content/Potency
Accuracy	–	+	–	+
Precision				
Repeatability	–	+	–	+
Intermediate Precision	–	+[a]	–	+[a]
Specificity[b]	+	+	+	+
Detection Limit	–	–[c]	+	–
Quantitation Limit	–	+	–	–
Linearity	–	+	–	+
Range	–	+	–	+

– Signifies that this characteristic is not normally evaluated

+ Signifies that this characteristic is normally evaluated

[a] In cases where reproducibility (see Glossary) has been performed, Intermediate Precision is not needed.

[b] Lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s).

[c] May be needed in some cases.

VALIDATION METHODOLOGY OVERVIEW

I. INTRODUCTION

All relevant data collected during validation and formulae used for calculating validation characteristics should be submitted and discussed as appropriate.

Approaches other than those set forth in this guideline may be applicable and acceptable. It is the responsibility of the applicant to choose the validation procedure and protocol most suitable for their product. However, it is important to remember that the main objective of validation of an analytical procedure is to demonstrate that the procedure is suitable for its intended purpose. Because of their complex nature, analytical procedures for biological and biotechnological products in some cases may be approached differently than in this document.

Well-characterized reference materials, with documented purity, should be used throughout the validation study. The degree of purity necessary depends on the intended use.

In accordance with the parent document, and for the sake of clarity, this document considers the various validation characteristics in distinct sections. The arrangement of these sections reflects the process by which an analytical procedure may be developed and evaluated.

In practice, it is usually possible to design the experimental work such that the appropriate validation characteristics can be considered simultaneously to provide a sound, overall knowledge of the capabilities of the analytical procedure, for instance, specificity, linearity, range, accuracy, and precision.

II. SPECIFICITY

An investigation of specificity should be conducted during the validation of identification tests, the determination of impurities, and the assay. The procedures used to demonstrate specificity will depend on the intended objective of the analytical procedure.

It is not always possible to demonstrate that an analytical procedure is specific for a particular analyte (complete discrimination). In this case, a combination of two or more analytical procedures is recommended to achieve the necessary level of discrimination.

A. Identification

Suitable identification tests should be able to discriminate between compounds of closely related structures, which are likely to be present. The discrimination of a procedure may be confirmed by obtaining positive results (perhaps by comparison with a known reference material) from samples containing the analyte, coupled with negative results from samples, which do not contain the analyte. In addition, the identification test may be applied to materials structurally similar to or closely related to the analyte to confirm that a positive response is not obtained. The choice of such potentially interfering materials should be based on sound scientific judgment with a consideration of the interferences that could occur.

B. Assay and Impurity Test(s)

For chromatographic procedures, representative chromatograms should be used to demonstrate specificity, and individual components should be appropriately labeled. Similar considerations should be given to other separation techniques.

Critical separations in chromatography should be investigated at an appropriate level. For critical separations, specificity can be demonstrated by the resolution of the two components, which elute closest to each other.

In cases where a nonspecific assay is used, other supporting analytical procedures should be used to demonstrate overall specificity. For example, where a titration is adopted to assay the drug substance for release, the combination of the assay and a suitable test for impurities can be used.

The approach is similar for both assay and impurity tests.

1. Impurities Are Available

For the assay, this should involve demonstration of the discrimination of the analyte in the presence of impurities and/or excipients; practically, this can be done by spiking pure substances (drug substance or drug product) with appropriate levels of impurities and/or excipients and demonstrating that the assay result is unaffected by the presence of these materials (by comparison with the assay result obtained on unspiked samples).

For the impurity test, the discrimination may be established by spiking drug substance or drug product with appropriate levels of impurities and demonstrating the separation of

these impurities individually and/or from other components in the sample matrix.

2. Impurities Are Not Available

If impurity or degradation product standards are unavailable, specificity may be demonstrated by comparing the test results of samples containing impurities or degradation products to a second well-characterized procedure, for example, pharmacopoeial method or other validated analytical procedure (independent procedure). As appropriate, this should include samples stored under relevant stress conditions: Light, heat, humidity, acid/base hydrolysis, and oxidation.

- For the assay, the two results should be compared.
- For the impurity tests, the impurity profiles should be compared.

Peak purity tests may be useful to show that the analyte chromatographic peak is not attributable to more than one component (e.g., diode array, mass spectrometry).

III. LINEARITY

A linear relationship should be evaluated across the range (see Section 3) of the analytical procedure. It may be demonstrated directly on the drug substance (by dilution of a standard stock solution) and/or separate weighings of synthetic mixtures of the drug product components, using the proposed procedure. The latter aspect can be studied during investigation of the range.

Linearity should be evaluated by visual inspection of a plot of signals as a function of analyte concentration or content. If there is a linear relationship, test results should be evaluated by appropriate statistical methods, for example, by calculation of a regression line by the method of least squares. In some cases, to obtain linearity between assays and sample concentrations, the test data may need to be subjected to a mathematical transformation prior to the regression analysis. Data from the regression line itself may be helpful to provide mathematical estimates of the degree of linearity.

The correlation coefficient, y-intercept, slope of the regression line, and residual sum of squares should be submitted. A plot of the data should be included. In addition, an analysis of the deviation of the actual data points from the regression line may also be helpful for evaluating linearity.

Some analytical procedures, such as immunoassays, do not demonstrate linearity after any transformation. In this case, the analytical response should be described by an appropriate function of the concentration (amount) of an analyte in a sample.

For the establishment of linearity, a minimum of five concentrations is recommended. Other approaches should be justified.

IV. RANGE

The specified range is normally derived from linearity studies and depends on the intended application of the procedure. It is established by confirming that the analytical procedure provides an acceptable degree of linearity, accuracy, and precision when applied to samples containing amounts of analyte within or at the extremes of the specified range of the analytical procedure.

The following minimum specified ranges should be considered:

- For the assay of a drug substance or a finished (drug) product: Normally from 80% to 120% of the test concentration.
- For content uniformity, covering a minimum of 70% to 130% of the test concentration, unless a wider more appropriate range, based on the nature of the dosage form (e.g., metered dose inhalers), is justified.
- For dissolution testing: +/–20% over the specified range.

For example, if the specifications for a controlled released product cover a region from 20%, after 1 hour, up to 90%, after 24 hours, the validated range would be 0% to 110% of the label claim.

- For the determination of an impurity: From the reporting level of an impurity to 120% of the specification.
- For impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the detection/quantitation limit should be commensurate with the level at which the impurities must be controlled.
  Note: For validation of impurity test procedures carried out during development, it may be necessary to consider the range around a suggested (probable) limit.
- If assay and purity are performed together as one test and only a 100% standard is used, linearity should cover the range from the reporting level of the impurities[1] to 120% of the assay specification.

V. ACCURACY

Accuracy should be established across the specified range of the analytical procedure.

A. Assay

1. Drug Substance

Several methods of determining accuracy are available:

(a) Application of an analytical procedure to an analyte of known purity (e.g., reference material).
(b) Comparison of the results of the proposed analytical procedure with those of a second well-characterized procedure, the accuracy of which is stated and/or defined [independent procedure, see Assay and Impurity Test(s)].
(c) Accuracy may be inferred once precision, linearity, and specificity have been established.

2. Drug Product

Several methods for determining accuracy are available:

1. Application of the analytical procedure to synthetic mixtures of the drug product components to which known quantities of the drug substance to be analyzed have been added.
2. In cases where it is impossible to obtain samples of all drug product components, it may be acceptable either to add known quantities of the analyte to the drug product or to compare the results obtained from a second, well-characterized procedure, the accuracy of which is stated and/or defined [independent procedure, see Assay and Impurity Test(s)].
3. Accuracy may be inferred once precision, linearity, and specificity have been established.

B. Impurities (Quantitation)

Accuracy should be assessed on samples (drug substance/drug product) spiked with known amounts of impurities.

In cases where it is impossible to obtain samples of certain impurities and/or degradation products, it is considered acceptable to compare results obtained by an independent procedure [see Assay and Impurity Test(s)]. The response factor of the drug substance can be used.

It should be clear how the individual or total impurities are to be determined, for example, weight/weight or area percent, in all cases with respect to the major analyte.

C. Recommended Data

Accuracy should be assessed using a minimum of nine determinations over a minimum of three concentration levels covering the specified range (e.g., three concentrations/three replicates each of the total analytical procedure).

Accuracy should be reported as percent recovery by the assay of known added amount of analyte in the sample or as the difference between the mean and the accepted true value together with the confidence intervals.

VI. PRECISION

Validation of tests for assay and for quantitative determination of impurities includes an investigation of precision.

A. Repeatability

Repeatability should be assessed using:

(a) A minimum of nine determinations covering the specified range for the procedure (e.g., three concentrations/three replicates each) or
(b) A minimum of six determinations at 100% of the test concentration

B. Intermediate Precision

The extent to which intermediate precision should be established depends on the circumstances under which the procedure is intended to be used. The applicant should establish the effects of random events on the precision of the analytical procedure. Typical variations to be studied include days, analysts, equipment, etc. It is not considered necessary to study these effects individually. The use of an experimental design (matrix) is encouraged.

C. Reproducibility

Reproducibility is assessed by means of an interlaboratory trial. Reproducibility should be considered in case of the standardization of an analytical procedure, for instance, for inclusion of procedures in pharmacopoeias. These data are not part of the marketing authorization dossier.

D. Recommended Data

The standard deviation, relative standard deviation (coefficient of variation), and confidence interval should be reported for each type of precision investigated.

VII. DETECTION LIMIT

Several approaches for determining the detection limit are possible, depending on whether the procedure is a non-instrumental or instrumental. Approaches other than those listed below may be acceptable.

A. Based on Visual Evaluation

Visual evaluation may be used for non-instrumental methods but may also be used with instrumental methods.

The detection limit is determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be reliably detected.

B. Based on Signal-to-Noise

This approach can only be applied to analytical procedures which exhibit baseline noise.

Determination of the signal-to-noise ratio is performed by comparing measured signals from samples with known low concentrations of analyte with those of blank samples and establishing the minimum concentration at which the analyte can be reliably detected. A signal-to-noise ratio between 3 or 2:1 is generally considered acceptable for estimating the detection limit.

C. Based on the Standard Deviation of the Response and the Slope

The detection limit (*DL*) may be expressed as:

$$DL = \frac{3.3\tilde{A}}{S}$$

where,

σ = the standard deviation of the response
S = the slope of the calibration curve

The slope S may be estimated from the calibration curve of the analyte. The estimate of σ may be carried out in a variety of ways, for example:

1. Based on the Standard Deviation of the Blank

Measurement of the magnitude of analytical background response is performed by analyzing an appropriate number of blank samples and calculating the standard deviation of these responses.

2. Based on the Calibration Curve

A specific calibration curve should be studied using samples containing an analyte in the range of *DL*. The residual standard deviation of a regression line or the standard deviation of y-intercepts of regression lines may be used as the standard deviation.

D. Recommended Data

The detection limit and the method used for determining the detection limit should be presented. If *DL* is determined based on visual evaluation or based on the signal-to-noise ratio, the presentation of the relevant chromatograms is considered acceptable for justification.

In cases where an estimated value for the detection limit is obtained by calculation or extrapolation, this estimate may subsequently be validated by the independent analysis of a suitable number of samples known to be near or prepared at the detection limit.

VIII. QUANTITATION LIMIT

Several approaches for determining the quantitation limit are possible, depending on whether the procedure is a non-instrumental or instrumental. Approaches other than those listed below may be acceptable.

A. Based on Visual Evaluation

Visual evaluation may be used for non-instrumental methods but may also be used with instrumental methods.

The quantitation limit is generally determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be quantified with acceptable accuracy and precision.

B. Based on Signal-to-Noise Approach

This approach can only be applied to analytical procedures that exhibit baseline noise.

Determination of the signal-to-noise ratio is performed by comparing measured signals from samples with known low concentrations of analyte with those of blank samples and by establishing the minimum concentration at which the analyte can be reliably quantified. A typical signal-to-noise ratio is 10:1.

C. Based on the Standard Deviation of the Response and the Slope

The quantitation limit (*QL*) may be expressed as:

$$QL = \frac{10\tilde{A}}{S}$$

where

σ = the standard deviation of the response
S = the slope of the calibration curve

The slope S may be estimated from the calibration curve of the analyte. The estimate of σ may be carried out in a variety of ways, for example:

1. Based on Standard Deviation of the Blank

Measurement of the magnitude of analytical background response is performed by analyzing an appropriate number of blank samples and calculating the standard deviation of these responses.

2. Based on the Calibration Curve

A specific calibration curve should be studied using samples containing an analyte in the range of *QL*. The residual standard deviation of a regression line or the standard deviation of y-intercepts of regression lines may be used as the standard deviation.

D. Recommended Data

The quantitation limit and the method used for determining the quantitation limit should be presented.

The limit should be subsequently validated by the analysis of a suitable number of samples known to be near or prepared at the quantitation limit.

IX. ROBUSTNESS

The evaluation of robustness should be considered during the development phase and depends on the type of procedure under study. It should show the reliability of an analysis with respect to deliberate variations in method parameters.

If measurements are susceptible to variations in analytical conditions, the analytical conditions should be suitably controlled or a precautionary statement should be included in the procedure. One consequence of the evaluation of robustness should be that a series of system suitability parameters (e.g., resolution test) is established to ensure that the validity of the analytical procedure is maintained whenever used.

Examples of typical variations are:

- Stability of analytical solutions
- Extraction time

In the case of liquid chromatography, examples of typical variations are:

- Influence of variations of pH in a mobile phase
- Influence of variations in mobile phase composition
- Different columns (different lots and/or suppliers)
- Temperature
- Flow rate

In the case of gas chromatography, examples of typical variations are:

- Different columns (different lots and/or suppliers)
- Temperature
- Flow rate

X. SYSTEM SUITABILITY TESTING

System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations, and samples to be analyzed constitute an integral system that can be evaluated as such. System suitability test parameters to be established for a particular procedure depend on the type of procedure being validated. See pharmacopoeias for additional information.

20. FDA Bioanalytical Method Validation Guidance for Industry

A. Introduction

This guidance helps sponsors of investigational new drug applications (INDs) or applicants of new drug applications (NDAs), abbreviated new drug applications (ANDAs), biologic license applications (BLAs), and supplements validate bioanalytical methods used in human clinical pharmacology, bioavailability (BA), and bioequivalence (BE) studies that require pharmacokinetic, toxicokinetic, or biomarker concentration evaluation. This guidance can also inform the development of bioanalytical methods used for nonclinical studies that require toxicokinetic or biomarker concentration data. For studies related to the veterinary drug approval process such as investigational new animal drug applications (INADs), new animal drug applications (NADAs), and abbreviated new animal drug applications (ANADAs), this guidance may apply to blood and urine BA, BE, and pharmacokinetic studies.

The information in this guidance applies to bioanalytical procedures such as chromatographic assays (CCs) and ligand binding assays (LBAs) that quantitatively determine the levels of drugs, their metabolites, therapeutic proteins, and biomarkers in biological matrices such as blood, serum, plasma, urine, and tissue such as skin.

This final guidance incorporates public comments to the revised draft published in 2013 and provides recommendations for the development, validation, and in-study use of bioanalytical methods. The recommendations can be modified with justification, depending on the specific type of bioanalytical method. This guidance reflects advances in science and technology related to validating bioanalytical methods.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended but not required.

B. Background

The 2001 guidance for industry on *Bioanalytical Method Validation* was originally based on the deliberations of two workshops described in publications entitled:

- *Analytical Methods Validation: Bioavailability, Bioequivalence, and Pharmacokinetic Studies*[1]
- *Bioanalytical Methods Validation: A Revisit With a Decade of Progress*[2]

Additional workshops, summarized in the following publications, have informed subsequent revisions (e.g., the 2013 draft guidance for industry entitled *Bioanalytical Method Validation*[3]):

- *Quantitative Bioanalytical Methods Validation and Implementation: Best Practices for Chromatographic and Ligand Binding Assays*[4]
- *The AAPS/FDA Workshop on Incurred Sample Reanalysis*[5]
- *The AAPS Workshop on Crystal City V—Quantitative Bioanalytical Method Validation and Implementation: 2013 Revised FDA Guidance*[6]

Validated analytical methods for the quantitative evaluation of analytes (i.e., drugs, including biologic products, and their metabolites) and biomarkers in a given biological matrix (e.g., blood, plasma, serum, or urine) are critical for the successful conduct of nonclinical, biopharmaceutics, and clinical pharmacology studies. These validated methods provide critical data to support the safety and effectiveness of drugs and biologic products. Validating the analytical method ensures that the data are reliable by addressing certain key questions, including:

- Does the method measure the intended analyte? For example, does anything interfere with the measurement, and is the method specific or selective for the analyte?
- What is the variability associated with these measurements? For example, what are the accuracy and precision of the method?
- What is the range in measurements that provide reliable data? For example, what is the sensitivity of the method [e.g., what is the lower limit of quantitation

(LLOQ) of the method, and what is the upper limit of quantitation the method (ULOQ)?]?
- How do sample collection, handling, and storage affect the reliability of the data from the bioanalytical method? For example, what steps need to be followed while collecting samples? Do the samples need to be frozen during shipping? What temperatures are required to store the samples, and how long can the samples be stored?

When changes are made to a validated method, the sponsor should conduct additional validation (i.e., partial or cross validation).

The fit-for-purpose (FFP) concept states that the level of validation should be appropriate for the intended purpose of the study. The key questions listed above should be evaluated relative to the stage of drug development. Pivotal studies submitted in an NDA, BLA, or ANDA that require regulatory decision making for approval, safety, or labeling, such as BE or pharmacokinetic studies, should include bioanalytical methods that are fully validated. Exploratory methods that would not be used to support regulatory decision making (e.g., candidate selection) may not require such stringent validation. This FFP concept applies to drugs, their metabolites, and biomarkers.

The analytical laboratory conducting toxicology studies for regulatory submissions should adhere to 21 CFR 58, Good Laboratory Practices (GLPs).[7] The bioanalytical method for human BA, BE, and pharmacokinetic studies must meet the criteria specified in 21 CFR 320 Bioequivalence and Bioavailability Requirements (i.e., 21 CFR 320.29).

The following sections discuss the development, validation, and in-study use of bioanalytical methods and how best to document validation methods and results. Refer to the Glossary for the definitions of assay parameters and analytical terms used in this guidance.

C. Bioanalytical Method Development and Validation

1. Guiding Principles

The purpose of bioanalytical method development is to define the design, operating conditions, limitations, and suitability of the method for its intended purpose and to ensure that the method is optimized for validation.

Before the development of a bioanalytical method, the sponsor should understand the analyte of interest (e.g., determine the physicochemical properties of the drug, in vitro and in vivo metabolism, and protein binding) and consider aspects of any prior analytical methods that may be applicable.

The elements and acceptance criteria of method development and validation are summarized in Table 7.1. Table 7.2 describes how the sponsor should document the development and validation of the bioanalytical assay and where it should be stored or submitted.

Method development involves optimizing the procedures and conditions involved with extracting and detecting the analyte. Method development includes the optimization of the following bioanalytical parameters (which are discussed in greater detail in Section III.B) to ensure that the method is suitable for validation:

- Reference standards
- Critical reagents
- Calibration curve
- Quality control samples (QCs)
- Selectivity and specificity
- Sensitivity
- Accuracy
- Precision
- Recovery
- Stability of the analyte in the matrix

Bioanalytical method development does not require extensive record keeping or notation. However, the sponsor should record the changes to procedures as well as any issues and their resolutions during development of the bioanalytical method to provide a rationale for any changes during the development of the method.

Bioanalytical method validation proves that the optimized method is suited to the analysis of the study samples. The sponsor should:

- Conduct a full validation of any new bioanalytical method for the analysis of a new drug entity, its metabolite(s), or biomarkers.
- Conduct a full validation for any revisions to an existing validated method that adds a metabolite or an additional analyte.
- Establish a detailed, written description [e.g., protocol, study plan, and/or standard operating procedure (SOP)] for the bioanalytical method before initiating validation. The description should identify procedures that control critical parameters in the method (e.g., environmental, matrix, procedural variables) from the time of collection of the samples to the time of analysis to minimize their effects on the measurement of the analyte in the matrix.
- Document and report (in the method validation report) all experiments used to make claims or draw conclusions about the validity of the method.
- Validate the measurement of each analyte in the biological matrix. The specific recommendations and acceptance criteria for each bioanalytical parameter are listed in Table 7.1.

2. Bioanalytical Parameters of CCs and LBAs

The bioanalytical parameters applicable to CCs and LBAs are discussed below. Issues unique to either CCs or LBAs are specifically identified.

1. Reference Standards and Critical Reagents

The sponsor should appropriately characterize and document (e.g., determine the identity, purity, and stability) all reference standards and critical reagents, such as antibodies, labeled analytes, and matrices, and store them under defined conditions.

a. Reference Standards The purity of reference standards used to prepare calibrators and QCs can affect the study data. Therefore, the sponsor should use authenticated analytical reference standards with known identities and purities to prepare solutions of known concentrations. The reference standard should be identical to the analyte; however, when this scenario is not possible, the sponsor can use an established chemical form (e.g., free base, free acid, or salt) of known purity.

The sponsor should provide the Certificates of Analysis (CoA), including the source, lot number, and expiration date [with the exception of United States Pharmacopeia (USP) standards] for commercially available reference standards. For internally or externally generated reference standards that do not have a CoA, the sponsor should provide evidence of the standard's identity and purity in addition to the source and the lot number. When using expired reference standards, the sponsor should provide an updated CoA or re-establish the identity and purity of the standard. If the reference standard expires, the sponsor should not make stock solutions with this lot of standard unless the standard's purity is re-established. For internal standards (ISs), the sponsor does not have to provide a CoA or evidence of purity if it demonstrates that the IS is suitable for the specific use (e.g., lack of interference with an analyte).

b. Critical Reagents The sponsor should appropriately characterize and document (i.e., determine the identity, purity, and stability) the critical reagents, including—but not limited to—any reference standards, antibodies, labeled analytes, and matrices.

Assay validation is important when there are changes to the critical reagents, such as lot-to-lot changes or switches to another reagent. For example, if there are changes to the labeled analytes, detector reagents, or antibodies, the sponsor should:

- Evaluate binding and re-optimize assays
- Verify performance with a standard curve and QCs
- Evaluate cross-reactivities

2. Calibration Curve

During method development, the sponsor should choose the quantitation range of the assay and the concentrations of the calibration standards on the basis of the concentration range expected in a particular study. For LBAs, in addition to the calibration standards, anchor points outside the range of quantification can facilitate the fitting of the curve. Anchor points should not be used as part of the acceptance criteria for the run. For most LBAs, calibration (standard) curves are inherently nonlinear, and in general, more calibration standards are needed to define the fit over the calibration curve range for LBAs than for CCs. In addition, the response–error relationship for LBA standard curves is a variable function of the mean response (i.e., heteroscadisticity).

The sponsor should use the simplest model that adequately describes the concentration–response relationship, as well as an appropriate weighting scheme and regression equation. For LBAs, the concentration–response relationship is most often fitted to a four- or five-parameter logistic model, although other models can be assessed.

When the method is validated, the calibration curve should be continuous and reproducible. The sponsor should prepare the calibration standards in the same biological matrix as the samples in the intended study. Study samples may contain more than one analyte. The sponsor should generate a calibration curve for each analyte in the sample. When surrogate matrices are necessary, the sponsor should justify and validate the calibration curves.

The requirements for the calibration curve, including the LLOQ, ULOQ, as well as the acceptance criteria are listed in Table 7.1.

3. Quality Control Samples

Quality controls are used to assess the precision and accuracy of an assay and the stability of the samples. Sponsors should prepare QCs in the same matrix as the study samples to be assayed with the validated method. Freshly prepared QCs are recommended for precision and accuracy analyses during method development, as stability data are generally not available at this time.

During method validation, QCs evaluate the performance of a method and the stability of an analyte. Performance QCs are included in validation runs to determine the precision and accuracy of the method (see Section III.B). Stability QCs evaluate the stability of an analyte under various stress conditions (refer to Section III.B for the selection of QC concentrations).

The sponsor should prepare any calibration standards and QCs from separate stock solutions. However, if the sponsor can demonstrate the precision and accuracy in one validation run using calibrators and QCs prepared from separate stock solutions, then the sponsor can use calibrators and QCs prepared from the same stock solution in subsequent runs. The sponsor should make up calibrators and QCs in lots of blank matrix that is free of interference or matrix effects.

4. Selectivity and Specificity

During method development, the sponsor should verify that the substance being measured is the intended analyte to minimize or avoid interference. Selectivity of the method is routinely demonstrated by analyzing blank samples of the appropriate biological matrix (e.g., plasma) from multiple sources. Depending on the intended use of the assay, the impact of hemolyzed samples, lipemic samples, or samples from special populations can be included in the selectivity

assessment. When using liquid chromatography/mass spectrometry (LC/MS) methods, the sponsor or applicant should determine the effects of the matrix on ion suppression, ion enhancement, or extraction efficiency. Internal standards should be assessed to avoid interference with the analyte. Potential interfering substances in a biological matrix include endogenous matrix components such as metabolites, decomposition products—and from the actual study—concomitant medications and other xenobiotics. If a stabilizer or enzyme inhibitor is used during sample collection, the sponsor should evaluate the potential for interference on the quantitation of the analyte. Sponsors should make a scientific judgment about the need to assess these (and any other) potential interferences during method development.

During validation, the sponsor should confirm that the assay is free of potential interfering substances including endogenous matrix components, metabolites, anticipated concomitant medications, etc. If the study sample contains more than one analyte and the analytes are intended to be quantified by different methods, the sponsor should test each method for interference from the other analyte.

The sponsor should analyze blank samples of the appropriate biological matrix (e.g., plasma) from at least six (for CCs) or ten (for LBAs) individual sources. The sponsor should ensure that there are no matrix effects throughout the application of the method. Refer to Table 7.1 for details of selectivity and specificity requirements and acceptance criteria.

For LBAs, it is important to investigate any interference originating from structurally or physiologically similar analytes (i.e., exogenous interference) or matrix effects (i.e., endogenous interference). Investigating exogenous interference involves determining the cross-reactivity of molecules that could potentially interfere with the binding interaction, including molecules structurally related to the drug, any metabolites, concomitant medications (and their significant metabolites), or endogenous matrix components. The sponsor should evaluate each factor individually and in combination with the analyte of interest to determine its ability to cause interference. Matrix effects evaluation involves comparing calibration curves in multiple sources of the biological matrix against a calibration curve in the matrix for parallelism (serial dilution of incurred samples) and nonspecific binding. The sponsor should eliminate or minimize any significant interference. If such attempts are unsuccessful, the sponsor could consider the development of an orthogonal method to eliminate or minimize the interference.

Carryover between samples can occur in analytical methods. The sponsor should eliminate any carryover during method development. If carryover cannot be eliminated, the sponsor should assess the impact of any carryover during method validation on the accuracy of the study sample concentrations.

5. *Sensitivity*

The LLOQ defines the method sensitivity and should be determined during method development. The method should be developed and validated such that it will be able to meet the requirements necessary for the intended study samples. The LLOQ evaluation can be done separately or as part of the precision and accuracy assessment for the calibration range. The specific recommendations to validate sensitivity are listed in Table 7.1.

6. *Accuracy, Precision, and Recovery*

Evaluating the accuracy and precision across the quantitation range during method development is essential to determine whether the method is ready for validation and involves analyzing replicate QCs at multiple concentrations across the assay range. Specifically, the sponsor should evaluate the performance at the LLOQ, low, mid, and high QCs (and the ULOQ for LBAs) to determine if the method is suitable to analyze study samples.

Method validation experiments for estimating accuracy and precision should include a minimum of three (for CCs) or six (for LBAs) independent runs [i.e., accuracy and precision (A & P) runs; see Table 7.1] conducted over several days. Each A & P run should include a calibration curve and multiple QC concentrations that are analyzed in replicates. The sponsor should determine the accuracy and precision of the method based on the performance of the QC in the A & P runs. The specific validation requirements for accuracy and precision and A & P runs are listed in Table 7.1. The sponsor should use freshly prepared calibrators and QCs in all A & P runs. Use of freshly prepared QCs in all A & P runs is preferred; however, if this is not possible, the sponsor should use freshly prepared QCs in one or more A & P runs.

The sponsor should optimize the recovery of the analyte to ensure that the extraction is efficient and reproducible. Recovery need not be 100%, but the extent of the recovery of an analyte and of the ISs should be consistent and reproducible. The sponsor should perform recovery experiments by comparing the analytical results of extracted samples with corresponding extracts of blanks spiked with the analyte post-extraction (i.e., to represent 100% recovery).

Recovery evaluation is not necessary for LBAs unless sample extraction is involved. Recovery experiments should be performed as described in Table 7.1.

7. *Stability*

During method development, the sponsor should determine the chemical stability of the analyte in a given matrix, including the effects of sample collection, handling, and storage of the analyte. The sponsor should assess autosampler, benchtop, processed or extracted samples, freeze-thaw, stock solution, and long-term stability of the analyte. The sponsor should assess the stability in the same matrix as that intended for in-study samples; however, when the matrix is rare, the sponsor can explore the use of suitable surrogate matrices.

For drugs administered as fixed combinations, or part of a specific drug regimen, the stability of the analyte should be assessed in the presence of the other drug. The sponsor should also consider the stability of the analyte in the

presence of other co-medications that are known to be regularly administered to patients for the indication of the drug under development.

Depending on the analyte as well as the sample collection and assay conditions, evaluating the stability of the analyte in whole blood during method development can be useful. For example, a drug can be unstable in whole blood or adsorb to cellular components during collection.

During validation, stability evaluations should cover the expected sample conditions before receipt at the analytical site (e.g., at the clinical site, during shipment, and at all other secondary sites) as well as during receipt and analysis at the analytical site. Validation of drug stability in a biological fluid is a function of the storage conditions, the physicochemical properties of the drug, the matrix, and the container system. The stability of an analyte in a particular matrix and container system is relevant only to that matrix and container system and should not be extrapolated to other matrices and container systems.

If the storage conditions changed or the sample analysis occurred outside of the validated storage condition, the stability should be re-established under these new conditions. Stability testing of the analyte in whole blood should be revalidated if necessary (e.g., if the analytes are unstable during blood collection). The specific recommendations and acceptance criteria for stability are listed in Table 7.1.

Matrix-related stability experiments should compare stability QCs against freshly prepared calibration curves and freshly prepared QCs. Although the use of freshly prepared calibrators and QCs is the preferred approach, in some cases (e.g., for macromolecules), it may be necessary to freeze them overnight. In such cases, the sponsor should provide valid justification and demonstrate the freeze-thaw stability.

All stability determinations (see list below) should use a set of samples prepared from a freshly made stock solution of the analyte in the appropriate analyte-free, interference-free biological matrix.

- **Autosampler stability**: The sponsor should demonstrate the stability of extracts in the autosampler only if the autosampler storage conditions are different or not covered by extract (processed sample) stability.
- **Bench-top stability**: The sponsor should determine the stability of samples under the laboratory handling conditions that are expected for the study samples (e.g., the stability of samples maintained at room temperature or stored in an ice bucket).
- **Extract (or processed sample) stability**: The sponsor should assess the stability of processed samples, including the residence time in the autosampler against freshly prepared calibrators.
- **Freeze-thaw stability**: The sponsor should assess the stability of the sample after a minimum of three freeze-thaw cycles. QC samples should be thawed and analyzed according to the same procedures as the study samples. QC samples should be frozen for at least 12 hours between cycles. Freeze-thaw stability QCs should be compared to freshly prepared calibration curves and QCs.
- **Long-term stability**: The sponsor should determine the long-term stability of the sample over a period of time equal to or exceeding the time between the date of first sample collection and the date of last sample analysis. The storage temperatures studied should be the same as those used to store study samples. Long-term stability QCs should be compared to freshly prepared calibration curves and QCs. Determination of stability at –20°C would cover stability at colder temperatures.
- **Stock solution stability**: Stock solutions should not be made from reference materials that are about to expire unless the purity of the analyte in the stock solutions is re-established. When the stock solution exists in a different state (e.g., solution vs. solid) or in a different buffer composition (which is generally the case for macromolecules) from the certified reference standard, the sponsor should generate stability data on stock solutions to justify the duration of stock solution storage stability.

8. *Dilution Effects*

If the method measures diluted samples, the integrity of the dilution should be monitored during validation by diluting QC samples above the ULOQ with like matrix to bring to within quantitation range, and the accuracy and precision of these diluted QCs should be demonstrated. Dilutions used during the validation should mimic the expected dilutions in the study. The prozone effect should be demonstrated in LBAs. Refer to the specific recommendations and acceptance criteria in Table 7.1.

9. *Partial and Cross Validations*

The following section defines other types of methods validation.

a. *Partial Validation*

Partial validations evaluate modifications of already validated bioanalytical methods. Partial validation can range from as little as one intra-assay accuracy and precision determination to a nearly full validation. Raw data on partial validations should be retained at the analytical site for inspection when requested. Typical bioanalytical method modifications or changes that fall into this category include, but are not limited to, the following:

- Bioanalytical method transfers between laboratories
- Changes in analytical methodology (e.g., a change in detection systems)
- Changes in sample processing procedures
- Changes in sample volume (e.g., the smaller volume of pediatric samples)
- Changes in instruments and/or software platforms

- Extensions of the assay range
- Changes in the anticoagulant (but not changes in the counter-ion) in harvesting biological fluids (e.g., heparin to EDTA)
- Changes in the matrix within species (e.g., switching from human plasma to human blood) or changes to the species within the matrix (e.g., switching from rat plasma to mouse plasma)
- Changes to the matrices (e.g., cerebrospinal fluid)
- Demonstrating the selectivity of an analyte in the presence of concomitant medications
- Changes in LBA critical reagents (e.g., lot-to-lot changes, changes in reagents)

b. Cross Validation

Cross validation is a comparison of validation parameters of two or more bioanalytical methods or techniques that are used to generate data within the same study or across different studies.

Also, cross validation is necessary when sample analyses within a single study are conducted at more than one site or more than one laboratory. In such cases, cross validation with shared matrix QCs and non-pooled subject samples should be conducted at each site or laboratory to establish interlaboratory reliability. Pooled incurred samples can be used when insufficient volume exists. An SOP or validation plan should define the criteria a priori.

3. Validated Methods: Expectations of In-Study Analysis and Reporting

This section describes the expectations for the use of a validated bioanalytical method for routine drug analysis. The specific recommendations and acceptance criteria are listed in Table 7.1.

- If system suitability is assessed, a specific SOP should be used. System suitability, including apparatus conditioning and instrument performance, should be determined using samples that are independent of the current study calibrators, QCs, and study samples. Records of system suitability should be maintained and available for audits.
- Calibration curves and QCs should be included in all analytical runs (see Table 7.1 for details). The QCs should cover the expected study sample concentration range.
- Typically, the same curve fitting, weighting, and goodness-of-fit determined during validation should be used for the calibration curve within the study. Changes in the response–function relationship between the validation and study sample analyses indicate potential problems. A SOP should be developed a priori to address such issues.
- Total QCs should number at least 5% of the total samples analyzed or be at least six in number (low-, mid-, and high-QCs, in duplicate), whichever is greater (see Table 7.1 for details). Duplicate low-, mid-, and high-QCs should be used on all distinct processing batches within a run.
- If the study sample concentrations are clustered in a narrow range of the standard curve, additional QCs should be added to cover the sample range. If the additional QC concentrations are not bracketed by QCs validated before the study, the accuracy and precision of the additional QCs should be demonstrated before continuing with the analysis. If the partial validation is acceptable, samples that have already been analyzed do not require reanalysis.
- The QCs should be interspersed with study samples during processing and analysis.
- In each analytical run, the lack of analyte interference at the LLOQ should be confirmed (see Table 7.1 for Selectivity and Sensitivity).
- The analytical run fails if the calibration and/or QC acceptance criteria are not met (see Table 7.1).
- QC results (including outliers) from analytical runs that meet the acceptance criteria should be included in the estimation of accuracy and precision during the study's sample analysis. The QC results from all analytical runs (passed and failed) should be reported, but QC results from failed runs need not be included as part of the estimation of accuracy and precision.
- If the bioanalytical method necessitates separation of the overall analytical run into distinct processing batches (e.g., groups of samples processed at distinctly different times or by different analysts), each distinct batch should process duplicate QCs at all levels (e.g., low, middle, high) along with the study samples. Examples might include when the number of samples exceeds the capacity of a 96-well plate or when a solid phase extraction manifold cannot accommodate all samples. See Table 7.1 for what constitutes an acceptable run based on QC acceptance criteria. A distinct batch or batches in an analytical run may be rejected when it fails to meet QC acceptance criteria, but the remaining batches may pass provided that the analytical run meets the overall QC acceptance criteria.
- Study samples with concentrations listed below the LLOQ should be reported as below the LLOQ (BQL). Study samples with concentrations above the ULOQ should be diluted and re-analyzed, or the standard curve should be extended and revalidated.
- Study sample dilutions should use the same matrix (e.g., human plasma to human plasma).
- Assays of all study samples of an analyte in a biological matrix should be completed within the time period for which stability data are available. If sample handling conditions are changed or exceed

validated stability data, then the stability of the sample should be established at the new conditions.
- For CCs, the IS response should be monitored for variability. An SOP should be developed a priori to address issues with IS variability.
- Drift should be monitored, and its impact on the accuracy of the estimated unknown sample concentrations, if any, should be addressed (e.g., the impact of drift on the accuracy of interspersed QCs).
- All study samples from a subject should be analyzed in a single run, especially for studies designed with repeated measures from individual subjects (e.g., crossover or sequential design required for BE studies). If other approaches are taken, the sponsor or applicant should justify the approach and take steps to minimize the variability between periods.
- Carryover, if any, should be monitored, and its impact on the quantitation of study samples should be addressed.
- Incurred sample reanalysis (ISR) should be performed (see Section IV, Table 7.1 and Table 7.2).
- An SOP or guideline describing the reasons for a repeat analysis should be established a priori. Repeat analysis is acceptable only for assignable causes (e.g., the samples are above the ULOQ, there are sample processing errors, there is an equipment failure, the chromatography is poor). The SOP should include the acceptance criteria for reanalysis, and the sponsor or applicant should report final values. The specific recommendations are described in Table 7.1 and Table 7.2. The rationale, approach, and all data for the repeat analysis and reporting should be clearly documented.
- For study samples involving multiple analytes, a valid result for one analyte should not be rejected because of another analyte failing the acceptance criteria.
- If a unique or disproportionately high concentration of a metabolite is discovered in human studies, a fully validated assay may need to be developed for the metabolite, depending upon its activity (refer to the FDA guidance for industry entitled *Safety Testing of Drug Metabolites*).[8]
- An SOP or guideline for sample data re-integration for CCs should be established a priori. This SOP or guideline should define the criteria for re-integration and how the re-integration will be performed. The rationale for the re-integration should be clearly described and documented. Audit trails should be maintained. Original and re-integrated data should be documented and reported.

D. Incurred Sample Reanalysis

ISR is a necessary component of bioanalytical method validation and verifies the reliability of the reported study sample analyte concentrations. ISR is conducted by repeating the analysis of a subset of subject or patient samples from a given study in separate runs, preferably during the study, to critically support the precision and accuracy measurements established with the QCs. The original and repeat analyses should be conducted using the same bioanalytical method procedures. If a bulk frozen calibration curve was used for the original analysis, then it is acceptable to use a frozen curve for the ISR evaluation. The calibration curve, QCs, and study samples for the ISR evaluation should be extracted or processed separately from those used in the original runs. Incurred samples should not be pooled. ISR should be conducted in all studies submitted in an NDA, BLA, or ANDA that provide pivotal data for the approval or labeling of the product, regardless of the matrix. For instance, ISR is expected for all in vivo human BE studies in ANDAs or all pivotal pharmacokinetic, pharmacodynamic, and biomarker studies in NDAs or BLAs. For non-clinical safety studies, the performing laboratory should conduct ISR at least once for each method and species. Table 7.1 lists the sample requirements and acceptance criteria for ISR. Written SOPs should be established for the conduct of ISR and to guide an investigation in the event of ISR failure to resolve the lack of reproducibility. All aspects of ISR evaluations should be documented to allow reconstruction of the study, as well as guide any investigations (see Table 7.2).

The percentage difference of the results between the original study and the repeat study is determined with the following equation:

$$\left[\left(\text{Repeat} - \text{Original}\right) * 100\right] / \text{Mean}$$

E. Additional Issues

1. Endogenous Compounds

For analytes that are also endogenous compounds, the accuracy of the measurement of the analytes poses a challenge when the assay cannot distinguish between the therapeutic agent and the endogenous counterpart. In such situations, the following approaches are recommended to validate and monitor assay performance. Other approaches, if justified by scientific principles, can also be considered.

- The biological matrix used to prepare calibration standards should be the same as the study samples and free of the endogenous analyte. To address the suitability of using an analyte-free biological matrix, the matrix should be demonstrated to have: (1) no measurable endogenous analyte; and (2) no matrix effect or interference when compared to the biological matrix. The use of alternate matrices (e.g., buffers, dialyzed serum) for the preparation of calibration standards should be justified. The QCs should be prepared by spiking known quantities of the analyte in the same biological matrix as the study samples. The endogenous concentrations of

the analyte in the biological matrix should be evaluated before QC preparation (e.g., by replicate analysis). The concentrations for the QCs should account for the endogenous concentrations in the biological matrix (i.e., additive) and be representative of the expected study concentrations.
- Parallelism should be evaluated for assays for endogenous compounds.

2. Biomarkers

The recommendations in this guidance only pertain to the validation of assays to measure in vivo biomarker concentrations in biological matrices such as blood or urine. Considerable effort also goes into defining the biological function of biomarkers, and confusion may arise regarding terminology (e.g., biomarker method validation vs. biomarker qualification).

Biomarkers are increasingly used to assess the effects of new drugs and therapeutic biological products in patient populations. Because of the important roles biomarkers can play in evaluating the safety, activity, or effectiveness of a new medical product, it is critical to ensure the integrity of the data generated by assays used to measure them. Biomarkers can be used for a wide variety of purposes during drug development; therefore, an FFP approach should be used when determining the appropriate extent of method validation. When biomarker data will be used to support regulatory decision making, such as the pivotal determination of safety and/or effectiveness or to support dosing instructions in product labeling, the assay should be fully validated.

For assays intended to support early drug development (e.g., candidate selection, go-no-go decisions, proof-of-concept), the sponsor should incorporate the extent of method validation they deem appropriate.

Method validation for biomarker assays should address the same questions as method validation for drug assays. The accuracy, precision, sensitivity, selectivity, parallelism, range, reproducibility, and stability of a biomarker assay are important characteristics that define the method. The approach used for drug assays should be the starting point for validation of biomarker assays, although the FDA realizes that some characteristics may not apply or that different considerations may need to be addressed.

3. Diagnostic Kits

Diagnostic kits are sometimes co-developed with new drug or therapeutic biological products as analytical methods that are used during the development of new drugs and therapeutic biologics. The recommendations in this section of the guidance do not apply to commercial diagnostic kits intended for point-of-care patient diagnosis (e.g., companion diagnostic kits), which are addressed in the following CDRH guidance documents:

- *Principles for Co-development of an In Vitro Companion Diagnostic Device with a Therapeutic Product*[9]
- *In Vitro Companion Diagnostic Devices*

However, when commercial diagnostic kits are repurposed as analytical methods to measure the concentrations of drugs, therapeutic biologics, or biomarkers in development, the FDA has the following recommendations:

- LBA kits with various detection platforms are sometimes used to determine analyte concentrations in pharmacokinetic or pharmacodynamic studies when the reported results must exhibit sufficient precision and accuracy. Because such kits are generally developed for use as clinical diagnostic tools, their suitability for use in such studies should be demonstrated.
- Diagnostic kit validation data provided by the manufacturer may not ensure that the kit method is reliable for drug development purposes. In such situations, the performance of diagnostic kits should be assessed in the facility conducting the sample analysis.

Validation considerations for kit assays include, but are not limited to, the following examples:

- Site-specific validation should be performed. The specificity, accuracy, precision, and stability of the assay should be demonstrated under actual conditions of use. Modifications from kit processing instructions should be completely validated.
- Kits that use sparse calibration standards (e.g., one- or two-point calibration curves) should include in-house validation experiments to establish the calibration curve with a sufficient number of standards across the calibration range as specified in Table 7.1.
- Actual QC concentrations should be known. Concentrations of QCs expressed as ranges are not sufficient for quantitative applications. In such cases, QCs with known concentrations should be prepared and used, independent of the kit-supplied QCs.
- Standards and QCs should be prepared in the same matrix as the subject samples. Kits with standards and QCs prepared in a matrix different from the subject samples should be justified, and appropriate cross-validation experiments should be performed. Refer to Section V.A of this guidance for additional discussion.
- If the analyte source (i.e., reference standard) in the kit differs from that of the subject samples (e.g., the sample is a protein isoform of the reference standard), testing should evaluate differences in assay performance of the kit reagents.
- If multiple kit lots are used within a study, lot-to-lot variability and comparability should be addressed for any critical reagents.

- Individual batches using multiple assay plates (e.g., 96-well ELISA plates) should include sufficient replicate QCs on each plate to monitor the accuracy of the assay. Acceptance criteria should be established for the individual plates and the overall analytical run (refer to Table 7.1 and Section III.B).

4. Bridging Data from Multiple Bioanalytical Technologies

The FDA encourages the development and use of new bioanalytical technologies. However, the use of two different bioanalytical technologies for the development of a drug may generate data for the same product that could be difficult to interpret. This outcome can occur when one platform generates drug concentrations that differ from another platform. Therefore, when a new platform is used in the development of a drug, the data it produces should be bridged to that of the other method. This is best accomplished by assessing the output of both methods with a set of incurred samples (a minimum of 20 samples). In cases where one method produces data with a constant bias relative to the other, concentrations can be mathematically transformed by that factor to allow for appropriate study interpretation. Sponsors are encouraged to seek feedback from the appropriate FDA review division early in drug development. The use of two methods for BE studies in ANDAs is discouraged.

5. Dried Blood Spots

Dried blood spot (DBS) technology has been under development for several years. The benefits of DBS include reduced blood sample volumes collected for drug analysis as well as ease of collection, storage, and transportation. Additional validation of this sampling approach is essential before using DBS in regulatory studies. This validation should address, at a minimum, the effects of the following issues: storage and handling temperatures, homogeneity of sample spotting, hematocrit, stability, carryover, and reproducibility, including ISR. Correlative studies with traditional sampling should be conducted during drug development. Sponsors are encouraged to seek feedback from the appropriate FDA review division early in drug development.

F. Documentation

General and specific SOPs and good record keeping are essential to a properly validated analytical method. The data generated for bioanalytical method development and/or validation should be documented and available for data audit and inspection. Documentation at the analytical site and for submission to the FDA is described in Table 7.2.

All relevant documentation necessary for reconstructing the study as it was conducted and reported should be maintained in a secure environment. Relevant documentation includes, but is not limited to, source data, protocols and reports, records supporting procedural, operational, and environmental concerns, and correspondence records between all involved parties.

Regardless of the documentation format (i.e., paper or electronic), records should be contemporaneous with the event, and subsequent alterations should not obscure the original data. The basis for changing or reprocessing data should be documented with sufficient detail, and the original record should be maintained.

1. Summary Information

Summary information should include the following items:

- A summary of assay methods used for each study protocol should be included. Each summary should provide the protocol number, the protocol title, the assay type, the assay method identification code, the bioanalytical report code, and the effective date of the method.
- For each analyte, a summary table of all the relevant method validation reports should be provided, including partial validation and cross validation reports. The table should include the assay method identification code, the type of assay, the reason for the new method or additional validation (e.g., to lower the limit of quantification), and the dates of final reports. Changes made to the method should be clearly identified.
- A summary table cross-referencing multiple identification codes should be provided when an assay has different codes for the assay method, the validation reports, and the bioanalytical reports.

2. Documentation for Method Validation and Bioanalytical Reports

Refer to Table 7.2 for the FDA's recommended documentation for method validation and bioanalytical reports.

G. APPENDIX

TABLE 7.1
Recommendations and Acceptance Criteria for Bioanalytical Method Validation and In-Study Conduct (Refer to Sections III.A and III.B for Additional Information)

	Validation Recommendations		
Parameters	**Chromatographic Assays (CCs)**	**Ligand Binding Assays (LBAs)**	**In-Study Analysis Recommendations**
Calibration Curve	Elements: • A blank (no analyte, no IS), a zero calibrator (blank plus IS), and at least six, non-zero calibrator levels covering the quantitation range, including LLOQ in every run. • All blanks and calibrators should be in the same matrix as the study samples. • The concentration–response relationship should be fit with the simplest regression model. Acceptance Criteria: • Non-zero calibrators should be ±15% of nominal(theoretical) concentrations, except at LLOQ where the calibrator should be ±20% of the nominal concentrations in each validation run. • 75% and a minimum of six non-zero calibrator levels should meet the above criteria in each validation run.	Elements: • A blank and at least six, non-zero calibrator levels covering the quantitation range, including LLOQ per validation run. • Calibration curves are usually run in duplicate. • Additional calibrators may be used as anchor points. • All blanks and calibrators should be in the same matrix as the study samples. • The concentration–response relationship is usually fit with a four- or five-parameter logistic model. Other models may be acceptable with justification. Acceptance Criteria: • Non-zero calibrators should be ±20% of nominal (theoretical) concentrations, except at LLOQ and ULOQ where the calibrator should be ±25% of the nominal concentrations in each validation run. • 75% and a minimum of six non-zero calibrator levels should meet the above criteria in each validation run. • Anchor points should not be included in the curve fit.	Elements: • A blank, a zero, and at least six (in duplicate for LBAs) non-zero calibrator levels covering the expected range, including LLOQ per analytical run. • All blanks and calibrators should be in the same matrix as the study samples. • The in-study analysis should use the same regression model as used in validation. Acceptance Criteria: • CC: Non-zero calibrators should be ±15%, except at LLOQ where the calibrator should be • ±20% of nominal concentrations in each run. • LBA: Non-zero calibrators should be ±20%, except at LLOQ and ULOQ where the calibrator should be ±25% of nominal concentrations in each run. • CC and LBA: 75% and a minimum of six non-zero calibrator levels should meet the above criteria in each run.
	Only data points that fail to meet acceptance criteria may be excluded. Exclusion should not change the model used.		
Quality Controls (QC)	Elements: • For A & P Runs: Four QCs, including LLOQ, low (L: defined as three times the LLOQ), mid (M: defined as mid-range), and high (H: defined as high-range) from at least five replicates in at least three runs. • For Other Validation Runs: L, M, and H QCs in duplicates. Acceptance Criteria: • Refer to A & P Runs, Other Validation Runs, and Stability Evaluations.	Elements: • For A& P Runs: Five QCs, including LLOQ, L, M, H, and ULOQ from at least three replicates in at least six runs. • For Other Validation Runs: L, M, and H QCs in duplicates. Acceptance Criteria: • Refer to A & P Runs, Other Validation Runs, and Stability Evaluations.	Elements: • ≥ three QC levels (L, M, amd H) and ≥ two replicates per QC level in each analytical run. • Total QCs should be 5% of unknown samples • or ≥ six, whichever number is greater. • If the analytical runs consist of distinct processing batches, the QC acceptance criteria should be applied for the whole run and for each distinct batch within the runs. Acceptance Criteria: • CC: ≥67% of QCs should be ±15% of the nominal, and ≥50% of QCs per level should be • ±15% of their nominal. • LBA: ≥67% of QCs should be ±20% of the • nominal, and ≥50% of QCs per level should be • ±20% of their nominal.

(*Continued*)

TABLE 7.1 (CONTINUED)
Recommendations and Acceptance Criteria for Bioanalytical Method Validation and In-Study Conduct (Refer to Sections III.A and III.B for Additional Information)

	Validation Recommendations		
Parameters	**Chromatographic Assays (CCs)**	**Ligand Binding Assays (LBAs)**	**In-Study Analysis Recommendations**
	Elements: • Analyze blank samples of the appropriate biological matrix from at least six individual sources.	Elements: • Investigate parallelism (for endogenous products). • Conduct an analysis of blank samples in the matrix from ≥ ten individual sources.	CC Acceptance Criteria: • In each analytical run, the blank and zero calibrators should be free of interference at the retention times of the analyte and the internal standard. • In each analytical run, the internal standard response in the blank should not exceed 5% of average internal standard response of the calibrators and QCs. LBA Acceptance Criteria: • The blank should be free of interference for the analyte. • Parallelism should be conducted if not done during validation.
Selectivity	Acceptance Criteria: • Blank and zero calibrators should be free of interference at the retention times of the analyte(s) and the IS. • Spiked samples should be ±20% LLOQ. • The IS response in the blank should not exceed 5% of the average IS responses of the calibrators and QCs.	Acceptance Criteria: • For ≥80% of sources, unspiked matrix should be BQL, and spiked samples should be ±25% at LLOQ, and ±20% at H QC.	
Specificity	Elements: • The method specificity should be assessed for interference by cross-reacting molecules, concomitant medications, bio-transformed species, etc.	Elements: • The method specificity should be assessed for interference by cross-reacting molecules, concomitant medications, bio-transformed species, etc. • Potential interfering materials should be added to calibration curves in buffer.	Elements: • Check as needed.
	Acceptance Criteria: • See Selectivity above.	Acceptance Criteria: • QCs should meet ±20%, or 25% at the LLOQ and ULOQ.	
Carryover	Elements: • The impact of carryover on the accuracy of the study sample concentrations should be assessed. Acceptance Criteria: • Carryover should not exceed 20% of LLOQ.	Not applicable	Elements: • Carryover, if any, should be monitored, and its impact on the quantitation of study samples should be addressed. Acceptance Criteria: • Carryover should not exceed 20% of LLOQ.
Sensitivity	Elements: • The lowest nonzero standard on the calibration curve defines the sensitivity (LLOQ). Acceptance Criteria: • The analyte response at the LLOQ should be ≥ five times the analyte response of the zero calibrator. • The accuracy should be ±20% of nominal concentration (from ≥ five replicates in at least three runs). • The precision should be ±20% CV (from ≥ five replicates in at least three runs).	Elements: • The lowest nonzero standard on the calibration curve defines the sensitivity (LLOQ). Acceptance Criteria: • The accuracy should be ±25% of the nominal concentration (from ≥ three replicates in at least six runs). • The precision should be ±25% CV (from ≥ three replicates in at least six runs). • The total error should be ≤40%.	Acceptance Criteria: In each analytical run: • The analyte response at the LLOQ should be ≥ five times the analyte response of the zero calibrator (CC). • The A & P for CC should be ±20% of nominal concentration. • The A & P for LBA should be ±25% of nominal concentration. • If the above criteria are not met, the next higher calibrator can be selected as the new LLOQ or the next lower point if the ULOQ fails (provided the resulting calibration curve meets acceptance criteria) and does not change the calibration model.

(*Continued*)

TABLE 7.1 (CONTINUED)
Recommendations and Acceptance Criteria for Bioanalytical Method Validation and In-Study Conduct (Refer to Sections III.A and III.B for Additional Information)

	Validation Recommendations		
Parameters	**Chromatographic Assays (CCs)**	**Ligand Binding Assays (LBAs)**	**In-Study Analysis Recommendations**
	Elements: • A & P should be established with at least three independent A & P runs, four QC levels per run (LLOQ, L, M, H QC), and ≥ five replicates per QC level.	Elements: • A & P should be established with at least six independent A & P runs, five QC levels per run (LLOQ, L, M, H, ULOQ QC), and ≥ three replicates per QC level.	Elements: • Not applicable
Accuracy and Precision (A & P)	• A & P Run Acceptance Criteria: • The run should meet the calibration curve acceptance criteria and include the LLOQ calibrator.	• A & P Run Acceptance Criteria: • The run should meet the calibration acceptance criteria and include the LLOQ calibrator.	
	• This run has no QC acceptance criteria.	• This run has no QC acceptance criteria.	Accuracy: Between runs: • CC: ± 15% of nominal concentrations. • LBA: ± 20% of nominal concentrations.
	Accuracy: Within-run and between runs: • ±15% of nominal concentrations; except • ±20% at LLOQ.	Accuracy: Within-run and between runs: • ±20% of nominal concentrations; except • ±25% at LLOQ, ULOQ.	
	Precision: Within-run and between runs: • ±15% CV, except ±20% CV at LLOQ.	Precision: Within-run and between runs: • ± 20% CV, except ± 25% at LLOQ, ULOQ.	Precision: Between runs: • CC: ±15% CV. • LBA: ±20% CV.
	Total Error: • Not applicable.	Total Error: • QCs should be ±30%, except at LLOQ, ULOQ ±40%.	Total Error: • Not applicable.
Other Validation Runs	Elements: • ≥ three QC levels (L, M, H) in at least duplicates in each run.	Elements: • ≥ three QC levels (L, M, H) in at least duplicates in each run.	• Not applicable.
	Run Acceptance Criteria: • Meet the calibration acceptance criteria • ≥67% of QCs should be ±15% of the nominal (theoretical) values, ≥50% of QCs per level should be ±15% of their nominal concentrations.	Run Acceptance Criteria: • Meet the calibration acceptance criteria • ≥67% of QCs should be ±20% of the nominal (theoretical) values, and ≥50% of QCs per level should be ±20% of their nominal concentrations.	
Recovery	Elements: • Extracted samples at L, M, and H QC concentrations vs. extracts of blanks • spiked with the analyte post extraction (at L, M, and H).	Elements: • Need to be demonstrated only if extraction is involved.	
Stability	Elements: • For auto-sampler, bench-top, extract, freeze-thaw, stock solution, and long-term stability, per format least three replicates at L and H QC concentrations.	Elements: • For auto-sampler, bench-top, extract, freeze-thaw, stock solution/reagent, and long-term stability, perform at least three replicates at Land H QC concentrations.	Elements: • Update stability parameters (e.g., long-term) as needed.
	Acceptance Criteria: • The accuracy (% nominal) at each level should be ±15%.	Acceptance Criteria: • The accuracy (% nominal) at each level should be ±20%.	

(*Continued*)

TABLE 7.1 (CONTINUED)
Recommendations and Acceptance Criteria for Bioanalytical Method Validation and In-Study Conduct (Refer to Sections III.A and III.B for Additional Information)

	Validation Recommendations		
Parameters	**Chromatographic Assays (CCs)**	**Ligand Binding Assays (LBAs)**	**In-Study Analysis Recommendations**
Dilution	Elements: • QCs for planned dilutions, five replicates per dilution factor: • Accuracy: ±15% of nominal concentrations. • Precision: ±15% CV.	Elements: • QCs for planned dilutions. • Demonstrate dilution linearity. • Demonstrate lack of prozone effect, i.e., increasing analyte concentration results in no change or decreased signals compared to the preceding concentration. • Five replicates per dilution factor: • Accuracy: ±20% of nominal concentrations. • Precision: ±20% CV.	Elements: • Dilution QC (if not a validated pre-study). Acceptance Criteria: • Same as described under "QCs" above.
Incurred Sample Reanalysis (ISR)	• Not applicable.	• Not applicable.	Elements: • Sample size: • 10% reanalysis of the first 1000 samples, and • 5% reanalysis of the remaining samples. • Sample selection: • Around C_{max} and in the elimination phase. Acceptance Criteria: • CC: 67% should be ±20% of the mean. • LBA: 67% should be ±30% of the mean.
Repeat Analysis	• No reanalysis of individual calibrators and QCs is permitted.	• No reanalysis of individual calibrators and QCs is permitted.	• Reanalysis should be based on reasons described in a pre-existing SOP. • No reanalysis of calibrators and QCs. • At least the same number of replicates for repeats as originally tested. • No confirmatory repeats for BE studies.

TABLE 7.2
Documentation and Reporting (Refer to Sections III.B and VI for Additional Information)

Items	**Documentation at the Analytical Site**	**Validation Report[a]**	**Analytical Study Report[a]**
System Suitability	• Dates, times, QCs, or samples used for suitability testing	• Not applicable	• Not applicable
Synopsis	• Not applicable	• Synopsis of method development (e.g., evolution of methods with multiple revisions, unique aspects) • Overall summary information	• Not applicable
Reference Standards and Critical Reagents	• Certificate of Analysis (CoA) or purity, stability/expiration data, batch number, and manufacturer • Log records of receipt, use, and storage • If expired, recertified CoA or retest of purity and identity with retest dates • Internal standard CoA, purity or demonstration of suitability	• Batch/lot number, purity, and expiration (see Appendix VII, Table 7.4) • If expired, purity and stability at the time of use and retest dates	• Batch/lot number, purity, and expiration (see Appendix VII, Table 7.4) • If expired, purity and stability at the time of use and retest dates

(*Continued*)

TABLE 7.2 (CONTINUED)
Documentation and Reporting (Refer to Sections III.B and VI for Additional Information)

Items	Documentation at the Analytical Site	Validation Report[a]	Analytical Study Report[a]
Stock Solutions	• Log records of preparation, and use • Storage location and condition	• Brief description of preparation • Preparation dates • Stock solution stability • Storage conditions	• Brief description of preparation • Preparation dates • Stock solution stability • Storage conditions
Blank Matrix	• Records of matrix descriptions, receipt dates, and storage • Records of interference checks • Matrix effect results	• Description, lot number, receipt dates • Description of interference check • Matrix effect results	• Description, lot number, receipt dates • Description of interference check
Calibrators and QCs	• Records of preparation • Record of storage (e.g., in/out dates, temperatures)	• Brief description of preparation • Preparation dates • Storage conditions	• Brief description of preparation • Preparation dates • Storage conditions
SOPs	SOPs for all aspects of analysis, such as: • Method/procedure (validation/analytical) • Acceptance criteria (e.g., run, calibration curve, QCs) • Instrumentation • Reanalysis • ISR • Record of changes to SOP (change, date, reason, etc.)	• A detailed description of the assay procedure	• Not applicable
Sample Tracking	• Study sample receipt and condition on receipt • Temperature during shipment • Sample inventory and reasons for missing samples • Location of storage • Tracking logs of QC, calibrators, and study samples • Freezer logs for QC, calibrators, and study samples entry and exit	• Storage condition and location of QCs and calibrators	• Dates of receipt of shipments and contents • Sample condition on receipt • Analytical site storage condition and location • Total duration of sample storage • Any deviations from planned storage conditions
Analysis	• Documentation and data for system suitability checks • Instrument use log, including dates of analysis for each run • Sample extraction logs, including documentation of processing of calibrators, QCs, and study samples for each run, including dates of extraction • Identity of QC and calibrator lots, and study samples in each run • Documentation of instrument settings and maintenance • 100% of run summary sheets of passed and failed runs, including calibration curve, regression, weighting function, analyte and IS response, response ratio, integration type • 100% e-chromatograms of original and re-integrations from passed and fail runs • Laboratory information management system (LIMS) • Validation information, including documentation and data for:	• Table of all runs (including failed runs), instrument ID, and analysis dates • Tables of calibrator concentration and response functions results of all runs with accuracy and precision • Tables of within- and between-run QC results (from accuracy and precision runs) • Interference/matrix effect, sensitivity, carryover, dilution, recovery • Bench-top, freeze-thaw, long-term, extract, and stock solution stability • Stability QC storage and handling conditions (dates, duration, temperature, etc.) • Partial/cross-validation, if applicable • Append separate report for additional validation, if any • Include total error for LBA methods	• Table of all runs, status (pass and fail), reason for failure, instrument ID, and analysis dates (see Appendix VII, Table 7.4). • Table of calibrator concentration and response function results of all runs (pass and fail) with accuracy and precision • Table of QC results of all runs (pass and fail) with accuracy and precision results of the QC samples and between-run accuracy and precision results from successful runs • Table of re-injected runs with results from original and re- injected runs and reason(s) for reinjection • QC graphs trend analysis encouraged • Study concentration results table

(*Continued*)

TABLE 7.2 (CONTINUED)
Documentation and Reporting (Refer to Sections III.B and VI for Additional Information)

Items	Documentation at the Analytical Site	Validation Report[a]	Analytical Study Report[a]
	• Selectivity, sensitivity, precision and accuracy, carryover, dilution, recovery, matrix effect • Bench-top, freeze-thaw, long-term, and extract stability • Cross/partial validations, if applicable		
Chromatograms and Re-integration	• Electronic audit trail: Original and re-integration • Reason for re-integration • Mode of re-integration	• Representative chromatograms (original and re-integration) • Reason for re-integration	• Chromatograms from 20% of • serially selected subjects for BE studies in ANDAs • Randomly selected chromatograms from 5% of • studies submitted in NDAs and BLAs • Original and re-integrated chromatograms and initial and repeat integration results for BE studies • Reason for re-integration • SOP for re-integration
Deviations from Procedures	• Contemporaneous documentation of deviations/ unexpected events • Investigation of unexpected events • Impact assessment • ISR failure investigations	• Description of deviations • Impact on study results • Description and supporting data of significant investigations	• Description of deviations • Impact on study results • Description and supporting data of significant investigations
Repeat Analysis	• SOP for reanalysis (refer to Analysis) • 100% of repeat data • Contemporaneous records of reason for repeats	• Not applicable	• Table of sample IDs, reason for re-assay, original and re-assay values, reason for reported values, and run IDs and percent difference between original and re-assay values • Reanalysis SOP
ISR	• SOP for ISR • ISR data: Run IDs, run summary sheets, chromatograms or other electronic instrument data files • Document ISR failure investigations, if any	• Not applicable	• SOP for ISR • ISR data table (original, reanalysis, percent difference, percent passed) • ISR failure investigations, if any
Communication	• Between involved parties (sponsor, contract research organizations (CROs), and consultants) related to study/assay	• Not applicable	• Not applicable

[a] The FDA expects the sponsor to maintain data at the analytical site to support summary data submitted in Validation and Analytical Study Reports.

TABLE 7.3
Example of an Overall Summary Table for a Method Validation Report[a] or a Clinical Study Report (This Table Contains Fictitious Information, Which Serves Illustrative Purposes Only) and Report Format Examples Are Pertinent for Applications to Either CDER or CVM. Summary Tables Should Be Included in Module 2 of the eCTD

Items	Results	Hyperlink[b]	Comments
Methodology	LC/MS/MS	01-SOP-001	
Method Validation Report (MVR) number	MVR-001	MVR-001	
Biological matrix	Human plasma	MVR-001	
Anticoagulant (if applicable)	EDTA	MVR-001	
Calibration curve range	XXX–YYY ng/mL	Summary tables 001MVR-01/CC Tables Report text 001MVR-01/CCText	
Analyte of interest	Compound A	NA	
Internal standard	Compound A internal standard	NA	
Inter-run accuracy (for each QC concentration)	Low QC (AA ng/mL): X% Medium QC (e.g., BB ng/mL): Y% High QC (e.g., CC ng/mL): Z%	Summary tables 001MVR-01/APTables Report text 001MVR-01/APText	
Inter-run precision (for each QC concentration)	Low QC (AA ng/mL): X% Medium QC (BB ng/mL): Y% High QC (CC ng/mL): Z%		
Dilution integrity (specify dilution factors, QC concentrations, and matrices that were evaluated)	Dilution QC: CC ng/mL (dilution factor: X) Accuracy: Y% Precision: Z%	Summary tables 001MVR-01/DILTables Report text 001MVR-01/DILText	
Selectivity	<20% of the lower limit of quantification (LLOQ) -list drugs tested	Summary tables 001MVR-01/SELTables Report text 001MVR-01/SELText	
Short-term or bench- top temperature stability	Demonstrated for X hours at Y°C	Summary tables 001MVR-01/STSTables Report text 001MVR-01/STSText	
Long-term stability	Demonstrated for X days at Y°C	Summary tables 001MVR-01/LTSTables Report text 001MVR-01/LTSText	
Freeze-thaw stability	Demonstrated for Y cycles at Z°C	Summary tables 001MVR-01/FTSTables Report text 001MVR-01/FTSText	
Stock solution stability	Demonstrated for X weeks at Y°C	Summary tables 001MVR-01/SSSTables Report text 001MVR-01/SSSText	
Processed sample stability	Demonstrated for Y hours at Z°C	Summary tables 001MVR-01/PSSTables Report text 001MVR-01/PSSText	

(*Continued*)

TABLE 7.3 (CONTINUED)
Example of an Overall Summary Table for a Method Validation Report[a] or a Clinical Study Report (This Table Contains Fictitious Information, Which Serves Illustrative Purposes Only) and Report Format Examples Are Pertinent for Applications to Either CDER or CVM. Summary Tables Should Be Included in Module 2 of the eCTD

Items	Results	Hyperlink[b]	Comments
ISR	>67% of samples acceptable	Summary tables 001MVR-01/ISRTables Report text 001MVR-01/ISRText	
Recovery: Extraction efficiency	Summary tables 001MVR-01/EXTTables Report text 001MVR-01/EXTText		
Matrix effects	Summary tables 001MVR-01/MATTables Report text 001MVR-01/MATText		

[a] Failed method validation experiments should be listed, and data may be requested.
[b] For eCTD submissions, a hyperlink should be provided for the summary tables and report text.

TABLE 7.4
Example of Summary Analytical Runs for a Bioanalytical Study Report[a] (This Table Contains Fictitious Information, Which Serves Illustrative Purposes Only). Sponsors and Applicants Should Provide a Table Summarizing Both the Failed and Accepted Runs for Each Study. Clinical Study XXYY-0032456

Analytical run*	Batch Number within Analytical Run	Dates of Analysis	Results (Accepted/ Rejected)	Hyperlink[b]	Comments (e.g., Information on Runs that Failed)
001-100-01	Not applicable	MM/DD/YY	Rejected	Summary tables for calibration curve standards and QCs 001BR-01/01CALTables 001BR-01/01QCTables Report text 001BR-01/01CALText 001BR-01/01QCText Raw Data 001BR-01/01CALData 001BR-01/01QCData	001BR-01/01Failure 67% of the QCs passed; however both QCs that exceeded ±15% were at the low QC concentration. The follow-up investigation concluded that the LC/MS/MS instrument required a recalibration.
001-100-02	Not applicable	MM/DD/YY	Accepted	Summary tables for calibration curve standards and QCs 001BR-01/02CALTables 001BR-01/02QCTables Report text 001BR-01/02CALText 001BR-01/02QCText Raw Data 001BR-01/02CALData 001BR-01/02QCData	This is the reanalysis of the samples from run 001-100-01.

[a] If multiple batches are analyzed within an analytical run, each batch should be separately evaluated to determine if the batch meets acceptance criteria.
[b] For eCTD submissions, a hyperlink should be provided for the summary tables, report text, and raw data.

GLOSSARY

Accuracy: The accuracy of an analytical procedure expresses the closeness of agreement between the value, which is accepted either as a conventional true value or an accepted reference value and the value found. This is sometimes termed trueness.

Accuracy: Accuracy is the degree of closeness of the determined value to the nominal or known true value under prescribed conditions. Accuracy is also sometimes termed trueness.

Analyte: An analyte is the specific chemical moiety being measured; it can be an intact drug, a biomolecule or its derivative, a metabolite, or a degradation product in a biologic matrix.

Analytical Procedure: The analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include but is not limited to the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc.

Analytical run: An analytical run is a complete set of analytical and study samples with an appropriate number of standards and QCs for their validation. Several runs can be completed in one day, or one run may take several days to complete.

Assay (content or potency): To provide an exact result, which allows an accurate statement on the content or potency of the analyte in a sample.

Autosampler stability: Autosampler stability is the stability of the analyte in the processed sample under the conditions in the autosampler.

Batch: For purposes of this guidance, a batch is a number of unknown samples from one or more patients in a study and QCs that are processed at one time.

Bench-top stability: Bench-top stability is the stability of an analyte in a matrix under conditions of sample handling during sample processing.

Between run: Between run refers to the distinct period between or among several analytical or validation runs.

Biological matrix: A biological matrix is discrete material of biological origin that can be sampled and processed in a reproducible manner. Examples are blood, serum, plasma, urine, feces, cerebrospinal fluid, saliva, sputum, and various discrete tissues.

Blank: A blank is a sample of a biological matrix to which no analytes have been added that is used to assess the selectivity of the bioanalytical method.

Calibration curve: The calibration curve—also known as the standard curve—is the relationship between the instrument response and the calibration standards within the intended quantitation range.

Calibrators/Calibration standards: Calibrators, or calibration standards, refer to a biological matrix to which a known amount of analyte has been added. Calibration standards are used to construct calibration curves from which the concentrations of analytes in QC samples and in-study samples are determined.

Carryover: Carryover is the appearance of an analyte in a sample from a preceding sample.

Critical reagents: Critical reagents are requisite components of an assay, which include antibodies, labeled analytes, matrices, etc.

Detection Limit: The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample, which can be detected but not necessarily quantitated as an exact value.

Dilutional linearity: Dilutional linearity demonstrates the accurate measurement of concentrations of spiked samples (i.e., QCs) exceeding the quantitation range when serially diluted to within the quantitative assay range.

Extract stability: Extract stability assesses the degradation of the processed sample relative to the starting material.

Extract: An extract is a sample treated to remove impurities or interfering substances (also known as a processed sample).

Freeze-thaw stability: Freeze-thaw stability refers to the stability of the analyte in the matrix upon freezing and thawing.

Freshly prepared: Freshly prepared refers to QC sample preparation (i.e., spiked) on the day of the experiment, not frozen before use.

Full validation: Full validation refers to the establishment of all validation parameters that apply to sample analysis for the bioanalytical method for each analyte.

Heteroscadisticity: Heteroscadisticity occurs when the variance of a response is not constant but changes with the response.

Hook effect: The hook effect occurs when increasing analyte concentrations result in no change or decreased signals when compared to the preceding concentration.

Identification: To ensure the identity of an analyte.

Incurred sample reanalysis (ISR): ISR is the repeated measurement of an analyte's concentration from study samples to demonstrate reproducibility. Incurred samples: Incurred samples are study samples or samples from subjects or patients who were dosed.

Interference: Interference refers to the action of sample components, including structurally similar analytes, metabolites, impurities, degradants, or matrix components, that may impact quantitation of the analyte of interest. Refer to Selectivity and Matrix effect for further information.

Intermediate Precision: Intermediate precision expresses within-laboratories variations: Different days, different analysts, different equipment, etc.

Internal standard (IS): ISs are test compounds (e.g., structurally similar analogs, stable isotope labeled compounds) added to both calibration standards and

samples at known and constant concentrations to facilitate quantification of the target analyte(s).

Lack of specificity: Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedure(s).

Linearity: The linearity of an analytical procedure is its ability (within a given range) to obtain test results, which are directly proportional to the concentration (amount) of analyte in the sample.

Long-term stability: Long-term stability assesses the degradation of an analyte in the matrix relative to the starting material after periods of frozen storage.

Lower limit of quantification (LLOQ): The LLOQ is the lowest amount of an analyte that can be quantitatively determined with acceptable precision and accuracy.

Matrix effect: The matrix effect is a direct or indirect alteration or interference in response because of the presence of unintended analytes (for analysis) or other interfering substances in the sample.

Method: A method is a comprehensive description of all procedures used in the collection, storage, and analysis of samples.

Nominal concentration: The nominal concentration is the actual or intended concentration of the calibrator or quality control samples.

Non-zero calibrator: A non-zero calibrator is a calibrator to which the internal standard is added.

Parallelism: Parallelism demonstrates that the serially diluted incurred sample response curve is parallel to the calibration curve. Parallelism is a performance characteristic that can detect potential matrix effects and interactions between critical reagents in an assay.

Precision: The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: Repeatability, intermediate precision, and reproducibility. Precision should be investigated using homogeneous, authentic samples. However, if it is not possible to obtain a homogeneous sample, it may be investigated using artificially prepared samples or a sample solution. The precision of an analytical procedure is usually expressed as the variance, standard deviation, or coefficient of variation of a series of measurements. Precision is the closeness of agreement (i.e., degree of scatter) among a series of measurements obtained from multiple sampling of the same homogenous sample under the prescribed conditions.

Processed sample: A processed sample is the final extract (before instrumental analysis) of a sample that has been subjected to various manipulations (e.g., extraction, dilution, concentration).

Processing batch: A processing batch is a group of unknown samples from one or more study subjects, calibrators, and a set of QCs that are subjected to the analytical methodology together.

Prozone: The prozone is an effect observed when increasing analyte concentrations result in either no change or decreased detector response when compared to the preceding concentration (also see the Hook effect).

Purity Tests: To ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte, that is, related substances test, heavy metals, residual solvents content, etc.

Quality control sample (QC): A QC is a biological matrix with a known quantity of analyte that is used to monitor the performance of a bioanalytical method and to assess the integrity and validity of the results of study samples analyzed in an individual run.

Quantification range: The quantification range is the range of concentrations, including the ULOQ and the LLOQ, that can be reliably and reproducibly quantified with accuracy and precision with a concentration–response relationship.

Quantitation Limit: The Quantitation Limit of an individual analytical procedure is the lowest amount of analyte in a sample, which can be quantitatively determined with suitable precision and accuracy. The Quantitation Limit is a parameter of quantitative assays for low levels of compounds in sample matrices and is used particularly for the determination of impurities and/or degradation products.

Range: The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy, and linearity.

Reproducibility: Reproducibility is the precision between two laboratories. It also represents the precision of the method under the same operating conditions over a short period of time.

Recovery: Recovery refers to the extraction efficiency of an analytical process, reported as a percentage of the known amount of an analyte carried through the sample extraction and processing steps of the method.

Reference standard: A reference standard is a chemical substance of known purity and identity which is used to prepare calibration standards and quality controls. Three types of reference standards are usually used: (1) certified (e.g., USP compendial standards), (2) commercially supplied, and (3) custom-synthesized.

Re-integration: Re-integration is a reanalysis of the chromatographic peak.

Repeatability: Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision.

Reproducibility: Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology).

Response function: Response function is the mathematical expression that describes the relationship between known sample concentrations and the response of the instrument (also refer to Calibration curve).

Robustness: The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

Sample: A sample is a generic term encompassing controls, blanks, unknowns, and processed samples.

Selectivity: Selectivity is the extent to which the method can determine a particular compound in the analyzed matrices without interference from matrix components.

Sensitivity: Sensitivity is defined as the lowest analyte concentration in the matrix that can be measured with acceptable accuracy and precision (i.e., LLOQ).

Specificity: Specificity is the ability to assess unequivocally the analyte in the presence of components, which may be expected to be present. Typically, these might include impurities, degradants, matrix, etc. Specificity is the ability of the method to assess, unequivocally, the analyte in the presence of other components that are expected to be present (e.g., impurities, degradation products, matrix components, etc.).

Spiked samples: A spiked sample is a general term that refers to calibrators (calibration standards) and quality controls.

Stability: Stability is a measure of the intactness an analyte (lack of degradation) in a given matrix under specific storage and use conditions relative to the starting material for given time intervals.

Standard curve: Refer to Calibration curve.

Stock solution: A stock solution refers to an analyte in a solvent or mixture of solvents at a known concentration, which is used to prepare calibrators or QCs.

Study samples: Study samples refer to samples from subjects or patients enrolled in a study.

System suitability: System suitability is a determination of instrument performance (e.g., sensitivity and chromatographic retention) by analyzing a set of reference standards before the analytical run.

Total error: Total error is the sum of the absolute value of the errors in accuracy (%) and precision (%). Total error is reported as percent (%) error.

Unknown: An unknown is a biological sample that is the subject of the analysis.

Upper limit of quantification (ULOQ): The ULOQ is the highest amount of an analyte in a sample that can be quantitatively determined with precision and accuracy.

Within-run: Within-run refers to the time period during a single analytical or validation run.

Zero calibrator: A zero calibrator is a blank sample to which the internal standard is added.

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8 Bioequivalence Testing of Topical Drugs

For topical dermatologic drug products, PK measurements in blood, plasma, and/or urine are usually not feasible to document BE because topical dermatologic products generally do not produce measurable concentrations in extracutaneous biological fluids. The BE determination for these products is thus often based on PD or clinical studies. An additional approach is to document BE through reliance on measurement of the active moiety(ies) in the stratum corneum. This approach is termed dermatopharmacokinetics (DPK). Although measurement of the active moiety(ies) in blood or urine is not regarded as an acceptable measurement of BE for dermatologic drug products, it may be used to measure systemic exposure.

I. INACTIVE INGREDIENTS

During the investigational new drug (IND) process for an NDA, the safety of inactive ingredients in a topical drug product should be documented by specific studies or may be based on a prior history of successful use in the same amount administered via the same route of administration in an approved product. The requisite safety studies to establish the safety of a new excipient during the investigational new drug (IND) process should be discussed with appropriate review staff at the FDA. For an ANDA, the safety of inactive ingredients in an ANDA can be based on a prior history of successful use in an NDA or ANDA. If the inactive ingredients in an ANDA are not the same as the reference listed drug, the applicant should demonstrate to the agency that the changes(s) do not affect the safety and/or efficacy of the proposed drug product. In some instances, a comparative bioavailability study will satisfy this recommendation. If preclinical or clinical studies are needed to demonstrate the safety of inactive ingredients(s) in the generic drug product, the ANDA may not be approved. In this circumstance, the applicant may wish to resubmit their application as an NDA under the provisions of 505(b)(1) or (b)(2) of the act.

II. WAIVER OF BIOEQUIVALENCE

In accordance with 21 CFR 314.94(a)(9)(v), generally, the test (generic) product intended for topical use must contain the same inactive ingredients as the RLD. For all topical drug products intended for marketing under an abbreviated application, documentation of in vivo bioequivalence is required under 21 CFR 320.21(b). For a topical solution drug product, in vivo bioequivalence may be waived if the inactive ingredients in the product are qualitatively identical and quantitatively essentially the same compared to the listed drug. In this setting, quantitatively *essentially the same* means that the amount/concentration of the inactive ingredient(s) in the test product cannot differ by more than ±5% of the amount/concentration of the listed drug. Where a test solution differs qualitatively or quantitatively from the listed drug, in vivo BE may be waived, provided the sponsor submits evidence that the difference does not affect safety and/or efficacy of the product at the time a waiver is requested.

III. BIOEQUIVALENCE APPROACHES

Comparative clinical trials are generally difficult to perform, highly variable, and insensitive. For these reasons, other approaches, such as DPK or pharmacodynamic (PD), may be used for BE determination.

A. Dermatopharmacokinetic Approaches

The DPK approach is comparable to a blood, plasma, urine PK approach applied to the stratum corneum. DPK encompasses drug concentration measurements with respect to time and provides information on drug uptake, apparent steady-state levels, and drug elimination from the stratum corneum based on a stratum corneum concentration–time curve.

When applied to diseased skin, topical drug products induce one or more therapeutic responses, where onset, duration, and magnitude depend on the relative efficiency of three sequential processes, namely, (1) the release of the drug from the dosage form, (2) penetration of the drug through the skin barrier, and (3) generation of the desired pharmacological effect. Because topical products deliver the drug directly to or near the intended site of action, measurement of the drug uptake into and drug elimination from the stratum corneum can provide a DPK means of assessing the BE of two topical drug products. Presumably, two formulations that produce comparable stratum corneum concentration–time curves may be BE, just as two oral formulations are judged BE if they produce comparable plasma concentration–time curves. Even though the target site for topical dermatologic drug products in some instances may not be the stratum corneum, the topical drug must still pass through the stratum corneum, except in instances of damage, to reach deeper sites of action. In certain instances, the stratum corneum itself is the site of action. For example, in fungal infections of the skin, fungi reside in the stratum corneum, and therefore DPK measurement of an antifungal drug in the stratum corneum represents direct measurement of drug concentration at the site of action. In instances where the stratum corneum is disrupted or damaged, in vitro drug release may provide additional information toward the BE assessment. In this context, the drug release rate may reflect drug delivery directly to the dermal skin site without passage through the stratum corneum. For antiacne drug products, target sites are the hair follicles and sebaceous glands. In this setting, the drug diffuses through the stratum corneum, epidermis, and

dermis to reach the site of action. The drug may also follow follicular pathways to reach the sites of action. The extent of follicular penetration depends on the particle size of the active ingredient if it is in the form of a suspension. Under these circumstances, the DPK approach is still expected to be applicable because studies indicate a positive correlation between the stratum corneum and follicular concentrations. Although the exact mechanism of action for some dermatologic drugs is unclear, the DPK approach may still be useful as a measure of BE because it has been demonstrated that the stratum corneum functions as a reservoir, and stratum corneum concentration is a predictor of the amount of drug absorbed.

For reasons thus cited, DPK principles should be generally applicable to all topical dermatologic drug products including antifungal, antiviral, antiacne, antibiotic, corticosteroid, and vaginally applied drug products. The DPK approach can thus be the primary means to document BA/BE. Additional information, such as comparative in vitro release data and particle size distribution of the active ingredient between the RLD and the test product, may provide additional supportive information. Generally, BE determinations using DPK studies are performed in healthy subjects because skin where disease is present demonstrates high variability and changes over time. Use of healthy subjects is consistent with similar use in BE studies for oral drug products.

A DPK approach is not generally applicable (1) when a single application of the dermatologic preparation damages the stratum corneum, (2) for otic preparations except when the product is intended for otic inflammation of the skin, and (3) for ophthalmic preparations because the cornea is structurally different from the stratum corneum. The following three sections of the guidance provide general procedures for conducting a BA/BE study using DPK methodology.

1. Performance and Validation of the Skin Stripping Technique

DPK studies should include validation of both analytical methods and the technique of skin stripping. Since the DPK approach involves two components of validation (sampling and analytical method), overall DPK variability may be greater than with other methodologies. For analytical methods, levels of accuracy, precision, sensitivity, specificity, and reproducibility should be documented according to established procedures. Although the forearm, back, thigh, or other part of the body can be used for skin stripping studies, most studies are conducted on the forearm, for reasons of convenience. Care should be taken to avoid any damage with physical, mechanical, or chemical irritants (e.g., soaps, detergents, agents). Usual hydration and environmental conditions should be maintained. After washing prior to treatment, sufficient time, preferably 2 hours, should be allowed to normalize the skin surface. Detailed and workable standard operating procedures (SOPs) for area and amount of drug application, excess drug removal, and skin stripping methodology should be developed. The product's stability during the course of the study should be established. If the product is unstable, the rate and extent of degradation in situ over the period should be determined accurately so that a correction factor may be applied. Skin on both left and right arms of healthy subjects may be used to provide eight or more sites per arm. The size of the skin stripping area is important to allow collection of a sufficient drug in a sample to achieve adequate analytical detectability. Inter- and intra-arm variability should be assessed, and the treatment sites should be randomized appropriately. If a sponsor or applicant is using multiple investigators to conduct a single study, the reproducibility of skin stripping data between the investigators should be established. Either of the following approaches are recommended:

- A dose–response relationship between the drug concentration in the applied dosage form and the drug concentration in the stratum corneum should be established using the skin stripping method. A DPK dose–response relationship is analogous to a dose proportionality study performed with solid oral dosage forms. This type of study can be readily performed using three different strengths of the formulations. These can be marketed or specially manufactured products. Alternatively, a solution of the active drug representing three concentrations can be prepared for this purpose. Amount of drug in the stratum corneum at the end of a specified time interval, such as 3 hours, can provide a dose–response relationship.
- The skin stripping method should be capable of detecting differences of ±25% in the strength of a product. This can be determined by applying different concentrations (e.g., 75%, 100%, 125%) of a test dosage form such as a simple solution to the skin surface for a specified exposure time such as 3 hours, executing the skin stripping method, and performing the appropriate statistical tests comparing the strength applied to the measured drug concentration in the stratum corneum.

Using the reference product, the approximate minimum time required for drug to reach saturation level in the stratum corneum should be determined. This study establishes the time point at which the elimination phase of the study may be initiated.

The drug concentration–time profile may vary with the drug, the drug potency class, formulation, subject, sites of application, circadian rhythm, ambient temperature, and humidity. These factors should be considered and controlled as necessary.

Circadian rhythms may be present and may affect the measurement of skin stripping drug concentration if the drug is also an endogenous chemical (e.g., corticosteroid or retinoic acid). In such circumstances, the baseline concentration of the endogenous compound should be measured over time from sites where no drug product has been applied.

IV. SAMPLE PILOT STUDY

The reference drug product is randomly applied to eight sites on one forearm, with skin stripping performed at incremental

times after application (e.g., 15, 30, 60, and 180 minutes) (see Figure 8.1). One site is used for each time point. Four additional sites at 180 minutes on the same arm should be assessed to provide a total of five replicates for the same time point. An additional site with no application of a drug product should be sampled as a control, yielding a total of nine sampling sites. The contralateral forearm may be used to assess dose–response and sensitivity relationships by applying at least three concentrations of the drug product or simple drug solution for 180 minutes in duplicates. Two additional applications of the reference drug product on the same arm should be tested for 180 minutes as well to provide additional information about inter- and intra-arm variability and reproducibility. A control site with no drug application should also be included for a total of nine sites on the contralateral arm. The pilot study should be carried out in at least six subjects. Stratum corneum samples are removed according to procedures described below and analyzed for drug concentration. Standard procedures should be followed in all elements of the study and should be carried through all subsequent studies.

A. DPK Bioequivalence Study Protocol

1. Protocol and Subject Selection

Healthy volunteers with no history of previous skin disease or atopic dermatitis and with healthy, homogeneous forearm (or other) skin areas sufficient to accommodate at least eight treatment and measurement sites (time points) should be recruited. The number of subjects to be entered may be obtained from power calculations using intra- and intersubject variability from the pilot study. Because skin stripping is highly sensitive to specific study site factors, care should be taken to perfecting the technique and enrolling a sufficient number of subjects. The following study design is based on a crossover study design, where the crossover occurs at the same time using both arms of a single subject. A crossover design in which subjects are studied on two different occasions may also be employed. If this design is employed, at least 28 days should be allowed to rejuvenate the harvested stratum corneum.

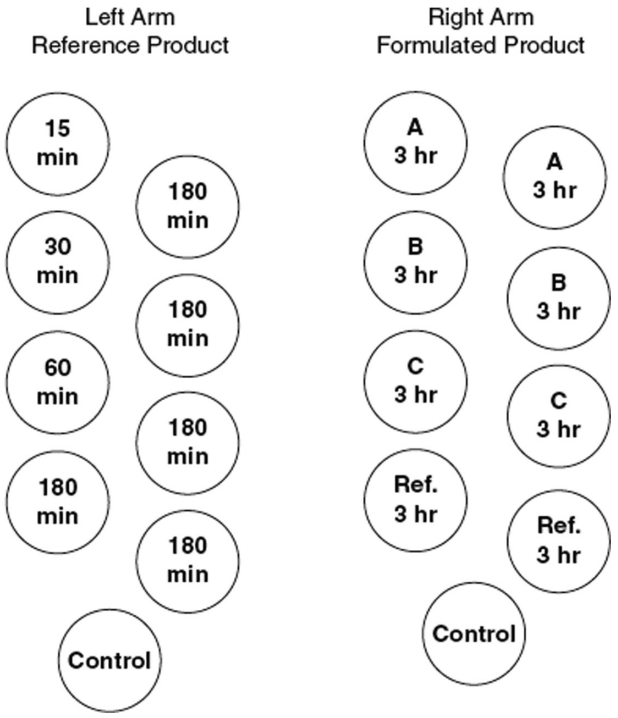

FIGURE 8.1 Schematic for drug application and removal sites for pilot study. (A) to (C) represent three concentrations of the drug product or drug solution.

2. Application and Removal of Test and Reference Products

The treatment areas are marked using a template without disturbing or injuring the stratum corneum/skin. The size of the treatment area will depend on multiple factors including drug strength, analytical sensitivity, the extent of drug diffusion, and exposure time. The stratum corneum is highly sensitive to certain environmental factors. To avoid bias and to remain within the limits of experimental convenience and accuracy, the treatment sites and arms should be randomized. Uptake, steady-state, and elimination phases, as described in more detail below, may be randomized between the right and left arms in a subject. Exposure time points in each phase may be randomized among various sites on each arm. The test and reference products for a particular exposure time point may be applied on adjacent sites to minimize differences. Test and reference products should be applied concurrently on the same subjects according to a SOP that has been previously developed and validated. The pre-marked sites are treated with predetermined amounts of the products (e.g., 5 mg/sq cm) and covered with a nonocclusive guard. Occlusion is used only if recommended in product labeling. Removal of the drug product is performed according to SOPs at the designated time points, using multiple cotton swabs or Q-tips with care to avoid stratum corneum damage. In case of certain oily preparations such as ointments, washing the area with a mild soap may be needed before skin stripping. If washing is carried out, it should be part of an SOP.

3. Sites and Duration of Application

The BE study should include measurements of drug uptake into the stratum corneum and drug elimination from skin. Each of these elements is important to establish bioavailability and/or bioequivalence of two products, and each may be affected by the excipients present in the product. A minimum of eight sites should be employed to assess uptake/elimination from each product. The time to reach steady state in the stratum corneum should be used to determine timing of samples. For example, if the drug reaches steady state in 3 hours, 0.25, 0.5, 1, and 3 hours posttreatment may be selected to determine uptake, and 4, 6, 8, and 24 hours may be used to assess elimination. A *zero* time point (control site away from test sites) on each subject should be selected to provide baseline data. If the test/reference drug products are studied on both forearms, randomly selected sites on one arm may

be designated to measure drug uptake/steady state. Sites on the contralateral arm may then be designated to measure drug elimination. During drug uptake, both the excess drug removal and stratum corneum stripping times are the same so that the stratum corneum stripping immediately follows the removal of the excess drug. In the elimination phase, the excess drug is removed from the sites at the steady-state time point, and the stratum corneum is harvested at succeeding times over 24 hours to provide an estimate of an elimination phase (see Figure 8.2).

4. Collection of Sample

Skin stripping proceeds first with the removal of the first one to two layers of stratum corneum with two adhesive tapes strip/disc applications, using a commercially available product (e.g., D-Squame, Transpore). These first two tape strips contain the generally unabsorbed, as opposed to penetrated or absorbed, drug and therefore should be analyzed separately from the rest of the tape strips. The remaining stratum corneum layers from each site are stripped at the designated time intervals. This is achieved by stripping the site with an additional ten adhesive tape strips. All ten tape strips obtained from a given time point are combined and extracted, with drug content determined using a validated analytical method. The values are generally expressed as amounts/area (e.g., ng/cm) to maintain uniformity in reported values. Data may be computed to obtain full drug concentration–time profiles, $C_{max\text{-}ss}$, $T_{max\text{-}ss}$, and AUCs for the test and reference products.

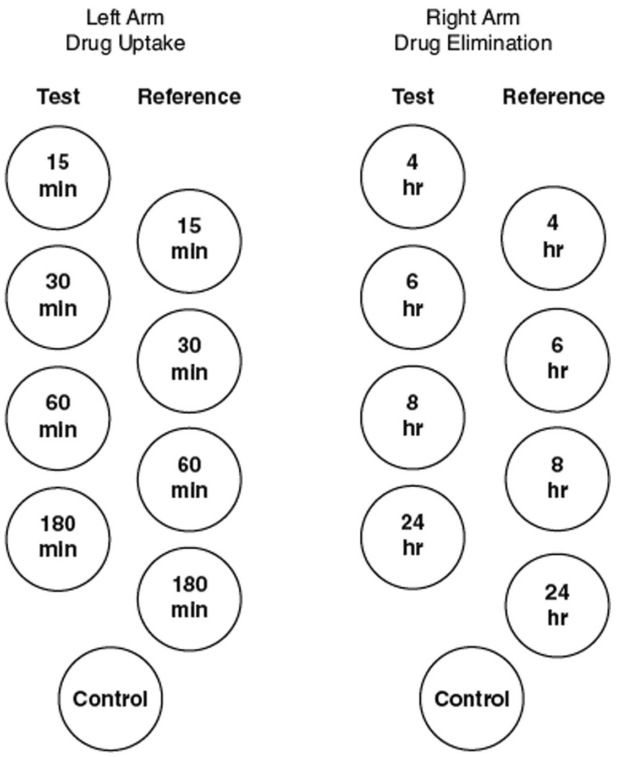

FIGURE 8.2 Schematic for drug uptake and drug elimination for bioequivalence study.

5. Procedure for Skin Stripping

The general test procedures in either the pilot study or the pivotal BA/BE study are summarized below.

To assess drug uptake:

- Apply the test and/or reference drug products concurrently at multiple sites.
- After an appropriate interval, remove the excess drug from a specific site by wiping three times lightly with a tissue or cotton swab.
- Using information from the pilot study, determine the appropriate times of sample collection to assess drug uptake.
- Repeat the application of adhesive tape two times, using uniform pressure, discarding these first two tape strips.
- Continue stripping at the same site to collect ten more stratum corneum samples.
- Care should be taken to avoid contamination with other sites.
- Repeat the procedure for each site at other designated time points.
- Extract the drug from the combined ten skin strippings, and determine the concentration using a validated analytical method.
- Express the results as amount of drug per square cm treatment area of the adhesive tape.

To assess drug elimination:

- Apply the test and reference drug product concurrently at multiple sites chosen based on the results of the pilot study. Allow sufficient exposure period to reach apparent steady-state level.
- Remove any excess drug from the skin surface as described previously, including the first two skin strippings.
- Collect skin stripping samples using ten successive tape strips at time intervals based on the pilot study and analyze them for drug content.

B. Metrics and Statistical Analyses

A plot of stratum corneum drug concentration vs. a time profile should be constructed to yield stratum corneum metrics of C_{max}, T_{max}, and AUC. The two one-sided hypotheses at the $p = 0.05$ level of significance should be tested for AUC and C_{max} by constructing the 90% confidence interval (CI) for the ratio between the test and reference averages. Individual subject parameters, as well as summary statistics (average, standard deviation, coefficient of variation, 90% CI) should be reported. For the test product to be BE, the 90% CI for the ratio of means (population geometric means based on log-transformed data) of test and reference treatments should fall within 80% to 125% for

AUC and 70% to 143% for C_{max}. Alternate approaches in the calculation of metrics and statistics are acceptable with justification.

V. PHARMACODYNAMIC APPROACHES

Sometimes topically applied dermatologic drug products produce direct/indirect PD responses that may be useful to measure BE. For example, topically applied corticosteroids produce a vasoconstrictor effect that results in skin blanching. This PD response has been correlated with corticosteroid potency and efficacy. Based on this PD response, FDA issued a guidance entitled *Topical Dermatological Corticosteroids: In Vivo Bioequivalence* (June, 1995). The guidance recommends that a pilot study be conducted to assess the dose–response characteristics of the corticosteroid followed by a formal study to assess BE. Topically applied retinoid produces transepidermal water loss that may be used as a PD measure to assess BE.

A. In Vitro Release Approaches (Lower Strength)

Usually, only one strength of a topical dermatologic drug product is available although sometimes two or, rarely, three strengths may be marketed. When multiple strengths are available, a standard practice is to create lower strengths by altering the percentage of active ingredients without otherwise changing the formulation or its manufacturing process. Topical dermatologic drug products usually contain relatively small amounts of the active drug substance, usually ≤5% and frequently ≤1%. In this setting, changes in the active ingredient may have little impact on the overall formulation.

Safety and efficacy should be documented for all strengths of topical drug products in the NDA submissions. Using some of the approaches suggested in this guidance, BA may also be documented for the highest strength. For lower strengths, where documentation of BA is considered important, this guidance suggests that in vitro release may be performed. Similarly, for an ANDA, when bioequivalence has been documented for the highest strength, in vitro release may also be used to waive in vivo studies to assess bioequivalence between these lower strengths and the corresponding strengths of the RLD. If this approach suggests bioinequivalence, further studies may be important.

To support the BE of lower strengths in an ANDA, the following conditions are important.

- Formulations of the two strengths should differ only in the concentration of the active ingredient and equivalent amount of the diluent.
- No differences should exist in manufacturing process and equipment between the two strengths.
- For an ANDA, the RLD should be marketed at both higher and lower strengths.
- For an ANDA, the higher strength of the test product should be BE to the higher strength of RLD.

In vitro drug release rate studies should be measured under the same test conditions for all strengths of both the test and RLD products. The in vitro release rate should be compared between (1) the RLD at both the higher (RHS) and lower strengths (RLS), and (2) the test (generic) products at both higher (THS) and lower strengths (TLS). Using the in vitro release rate, the following ratios and comparisons should be made:

Release rate of RHS/Release rate of RLS ≈ Release rate of THS/Release rate of TLS

The ratio of the release rates of the two strengths of the test products should be about the same as the ratio of the release rate of reference products, that is:

(Release rate of RHS × Release rate of TLS)/Release rate of RLS × Release rate of THS) ≈ 1. Using appropriate statistical methods, the standard BE interval (80–120) for a lower strength comparison of test and reference products should be used.

After approval, a sponsor may wish to develop an intermediate strength of a topical dermatologic drug product when two strengths have been approved and are in the marketplace. In this case, the in vitro release rate of the intermediate strength should fall between the in vitro release rates of the upper and lower strengths. Modifications of the approach described in this section of the guidance can thus be applied, providing all strengths differ only in the amount of active ingredient and do not differ in manufacturing processes and equipment.

B. In Vitro Release: Extension of the Methodology

Drug release from semisolid formulations is a property of the dosage form. Current scientific consensus is that in vitro release is an acceptable regulatory measure to signal inequivalence in the presence of certain formulation and manufacturing changes. With suitable validation, in vitro release may be used to assess batch-to-batch quality, replacing a series of tests that in the aggregate assess product quality and drug release (e.g., particle size determination, viscosity, and rheology). Because topical dosage forms are complex dosage forms, manufacturers should optimize the in vitro release test procedure for their product in a manner analogous to the use of in vitro dissolution to assess the quality of extended-release products from batch to batch. In addition, in vitro release might be used in a sponsor-specific comparability protocol to allow more extensive post-approval changes in formulation and/or manufacturing, provided that BE between two products representing the extremes of the formulation and manufacturing changes have been shown to be bioequivalent, using approaches recommended earlier in this document.

C. Systemic Exposure Studies

To ensure safety, and, when appropriate, comparable safety, information on systemic exposure is important for certain types of topical dermatologic drug products, such as retinoid and high-potency corticosteroids. The degree of systemic exposure for the majority of topical dermatologic drug products may be determined via standard in vivo blood, plasma, or urine PK techniques. For corticosteroids, an in vivo assessment of the HPA axis suppression test may provide the information. For other topical dermatologic drug products, such tests may not be needed.

9 Active Pharmaceutical Ingredients: GMP Compliance and Inspection

COMPLIANCE

I. INTRODUCTION

The U.S. FDA has recently updated a program in its Compliance Program Guidance Manual chapter on Drug Quality Assurance, entitled *Active Pharmaceutical Ingredient (API) Process Inspection* (Compliance Program). The program has been updated to address API compliance with the adulteration provisions of the Federal Food, Drug, and Cosmetic Act (the Act) in light of FDAs efforts as part of its "Pharmaceutical CGMPs for the 21st Century" initiative. Among other things, the revised program elaborates on the Agency's current risk-based, systems approach to inspections as it applies to the manufacture of APIs and incorporates an ICH-developed guidance document, ICH Q7A, to clarify appropriate good manufacturing practice requirements for APIs.

Active pharmaceutical ingredients, colloquially referred to as "APIs," are considered adulterated

> if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of … safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

The act does not distinguish between APIs and drug products regarding what constitutes adulteration or current good manufacturing practices (cGMPs). However, FDA has delineated the two. FDA has promulgated regulations establishing the cGMPs for finished pharmaceuticals, found in 21 CFR Parts 210 and 211, but has not developed similar regulations specifically for APIs or drug components.

FDA has consistently maintained that the concepts provided for finished pharmaceutical cGMPs in parts 210 and 211 are valid and applicable "in concept" when considering API manufacturing. Among the several concepts described in the finished pharmaceutical cGMPs are the ideas of building quality into the drug by using suitable equipment and employing appropriate personnel, establishing and implementing adequate written procedures and controls to assure that the processes and controls used in manufacturing are valid, and ensuring drug stability throughout the product's intended use period.

Although the concepts are universal, as FDA contends, the processes used in the manufacture of APIs and drug products are not. In fact, the process characteristics of an API and a drug product are fundamentally different. API processing includes chemical and biological processing, including synthesis, fermentation, extraction, and purification, while drug product processing includes physical processing, such as granulating, dissolving, mixing, and compressing. Because of this difference, API and drug product processing employ distinct facilities, equipment, and processes. This process distinction results in differences in process water quality, in process controls, process validation, reprocessing and rework, and recovery of materials and solvents. To help illuminate what constitutes cGMPs for APIs, FDA has adopted as part of the Compliance Program an internationally harmonized guidance, *ICH Q7A, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*, which was developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and which specifically addresses the distinctive attributes of API processes.

As FDA reminds in the Compliance Program, the guidance represents its current thinking on cGMPs for APIs. Moreover, the Compliance Program adopts the ICH Q7A definition of "active pharmaceutical ingredient," which is defined under the guidance as

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

The adoption and incorporation of ICH Q7A into the Compliance Program reaffirms FDA's abandonment of its March 1998 Draft Guidance to Industry on *Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients*, even though the document has not been officially withdrawn. Thus, ICH Q7A is essential to the Compliance Program; not only does it establish the definition FDA applies to determine what constitutes an API, but it also serves as the guidelines to FDA for inspecting the processes of API manufacturers. Nevertheless, even given ICH Q7A's importance to the Compliance Program, FDA openly acknowledges there are approaches not considered in ICH Q7A that may meet the cGMP requirements for API manufacture and that such approaches may be used if they satisfy the underlying statutory requirement. This position reflects FDA's current "science-based" policies.

II. FDA'S RISK-BASED, SYSTEMS APPROACH TO API INSPECTIONS

FDA maintains the goal of conducting inspections of API firms once every 2 years. In addition, the Center for Drug Evaluation and Research supplements this biennial target by providing additional API firms for inspection pursuant to Agency performance goals. FDA applies a risk-based strategy in inspecting these API manufacturers. This means that the frequency and depth of coverage of inspections is expected to reflect the relative risks associated with a firm's operations, including elements such as the firm's compliance history, the types of technology employed by the firm, and the intended use of the finished API. The risk-based approach allows the agency to adjust the regulatory scrutiny in a given circumstance to a level proportionate to the public health risks involved, to apply a uniform approach to the regulatory inspection process, and to place resources into the most useful and needed inspections.

The Compliance Program defines FDA's systems-based approach for the conduct of API inspections, which has been customized to evaluate API processes rather than drug product processes. Inspections of API facilities include an audit of two or more "systems," which are described generally by FDA as:

Quality System: The Quality System assures overall compliance with cGMPs and a company's internal procedures and specification.

Facilities and Equipment System: The Facilities and Equipment System comprises the physical environment and resources used to produce APIs.

Materials System: The Materials System includes the mechanisms by which starting materials, intermediates, and containers are controlled, including validation of computerized control processes, storage, and distribution controls.

Production System: The Production System is the scheme for controlling the manufacture of APIs; this includes in-process sampling/testing and process validation.

Packaging and Labeling System: The Packaging and Labeling System consists of elements that control the packaging and labeling of intermediates and APIs.

Laboratory Control System: The Laboratory Control System is the system used to direct laboratory procedures, testing, analytical methods development, and methods validation or verification, as well as the stability program.

These six areas of measures and activities form the basis of FDA's general regulatory inspection scheme.

As noted, every inspection of an API facility conducted by FDA includes a review of the Quality System. FDA will also apply its risk-based approach and select one or more additional systems for review. By reviewing at least two of the six systems, FDA believes it can adequately assess the overall "health" of the manufacturing practices utilized by the firm and forms an opinion of overall cGMP compliance based solely on the systems reviewed. FDA considers the inspection of the Quality System and the other selected systems to be applicable to each API product using the system and encourages inspectors to select a sufficient number and type of APIs to adequately review the system's coverage. The selected APIs are intended and expected to be representative of the firm's overall cGMP capabilities.

The Quality System

During each inspection, FDA will scrutinize an API manufacturer's Quality System, an assessment FDA views as having two phases. First, the inspector will evaluate whether the Quality Unit has fulfilled its responsibility to review and approve all procedures related to production, quality assurance, and quality controls and whether the procedures are adequate to fulfill their stated purpose, including associated record-keeping systems. Second, the inspector will assess the data collected pursuant to these specified procedures to identify quality problems. The Quality System evaluation may trigger a review of other major systems that were not otherwise slated for inspection.

Under the Compliance Program, an inspector is instructed to review and assess specified written and approved procedures and corresponding documentation resulting from implementation of the specified procedures that characterize an API manufacturer's Quality System. These include procedures and data regarding:

- The adequacy of staffing, as well as the training and qualification of employees in quality control functions
- The conduct of periodic quality reviews and complaint reviews
- Any discrepancy and failure investigations related to manufacturing and testing
- Batches manufactured since last inspection (to appraise any rejections or conversions)
- Change control
- Returns and salvages
- Rejects
- Reprocessing/reworking events
- Recalls
- The system for raw material release
- Stability failures and
- The status of validation activities

MANUFACTURING FACILITY INSPECTION

PART I—BACKGROUND

General

APIs are subject to the adulteration provisions of Section 501(a)(2)(B) of the act, which requires all drugs to be manufactured in conformance with cGMP. No distinction is made between an API and a finished pharmaceutical in the act,

and the failure of either to comply with cGMP constitutes a violation of the act. FDA has not promulgated cGMP regulations specifically for APIs or drug components (as we have for finished pharmaceuticals). Thus, the use of "cGMP" in this document refers to the requirements of the act rather than the requirements of 21CFR Parts 210 and 211 regulations for finished pharmaceuticals.

FDA has long recognized that the cGMP requirements in the good manufacturing practice regulations for finished pharmaceuticals (21 CFR Parts 210 and 211) are valid and applicable in concept to API manufacturing. These concepts include, among others, building quality into the drug by using suitable equipment and employing appropriately qualified and trained personnel, establishing adequate written procedures and controls designed to assure manufacturing processes and controls are valid, establishing a system of in-process material and final drug tests, and ensuring stability of drugs for their intended period of use. In 2001, FDA adopted an internationally harmonized guidance to industry on API cGMPs in conjunction with regulatory partners in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This guidance is ICH Q7A, *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients.* ICH Q7A represents the FDA's current thinking on cGMPs for APIs. Thus, API and related manufacturing and testing facilities that follow this guidance generally will be considered to comply with the statutory cGMP requirement. However, alternate approaches may be used if such approaches satisfy the requirements of Section 501(a)(2)(B) of the act as long as the approach ensures that the API meets its purported or represented purity, identity, and quality characteristics.

The term "active pharmaceutical ingredient" (API) is used in this program consistent with the meaning of this term as defined in ICH Q7A. An active pharmaceutical ingredient is defined in ICH Q7A as

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

Currently, other terms are also used by FDA and industry to mean an API. "Drug substance" and "bulk pharmaceutical chemical" (BPC) are the terms commonly used to mean API and, for BPC, inactive ingredients. The use of these terms to describe active ingredients may be considered equivalent to the term used here, API.

FDA expects API manufacturers to apply cGMPs to the API process beginning with the use of starting materials, and to validate critical process steps that impact the quality and purity of the final API. Controls over material quality are expected to increase as the process approaches the final API. The level of control needed is highly dependent on the manufacturing process and increases throughout the process as it proceeds from early intermediate steps to final isolation and purification steps. The appropriate level of control depends on the risk or criticality associated with each specific process step.

ICH Q7A contains general guidance to industry on the extent and application of cGMP for manufacturing APIs under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the quality and purity characteristics that they purport or are represented to possess. ICH Q7A is to be used as a guideline for inspecting API manufacturers and related facilities. If an investigator believes that a particular practice conforming to this guidance is believed to be deficient, the investigator or district should consult with CDER DMPQ before making an observation that is in conflict with ICH Q7A. A firm may also use alternate approaches to those described in ICH Q7A.

API manufacturers must register, and APIs in commercial distribution must be listed under Section 510(g) of the act unless exempted under 21 CFR 207.10. Foreign drug manufacturers are also required to register and list all drugs imported or offered for import into the United States. Refer to 21 CFR 207.40 for additional information on establishment registration and drug listing requirements for foreign drug facilities.

The inspection guidance in this program is structured for the efficient use of resources planned for routine surveillance coverage of API manufacturing facilities, recognizing that in-depth coverage of all systems and all processes is not feasible for all firms on a biennial basis. It also provides for follow-up compliance coverage as needed.

Scope of APIs Covered by This Program

An API process is a related series of operations which result in the preparation of an active pharmaceutical ingredient. Major operations or steps in an API process may include multistep chemical synthesis and fermentation, purification, crystallization, drying, milling, packing, labeling, and testing.

Some drugs processed similarly to an API may in fact be bulk finished product and subject to the requirements of 21 CFR Parts 210 and 211. If the drug material will not undergo further processing or compounding after its synthesis/fermentation/extraction but is merely repackaged into market containers, it is a bulk finished product. However, investigators should use this program as guidance when covering the synthesis/fermentation processes that result in such APIs rather than the program for dosage forms (CP 7356.002).

This program does not cover all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs as these drugs are regulated under the jurisdiction of the Center for Biologics Evaluation and Research.

The following APIs are to be inspected using CP7256.002M, Inspections of Licensed Biological Therapeutic Drug Products:

- Biotechnology-derived APIs, including those expressed from mammalian or bacterial cell cultures
- Polypeptides

Neither this Compliance Program nor ICH Q7A will provide guidance on the sterilization and aseptic processing of sterile APIs (see Q7A Section 1.3). Investigators are to use the finished product regulations (21 CFR 210 and 211) as guidance and follow CP 7356.002A, *Sterile Drug Process Inspections*, when inspecting the sterile processing of APIs labeled as sterile. Investigators are also to use FDA guidance on aseptic processing, *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, 2004, in evaluating aseptic processing conditions for sterile APIs.

PART II—IMPLEMENTATION

Objective

The primary objective of this Compliance Program is to provide comprehensive cGMP inspectional coverage of the domestic and foreign API industry in all profile classes (i.e., types of API manufacturing processes) to determine whether a manufacturer is operating in a state of control. An API manufacturer is considered to be operating in a state of control when it employs conditions and practices that assure compliance with the intent of Section 501(a)(2)(B) of the act. A firm in a state of control produces APIs for which there is an adequate level of assurance of quality, identity, and purity.

A firm is not in a sufficient state of control if any one system, as defined in this program, is found to be significantly noncompliant with cGMPs, such that the quality, identity, and purity of the API resulting from that system cannot be adequately assured. Documented cGMP deficiencies provide the evidence for concluding that a system is not operating in a state of control. See Part V, *Regulatory/Administrative Strategy*, for a discussion of compliance actions based on inspection findings demonstrating that a system(s) is not in a state of control.

Profile classes generalize inspection coverage from a small number of specific APIs to all APIs in that class. This program establishes a systems approach to further generalize inspection coverage from a small number of profile classes to an overall evaluation of the firm. This allows for preapproval program inspections to focus on the specific issues related to a given application and improves the review process by providing timely and efficient support for application decisions.

Inspection of API manufacturers should be conducted and reported using the system definitions and organization in this Compliance Program. Focusing on systems, rather than just profile classes, will increase efficiency in conducting inspections because the systems are often applicable to multiple profile classes. An inspection under this program is profileable and will result in a determination of acceptability/non-acceptability for all API profile classes. Inspection coverage should be representative of all API profile classes manufactured by the firm. All other profile classes should be covered under the main program CP 7356.002, or related program circular, as appropriate.

Program Management Instructions

The Field will conduct API manufacturing inspections and maintain profiles or other monitoring systems with the goal that each API firm will receive biennial inspectional coverage. CDER will also identify firms for inspection coverage under this program to fulfill CDER and agency annual performance goals and as part of an initiative to ensure risk-based prioritization of inspection coverage.

Unless specifically directed by CDER, the District Office is responsible for determining the frequency and depth of coverage given to each API firm consistent with this Compliance Program's instructions. cGMP inspectional coverage under this program shall be sufficient to assess the state of compliance for each firm.

An inspection under this program is defined as audit coverage of two or more systems (the "systems" are defined below in this section and are consistent with the main program, 7356.002), with mandatory coverage of the Quality System. Inspecting at least two systems (i.e., the Quality System and one other system) will provide the basis for an overall cGMP decision.

Coverage of a system should be sufficiently detailed, with specific examples selected, so that the system inspection outcome reflects the state of control in that system for every profile class. If a particular representative system is adequate, it should be adequate for all profile classes manufactured by the firm.

If an API selected for inspection coverage is associated with a unique processing or control function in a system not chosen for coverage, you may cover the unique function for that API. In doing so, you need not give full coverage to that system. For example, if an API chosen for coverage uses high purity water alone in its manufacture, you may inspect the water purification system without having to give full inspection coverage of the Materials System.

In some circumstances, it may not be possible to generalize certain deficiencies in a system to all API profile classes. If so, the unaffected profile classes may be considered acceptable if found otherwise acceptable.

Selecting unique functions within a system will be at the discretion of the investigator. Any given inspection need not cover every system.

Complete inspection of one system may necessitate further follow-up of some aspects of another system to fully document the findings. However, this coverage does not constitute nor require complete coverage of the other system.

A general scheme of systems for auditing the manufacture of API consists of the following:

1. *Quality System* assures overall compliance with cGMPs and internal procedures and specifications.
2. *Facilities and Equipment System* includes activities which provide an appropriate physical environment and resources used in the production of APIs.
3. *Materials System* includes measures and activities to control starting materials, intermediates, and containers. It includes validation of computerized and

inventory control processes, storage, and distribution controls.
4. *Production System* includes measures and activities to control the manufacture of APIs, including in-process sampling and testing, and process validation.
5. *Packaging and Labeling System* includes measures and activities that control the packaging and labeling of intermediates and APIs.
6. *Laboratory Control System* includes measures and activities related to laboratory procedures, testing, analytical methods development and methods validation or verification, and the stability program.

Detailed inspection coverage guidance under these systems is given in Appendix A of this program.

Inspection Planning

This program is intended to provide for a risk-based inspection strategy. Inspection depth should therefore reflect appropriate risks associated with a particular firm's operations, such as the firm's compliance history, the technology employed, the labeled and purported characteristics, and the intended use in the finished product, if known, of the APIs.

When a system is inspected, the inspection of that system may be considered applicable to all API products which use it. Investigators should select an adequate number and type of APIs to accomplish coverage of the system. APIs selected for coverage should be representative of the firm's overall abilities in manufacturing within cGMPs. (A profile classification scheme is used to categorize APIs by the nature of their processing, as described below.)

Profile class codes or APIs selected for coverage are to be representative of all APIs processed at the firm being inspected. Profile class codes may also be grouped by similarity, such that coverage of one profile class is sufficient to demonstrate cGMP conditions for another profile class. For example, inspecting a CSS API could amount to surrogate coverage of CSN. Similarly, inspecting a CBI could amount to surrogate coverage of other profile classes, such as CFN, CFS, and perhaps CEX.

The public health significance of certain cGMP deviations may be lower when the API is intended for a dosage form that has no dosage limitation, such as in products like calamine lotion or some OTC-medicated shampoos. Such APIs should be given inspection coverage of reduced depth and intensity.

Profile Classes

The inspection findings will be used as the basis for updating all profile classes in the profile screen of the FACTS EIR coversheet that is used to record profile/class determinations. *Normally, an inspection under this system approach will result in all profile classes being updated.* Effective with this program circular is a list of profile class codes that are used to report the processes covered during API inspections. These are as follows:

Profile Class	Full Description
CSN	Non-sterile API by chemical synthesis
CSS	Sterile API by chemical synthesis
CFN	Non-sterile API by fermentation
CFS	Sterile API by fermentation
CEX	Plant/animal extraction API
CTL	Control testing laboratory
CTX	Testing laboratory plus manufacturer
CRU	Crude bulk not elsewhere classified (CRU of bulk intermediates, and contract micronizers)

Types of Inspections

There are two basic types of inspections: Surveillance and compliance. Surveillance inspections are conducted on a routine basis to satisfy FDA's responsibilities to inspect drug manufacturing facilities. Compliance inspections are conducted in response to violative surveillance inspections and when a need arises to inspect a facility for-cause.

This program follows the approach in the main Compliance Program, 7356.002. There are two alternate approaches to inspect a facility to satisfy FDA inspection obligations; these are termed "Full Inspection" and "Abbreviated Inspection." These are described in Part III, *Inspectional*, of this program.

PART III—INSPECTIONAL

Inspections of API manufacturers, whether foreign or domestic, should be conducted by experienced investigators with education and/or training particularly in fermentation (see also 7356.002M for additional inspection guidance) and chemical synthesis manufacturing methods. Use of chemists and/or microbiologists during API inspections is recommended, particularly for evaluating laboratory operations (e.g., analytical methods evaluation, analytical data, laboratory procedures, and instrumentation), analytical review of methods used to establish impurity profiles, fermentation manufacturing processes, and complex multistep chemical synthesis processes.

Investigators conducting API inspections must understand the basic differences between the processes used for the production of APIs and those used for finished dosage forms. APIs are usually produced by chemical synthesis or by cell culture and extraction. Thus, the production of APIs typically involves significant changes of starting materials or intermediates by various chemical, physical, and biological processing steps. The ultimate objective in API processing generally is to achieve a pure compound of certain identity, whereas the ultimate objective of finished dosage form manufacturing generally is to achieve the uniform distribution of an API among many dosing units designed to deliver a precise amount of API to a specific area of the body.

Since manufacturers of APIs are often referenced in many drug applications, each inspection should cover representative APIs when covering the systems selected (e.g., if inspecting the Production System for a site making an API

by fermentation and another by synthesis, the inspection should include physical inspection and audit a sampling of records for both types of processing). This strategy, together with the classification of all profile classes upon completion of the inspection, will maximize the use of agency resources and avoid repeated visits to the same manufacturing site to cover different API profile classes referenced in subsequent applications. Any inspection of an API manufacturer should be recorded as a cGMP qualifying inspection.

Inspections should cover any specific APIs referenced in the assignment and any other representative APIs not inspected in the last 2 years. For foreign API firms, investigators should cover only APIs intended to be marketed or already marketed in the United States.

APIs selected for coverage should include those that are referenced in drug applications, are therapeutically significant, are intended for use in parenteral drug products, are difficult to manufacture, or are documented as having past compliance problems. However, this does not preclude the selection of less therapeutically significant APIs to evaluate specific APIs (or profile classes) not previously given in-depth coverage at the facility.

Investigators conducting API inspections should understand the general inspection strategy set forth in this program. Recognizing that API firms vary greatly in size, diversity of operations, and quality assurance systems, investigators should carefully plan their inspectional strategy at each firm. Further guidance on preparing an inspection strategy appears later.

Investigators should also review the firm's rationale for the point at which cGMPs begin, which is expected to vary by type of process (e.g., synthetic, fermentation, extraction, purification).

For an API inspection that is initiated by a preapproval assignment, CP 7346.832, Pre-Approval Inspections/ Investigations, inspection time should be reported under the appropriate program assignment codes referenced in both Compliance Programs based on the actual time spent in each program.

Inspection Approaches

This program provides two surveillance inspectional options:

Full Inspection Option and Abbreviated Inspection Option

Either option may satisfy the biennial inspection requirement.

Full Inspection Option

The full inspection option is a surveillance or compliance inspection which is meant to provide a broad and in-depth evaluation of the firm's conformity to cGMPs. The full inspection option is an inspection of at least four of the six systems as listed in Part II and Appendix A of this program, one of which must be the Quality System.

A Full Inspection Is Appropriate

a. For an initial FDA inspection of a facility, or after a significant change in management or organizational procedures, such as might occur after a change in ownership.
b. For a firm with a history of noncompliance or a recidivist firm whose ability to comply is short-lived. To determine if the firm meets this criterion, the District should use all information at its disposal, such as current and past inspection findings, results of sample analyses, complaints, recalls, and compliance actions.
c. To evaluate if important changes have occurred in the firm's state of control by comparing current operations against the EIR for the previous Full Inspection (e.g., by conducting a Full Inspection at every fourth inspection cycle.) In addition to changes in management or ownership, the following types of changes are typical of those that warrant the full inspection option:
    1. New potential for cross-contamination arising through changes in processing or type of APIs using that equipment
    2. Use of new technology requiring new expertise, significant equipment changes and/or additions, or new facilities
d. When District management or CDER specifically requests this option.
e. To follow up on a Warning Letter or other regulatory action.

Abbreviated Inspection Option

The abbreviated inspection option is a surveillance or compliance inspection which is meant to provide an efficient update evaluation of the firm's conformity to cGMPs. A satisfactory Abbreviated Inspection will provide documentation for continuing a firm in an acceptable cGMP compliance status. The abbreviated inspection option is an inspection audit of at least two systems but not more than three systems, one of which must be the Quality System. During the course of an Abbreviated Inspection, verification of Quality System activities may require limited coverage in other systems.

An Abbreviated Inspection is appropriate when the full inspection option is not warranted, including the following:

- To maintain surveillance over a historically compliant firm's activities and to provide input to the firm on maintaining and improving the cGMP level of assurance of quality of its APIs.
- When an intended Full Inspection finds objectionable conditions as listed in Part V of this program in one or more systems (a minimum of two systems must be completed) and District management and, as necessary, CDER Office of Compliance, concurs with reducing inspection coverage in order to expedite the issuance of a Warning Letter to correct violations.

Compliance Inspections

Compliance inspections are inspections done "for-cause" and to evaluate or verify corrective actions after a regulatory action has been taken. The coverage given in compliance inspections must be related to the areas found deficient and subjected to corrective actions.

In addition, coverage must be given to other systems because a determination must be made on the overall compliance status of the firm after the corrective actions are taken. The firm is expected to address all of its operations in its corrective action plan after a previously violative inspection, not just the deficiencies noted in the FDA-483. The full inspection option should be used for a compliance inspection, especially if the abbreviated inspection option was used during the violative inspection.

Compliance inspections include "For-Cause Inspections." For-Cause Inspections are for the purpose of investigating a specific problem that has come to the attention of the agency and may not result in the coverage of systems as described in this program. The problem may be identified by a complaint, recall, or other indicator of defective API or poorly controlled process. Coverage of these problems may be assigned under other Compliance Programs or PACs; however, expansion of the coverage to a cGMP inspection is to be reported under this program. For-Cause Inspections may be assigned under this program as the need arises.

Selecting Systems for Coverage

A complete description of each system and the areas for coverage are in Appendix A of this program. The selection of the system(s) for coverage and the relative depth or intensity of audit coverage should take into consideration the relative significance of a particular system for the firm's specific operating conditions, history of previous coverage, and history of cGMP compliance. It is expected that a Full Inspection will not be conducted every two years at most firms. Districts should select different systems for inspection coverage as a cycle of Abbreviated Inspections is carried out to build comprehensive information on the firm's total manufacturing activities over time.

Preparing the Inspection Strategy

This guidance is in addition to that given in the *Investigations Operations Manual*.

1. Select two or more, as appropriate, systems for inspection coverage as guided by this program (see Inspection Approaches above). Appendix A contains a detailed description of the inspection coverage to be given each system when selected for inspection.
2. Select significant APIs for inspection coverage, if not specified in the assignment. Significant APIs are those which use all the systems in the firm very broadly and/or use special manufacturing features, e.g., complex chemical synthesis, highly sensitizing material, material of an infectious nature, or a new chemical entity made under an approved drug application. Review the firm's FACTS listing, Drug Master Files (DMF), or A/NDA files.
3. If a CDER product or cGMP/regulatory reviewer (compliance officer) is assigned to participate as a member of the inspection team, the lead investigator is to brief them on the intended inspection strategy and explain their supporting role and responsibilities for the inspection. The lead investigator should consult the reviewer on any specific A/NDA Chemistry, Manufacturing and Controls issues (whether premarket or postmarket) to be covered during the inspection.
4. Review the impurity profile for each API process to be covered during the inspection and compare these to the impurity profiles submitted in the application or DMF, if filed. (Investigators and Chemists should be particularly familiar with USP <1086> Impurities in Official Articles.) If the impurity profile has not been filed to CDER, review the guidance on establishing impurity profiles in ICH Q3A and Q3C.
5. Review any compendia monographs for the APIs to be inspected to verify conformity, as appropriate.
6. Before or during the inspection, determine if the firm has made process changes by comparing current operations against the EIR for the previous inspection. Also compare the current operations with those filed in the DMF or the drug application to determine whether the firm is complying with commitments made to the agency. (See also CP 7346.832 for conducting a preapproval inspection of an API.) The following changes are typical of those that would warrant extensive coverage during the inspection:
   a. New potential for cross-contamination arising through changes in API processes or product-type lines, to include processing numerous APIs of varying toxicity in common equipment and/or facilities.
   b. Use of new technology requiring new expertise, significantly new equipment, or new facilities.
   c. Changes in starting materials, intermediates, equipment, facilities, support systems, processing steps, packaging materials, or computer software, particularly those that are not referenced in the DMF or application.
7. For foreign firms, Division of Field Investigations (DFI) will assist investigators in obtaining file information from the appropriate CDER reviewing division or compliance unit. Investigators may also request background information about the site assigned for inspection directly from the U.S. Agent before the initiation of the inspection.

Special Inspection Reporting Instructions

Investigators should describe in the EIR their inspection coverage and findings in sufficient detail for further agency evaluation of the firm's state of control and conformance to cGMPs.

ICH Q7A may be used as a guideline in describing coverage and any findings and deficiencies observed. However, do not reference specific ICH Q7A sections in the FDA 483 observations or in the EIR. The FDA 483, if issued, is to be organized into sections for each of the systems covered. In addition to the *Investigations Operations Manual* format and information reporting requirements, all EIRs of API manufacturers must include

1. A list of APIs manufactured (or categories of drugs, if many) along with the general manufacturing process for each (e.g., chemical synthesis, fermentation, extraction of botanical material)
2. For foreign API manufacturers, the names, titles, complete mailing address, telephone and fax number of the firm's U.S. Agent
3. For foreign API manufacturers, a report of all APIs imported into the United States in the last 2 years, their consignees, and an estimate of the frequency and quantity of shipments to these consignees
4. A description of each of the systems selected for coverage, (i.e., areas, processes, and operations), what was covered, who was interviewed, and what manufacturing activities were taking place during the inspection
5. An explanation of the choice of APIs selected for coverage and
6. Any significant changes to a firm's packaging, labeling, product line, or processes, particularly those changes not properly filed, submitted, or reported in a DMF or A/NDA

Special Instructions for Foreign Drug Inspections

The DFI schedules foreign inspections, makes travel arrangements for inspection teams, and resolves logistical problems. CDER's Office of Compliance, Foreign Inspection Team (FIT), receives and reviews all foreign establishment inspection reports, receives and reviews all foreign firms' responses to an FDA 483, and handles all correspondence regarding inspection outcomes with foreign firms. CDER/FIT maintains the complete file for each foreign drug facility.

Investigators should instruct management at foreign firms to submit their original written response to an FDA 483 directly to CDER's Office of Compliance, with a copy to the investigator. The original response with appropriate documentation should be submitted to the following address:

Food and Drug Administration
Foreign Inspection Team, HFD-325
Division of Manufacturing and Product Quality
Center for Drug Evaluation and Research
11919 Rockville Pike
Rockville, Maryland 20852–2784
USA

Investigators and analysts are to submit their written comments to a foreign firm's response to their issued FDA 483 directly to CDER's FIT as soon as possible. After appropriate district office review and endorsement, all foreign establishment inspection reports will be promptly forwarded to FIT for review and final classification.

FIT will draft and coordinate the issuance of Warning Letters, Untitled Letters, and other correspondence to foreign firms. FIT will also recommend automatic detention of foreign firms/APIs, make recommendations to review units, and request follow-up inspections, as appropriate.

PART IV—ANALYTICAL

API samples collected by the investigator for the purpose of evaluating quality are to be submitted to the appropriate servicing laboratory. A list of each analyzing laboratory for API testing is maintained in Compliance Program Guidance 7356.002 and 7346.832. However, it should be noted that physical API samples are not required to support regulatory or administrative action against a violative firm or drug.

Forensic Chemistry Center (FCC) will request profile (also called "forensic" and "fingerprint") samples of both foreign and domestic source APIs directly from the manufacturer. Investigators are to collect API samples for profile analysis only upon specific request for collection from FCC. Such requests will be made through DFI. If an investigator is instructed to collect a profile sample, FCC will provide specific instructions as to method and amount of collection and shipping. FCC contact information is in Part VI, *Program Contacts*.

Prior to each foreign API site inspection, DFI will provide FCC with the inspection dates, the investigator's name, firm's name, address, telephone number, fax number, FEI number, any related product and application numbers, and the name of the contact person. FCC will then directly request a sample from the firm as needed. FCC may contact the investigator to request their collection of any specific information. The inspection dates will provide FCC information so they can access FACTS to obtain the EIR coversheet.

FCC is responsible for API profile sample collection and analysis and will provide periodic reports of such analysis and assist CDER in evaluating this program's effectiveness.

PART V—REGULATORY/ ADMINISTRATIVE STRATEGY

An inspection report that documents that one or more systems is out of control should be classified OAI (Office Action Indicated). Districts may recommend the issuance of a Warning Letter in accordance with the RPM (Regulatory Procedure Manual). Normally, the issuance of a Warning Letter or the taking of other regulatory or administrative action should result in a classification of all profile classes as unacceptable. A CDER disapproval of a recommendation for Warning Letter or other regulatory action should result in a classification of all profile classes as acceptable.

A Warning Letter with a cGMP charge [i.e., 501(a)(2)(B) adulteration] involving a domestic API manufacturer requires

CDER review and concurrence before issuance. See and follow FDA *Regulatory Procedures Manual* procedures for clearing Warning Letters and Untitled Letters.

A recommendation for regulatory action for API cGMP deficiencies is to cite the statute [501(a)(2)(B) or United States Code, 21 USC 351(a)(2)(B)] and not the finished pharmaceutical regulations at 21CFR 210 and 211. A recommendation should also not cite to ICH Q7A but may use ICH Q7A as a guideline in describing the deficiencies observed. Any regulatory action based upon cGMP noncompliance for APIs should demonstrate how the observed deviations could or did result in actual or potential defects or risk to contamination. In evaluating whether to recommend regulatory or administrative action, consider the critical attributes of the API, its therapeutic significance, and its intended use in finished drug product manufacturing.

Evidence that supports a significant deficiency or pattern of deficiencies within a system may demonstrate the failure of a system. A failure of a system puts all drugs at risk and is to be promptly corrected. The following lists the deficiencies that should result in a recommendation for regulatory action to CDER; other deficiencies may also warrant regulatory action:

1. Contamination of APIs with filth, objectionable microorganisms, toxic chemicals, or significant amounts of other types of chemicals, or a reasonable potential for such contamination because of a finding of a demonstrated route of contamination. (Facilities and Equipment System; Production System)
2. Failure to show that API batches conform to established specifications, such as NDA, USP, customer specifications, and label claims. See also Compliance Policy Guide (CPG) 7132.05. (Quality System)
3. Failure to comply with commitments in drug applications, including DMFs, which should be accurate and current with respect to all required information, such as manufacturing process, impurity profiles (if filed), and other specifications or procedures associated with the manufacture of the API. (Quality System)
4. Distribution of an API that does not conform to established specifications. (Quality System)
5. Deliberate blending of API batches to dilute or hide filth or other noxious contaminants or blending to disguise a critical quality defect in an attempt to obtain a batch that meets its specifications. (Production System)
6. Failure to demonstrate that water, including validation of the process water purification system, and any other solvents used in the final step of the API process are chemically and microbiologically suitable for their intended use and do not adversely alter the quality of the API. (Materials System)
7. Lack of adequate validation of critical steps in the API process, particularly concerning final separation and purification of the API or when there is evidence that an API process is not adequately controlled. Lack of adequate control may be indicated by repeated batch failures or wide variation in final yields as compared to process average over time. See also the revised CPG 7132c.08, *Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval*. (Quality System; Production System)
8. Implementation of retrospective process validation for an existing API process when the process has changed significantly, when the firm lacks impurity profile data, or when there is evidence of repeated batch failures due to process variability. (Quality System; Production System)
9. Failure to establish an impurity profile for each API process. FDA expects manufacturers to establish complete impurity profiles for each API as part of the process validation effort. This includes collecting data on (1) actual and potential organic impurities that may arise during synthesis, purification, and storage of the API; (2) inorganic impurities that may derive from the API process; and (3) organic and inorganic solvents used during the manufacturing process that are known to carry over to the API. Impurity profile testing of each batch or after a specified number of batches may detect new impurities that may appear because of a deliberate or nondeliberate change in the API manufacturing process. (Laboratory Control System)
10. Failure to show that a reprocessed batch complies with all established standards, specifications, and characteristics. (Quality System; Laboratory Control System)
11. Failure to test for residues of organic/inorganic solvents used during manufacturing that may carry over to the API using analytical procedures with appropriate levels of sensitivity. (Laboratory Control System)
12. Failure to have a formal process change control system in place to evaluate changes in starting materials, facilities, support systems, equipment, processing steps, and packaging materials that may affect the quality of APIs. (All systems)
13. Failure to maintain batch and quality control records. (Quality System)
14. Incomplete stability studies to establish API stability for the intended period of use, and/or failure to conduct forced degradation studies on APIs to isolate, identify, and quantify potential degradants that may arise during storage. (Laboratory Control System)
15. Use of laboratory test methods that are inadequate or have not been validated or the use of an inadequately qualified or untraceable reference standard. (Laboratory Control System)
16. Packaging and labeling in such a way that introduces a significant risk of mislabeling. (Packaging and Labeling System)

PART VI—REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

Bibliography

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PART VII—CENTER RESPONSIBILITIES

Center responsibilities are as described in Drug Manufacturing Inspections Compliance Program Guidance 7356.002 and Pre-Approval Inspection/Investigations Compliance Program Guidance 7346.832.

Appendix A: Description of Each System and Areas of Coverage

Quality System

Assessment of the Quality System has two phases. The first phase is to evaluate whether the Quality Unit has fulfilled the responsibility to review and approve all procedures related to production, quality control, and quality assurance and assure the procedures are adequate for their intended use. This also includes the associated recordkeeping systems. The second phase is to assess the data collected to identify quality problems and may link to other major systems for inspectional coverage.

For each of the following bulleted items, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to the final APIs only but may also include starting materials and intermediates. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. All areas under this system should be covered; however, the actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

- Adequacy of staffing to ensure fulfillment of quality unit duties.
- Periodic quality reviews as described in ICH Q7A Section 2.5, *Product Quality Review*; inspection audit coverage should include API types that are representative of manufacturing at this site; inspection audit should also examine some batch and data records associated with each API quality review to verify that the firm's review was sufficiently complete; and audit should confirm that the firm has identified any trends and has corrected or mitigated sources of unacceptable variation.
- Complaint reviews (quality and medical): Documented, evaluated, and investigated in a timely manner, and also these include corrective action where appropriate. Determine whether pattern of complaints and records of internal rejection or reprocessing/reworking of API batches warrant expanding the inspection.
- Discrepancy and failure investigations related to manufacturing and testing: Documented, evaluated, critical deviations investigated in a timely manner and expanded to include any related APIs and material, and also these include corrective action where appropriate.
- Change control (including "process improvements"): Documented, evaluated, approved, and need for revalidation assessed.
- Returns/salvages: Assessment, investigation expanded where warranted, and final disposition.
- Rejects: Investigation expanded where warranted and corrective action where appropriate.
- System to release raw materials.
- Batches manufactured since last inspection to evaluate any rejections or conversions (i.e., from drug to nondrug use) due to processing problems.
- Reprocessing and/or reworking events are properly approved and evaluated for impact on material quality.

- Recalls (including any attempt to recover distributed API not meeting its specifications or purported quality), determine cause, and corrective actions taken.
- Stability failures: Investigation expanded where warranted and disposition. Determine if stability data supports API retest or expiry dates and storage conditions.
- Validation: Status of validation/revalidation activities (e.g., computer, manufacturing process, laboratory methods), such as reviews and approvals of validation protocols and reports.
- Training/qualification of employees in quality control unit functions.

ICH Q7A references for Quality System are as follows:

- Section 2, Quality Management
- Section 13, Change Control
- Section 14, Rejection and Reuse of Materials
- Section 15, Complaints and Recalls
- Section 16, Contract Manufacturers (including laboratories)

FACILITIES AND EQUIPMENT SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed below should be covered; however, the actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

1. Facilities
   - Cleaning and maintenance
   - Facility layout, flow of materials and personnel for prevention of cross-contamination, including from processing of nondrug materials
   - Dedicated areas or containment controls for highly sensitizing materials (e.g., penicillin, β-lactams, steroids, hormones, and cytotoxics)
   - Utilities such as steam, gas, compressed air, heating, ventilation, and air-conditioning should be qualified and appropriately monitored (*note*: this system includes only those utilities whose output is not intended to be incorporated into the API, such as water used in cooling-/heating-jacketed vessels)
   - Lighting, sewage and refuse disposal, washing, and toilet facilities
   - Control system for implementing changes in the building
   - Sanitation of the building including use of rodenticides, fungicides, insecticides, cleaning, and sanitizing agents
   - Training and qualification of personnel
2. Process Equipment
   - Equipment installation, operational, performance qualification where appropriate.
   - Appropriate design, adequate size, and suitably located for its intended use.
   - Equipment surfaces should not be reactive, additive, or absorptive of materials under process so as to alter their quality.
   - Equipment (e.g., reactors, storage containers) and permanently installed processing lines should be appropriately identified.
   - Substances associated with the operation of equipment (e.g., lubricants, heating fluids, or coolants) should not come into contact with starting materials, intermediates, final APIs, and containers.
   - Cleaning procedures and cleaning validation and sanitization studies should be reviewed to verify that residues, microbial, and, when appropriate, endotoxin contamination are removed to below scientifically appropriate levels.
   - Calibrations using standards traceable to certified standards, preferably NIST, USP, or counterpart, recognized national government standard-setting authority.
   - Equipment qualification, calibration, and maintenance, including computer qualification/validation and security.
   - Control system for implementing changes in the equipment.
   - Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System).
   - Training and qualification of personnel.

ICH Q7A references for Facilities and Equipment System are as follows:

- Section 4, Buildings and Facilities
- Section 5, Process Equipment
- Section 6, Documentation and Records

MATERIALS SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to the final API only but may also incorporate starting materials and intermediates. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed below should be covered; however, the actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

- Training/qualification of personnel.
- Identification of starting materials and containers.

- Storage conditions.
- Holding of all material and APIs, including reprocessed material, under quarantine until tested or examined and released.
- Representative samples are collected, tested, or examined using appropriate means and against appropriate specifications.
- A system for evaluating the suppliers of critical materials.
- Rejection of any starting material, intermediate, or container not meeting acceptance requirement.
- Appropriate retesting/reexamination of starting materials, intermediates, or containers.
- First-in/first-out use of materials and containers.
- Quarantine and timely disposition of rejected materials.
- Suitability of process water used in the manufacture of API, including as appropriate the water system design, maintenance, validation, and operation.
- Suitability of process gas used in the manufacture of API (e.g., gas use to sparge a reactor), including as appropriate the gas system design, maintenance, validation, and operation.
- Containers and closures should not be additive, reactive, or absorptive.
- Control system for implementing changes.
- Qualification/validation and security of computerized or automated process.
- Finished API distribution records by batch.
- Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System).

ICH Q7A references for Materials System are as follows:

- Section 7, Materials Management
- Section 10, Storage and Distribution
- Section 4.3, Water
- Section 6, Documentation and Records

PRODUCTION SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to the final API only but may also incorporate starting materials and intermediates. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed below should be covered; however, the actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

- Training/qualification of personnel.
- Establishment, adherence, and documented performance of approved manufacturing procedures.
- Control system for implementing changes to process.
- Controls over critical activities and operations.
- Documentation and investigation of critical deviations.
- Actual yields compared with expected yields at designated steps.
- Where appropriate established time limits for completion of phases of production.
- Appropriate identification of major equipment used in production of intermediates and API.
- Justification and consistency of intermediate specifications and API specification.
- Implementation and documentation of process controls, testing, and examinations (e.g., pH, temperature, purity, actual yields, clarity).
- In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material.
- Recovery (e.g., from mother liquor or filtrates) of reactants; approved procedures and recovered materials meet specifications suitable for their intended use.
- Solvents can be recovered and reused in the same processes or in different processes provided that solvents meet appropriate standards before reuse or commingling.
- API micronization on multiuse equipment and the precautions taken by the firm to prevent or minimize the potential for cross-contamination.
- Process validation, including validation and security of computerized or automated process.
- Master batch production and control records.
- Batch production and control records.
- Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System).

ICH Q7A references for Production System are as follows:

- Section 6, Documentation and Records
- Section 8, Production and In-Process Controls
- Section 12, Validation
- Section 18, Specific Guidance for APIs Manufactured by Cell Culture/Fermentation

See also 7356.0002M for additional inspection guidance on fermentation, extraction, and purification processes.

PACKAGING AND LABELING SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to the final API only but may also incorporate starting materials and intermediates. These areas may indicate deficiencies not only in this system but also in other systems that

would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed below should be covered; however, the actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

- Training/qualification of personnel
- Acceptance operations for packaging and labeling materials
- Control system for implementing changes in packaging and labeling operations
- Adequate storage for labels and labeling, both approved and returned after issued
- Control of labels which are similar in size, shape, and color for different APIs
- Adequate packaging records that will include specimens of all labels used
- Control of issuance of labeling, examination of issued labels, and reconciliation of used labels
- Examination of the labeled finished APIs
- Adequate inspection (proofing) of incoming labeling
- Use of lot numbers, destruction of excess labeling bearing lot/control numbers
- Adequate separation and controls when labeling more than one batch at a time
- Adequate expiration or retest dates on the label
- Validation of packaging and labeling operations including validation and security of computerized process
- Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System)

ICH Q7A references for Packaging and Labeling System are as follows:

- Section 9, Packaging and Identification Labeling of APIs and Intermediates
- Section 17, Agents, Brokers, Traders, Distributors, Repackers, and Relabellers (applies to the handling of APIs after original site of manufacture and before receipt by the dosage manufacturer)

LABORATORY CONTROL SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to the final API only but may also incorporate starting materials and intermediates. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed below should be covered; however, the actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

- Training/qualification of personnel.
- Adequacy of staffing for laboratory operations.
- Adequacy of equipment and facility for intended use.
- Calibration and maintenance programs for analytical instruments and equipment.
- Validation and security of computerized or automated processes.
- Reference standards: Source, purity and assay, and tests to establish equivalency to current official reference standards as appropriate.
- System suitability checks on chromatographic systems.
- Specifications, standards, and representative sampling plans.
- Validation/verification of analytical methods.
- Required testing is performed on the correct samples and by the approved or filed methods or equivalent methods.
- Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System).
- Complete analytical records from all tests and summaries of results.
- Quality and retention of raw data (e.g., chromatograms and spectra).
- Correlation of result summaries to raw data; presence and disposition of unused data.
- Adherence to an adequate out of specification procedure, which includes timely completion of the investigation.
- Test methods for establishing a complete impurity profile for each API process (*note*: impurity profiles are often process related).
- Adequate reserve samples; documentation of reserve samples' examination.
- Stability testing program, including demonstration of stability-indicating capability of the test methods.

ICH Q7A references for Laboratory System are as follows:

- Section 11, Laboratory Controls
- Section 6, Documentation and Records
- Section 12, Validation

ICH Q7A Sections 3, Personnel, and 6, Documentation and Records, apply to all systems. Section 19, APIs for Use in Clinical Trials, applies to APIs intended for the production of dosages solely for use in a clinical trial.

The organization and personnel, including appropriate qualifications and training, employed in any given system, will be evaluated as part of that system's operation. Production, control, or distribution records are required to maintain cGMPs and those selected for review should be included for inspection audit within the context of each of the above systems. Inspection of contract companies should be within the system for which the intermediate or API or service is contracted and also include evaluation of their Quality System.

GLOSSARY

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

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

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

API: Active Pharmaceutical Ingredient.

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

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

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

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

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

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

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

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

CDER: Center for Drug Evaluation and Research, FDA.

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

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

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

Contamination: The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage, or transport.

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

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

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

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

Deviation: Departure from an approved instruction or established standard.

DMPQ: Division of Manufacturing and Product Quality, FDA.

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

Drug Substance: See Active Pharmaceutical Ingredient.

EES: Establishment Evaluation System.

EIR: Establishment Inspection Report.

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

FCC: Forensic Chemistry Center.

FEI: Federal Employment Identification.

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

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

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

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

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

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

Lot: See Batch.

Lot Number: See Batch Number.

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

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

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

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

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

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

OAI: Office Action Indicated.

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

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

PACS: Picture archiving and communication systems.

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

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

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

Process Control: See In-Process Control.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Signature (Signed): See definition for Signed.

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

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

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

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

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

Validation: A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria. Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material,

activity, or system actually leads to the expected results (see also Qualification).

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

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

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

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10 Test Procedures and Acceptance Criteria for New Chemical Drug Substances and Drug Products

I. INTRODUCTION

A. Objective of the Guideline

This guideline is intended to assist to the extent possible, in the establishment of a single set of global specifications for new drug substances and new drug products. It provides guidance on the setting and justification of acceptance criteria and the selection of test procedures for new drug substances of synthetic chemical origin, and new drug products produced from them, which have not been registered previously in the United States, the European Union, or Japan.

B. Background

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

Specifications are one part of a total control strategy for the drug substance and drug product designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterization during development, upon which specifications are based, and adherence to Good Manufacturing Practices, for example, suitable facilities, a validated manufacturing process, validated test procedure, raw material testing, in-process testing, stability testing, etc.

Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and drug product.

C. Scope of the Guideline

The quality of drug substances and drug products is determined by their design, development, in-process controls, GMP controls, and process validation and by specifications applied to them throughout development and manufacture. This guideline addresses specifications, that is, those tests, procedures, and acceptance criteria which play a major role in assuring the quality of the new drug substance and new drug product at release and during shelf life. Specifications are an important component of quality assurance but are not its only component. All of the considerations listed above are necessary to ensure consistent production of drug substances and drug products of high quality.

This guideline addresses only the marketing approval of new drug products (including combination products) and, where applicable, new drug substances; it does not address drug substances or drug products during the clinical research stages of drug development. This guideline may be applicable to synthetic and semisynthetic antibiotics and synthetic peptides of low molecular weight; however, it is not sufficient to adequately describe specifications of higher molecular weight peptides and polypeptides and biotechnological/biological products. The ICH guideline *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* addresses guideline specifications, tests, and procedures for biotechnological/biological products. Radiopharmaceuticals, products of fermentation, oligonucleotides, herbal products, and crude products of animal or plant origin are similarly not covered.

Guidance is provided with regard to acceptance criteria, which should be established for all new drug substances and new drug products, that is, universal acceptance criteria, and those that are considered specific to individual drug substances and/or dosage forms. This guideline should not be considered all encompassing. New analytical technologies, and modifications to existing technology, are continually being developed. Such technologies should be used when justified.

Dosage forms addressed in this guideline include solid oral dosage forms, liquid oral dosage forms, and parenterals (small and large volume). This is not meant to be an all-inclusive list or to limit the number of dosage forms to which this guideline applies. The dosage forms presented serve as models, which may be applicable to other dosage forms, which have not been discussed. The extended application of the concepts in this guideline to other dosage forms, for example, to inhalation dosage forms (powders, solutions, etc.), to topical formulations (creams, ointments, gels), and to transdermal systems, is encouraged.

II. GENERAL CONCEPTS

The following concepts are important in the development and setting of harmonized specifications. They are not universally applicable, but each should be considered in particular circumstances. This guideline presents a brief definition of each concept and an indication of the circumstances under which it may be applicable. Generally, proposals to implement these concepts should be justified by the applicant and approved by the appropriate regulatory authority before being put into effect.

A. Periodic or Skip Testing

Periodic or skip testing is the performance of specified tests at release on preselected batches and/or at predetermined intervals, rather than on a batch-to-batch basis with the understanding that those batches not being tested still must meet all acceptance criteria established for that product. This represents a less than full schedule of testing and should therefore be justified and presented to and approved by the regulatory authority prior to implementation. This concept may be applicable to, for example, residual solvents and microbiological testing, for solid oral dosage forms. It is recognized that only limited data may be available at the time of submission of an application (see Section 2.5). This concept should therefore generally be implemented post-approval. When tested, any failure to meet acceptance criteria established for the periodic test should be handled by proper notification of the appropriate regulatory authority(ies). If these data demonstrate a need to restore routine testing, then batch-by-batch release testing should be reinstated.

B. Release vs. Shelf Life Acceptance Criteria

The concept of different acceptance criteria for release vs. shelf-life specifications applies to drug products only; it pertains to the establishment of more restrictive criteria for the release of a drug product than are applied to the shelf life. Examples where this may be applicable include assay and impurity (degradation product) levels. In Japan and the United States, this concept may only be applicable to in-house criteria and not to the regulatory release criteria. Thus, in these regions, the regulatory acceptance criteria are the same from release throughout shelf life; however, an applicant may choose to have tighter in-house limits at the time of release to provide increased assurance to the applicant that the product will remain within the regulatory acceptance criterion throughout its shelf life. In the European Union, there is a regulatory requirement for distinct specifications for release and for shelf life where different.

C. In-Process Tests

In-process tests, as presented in this guideline, are tests which may be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal battery of tests which are conducted prior to release.

In-process tests, which are only used for the purpose of adjusting process parameters within an operating range, for example, hardness and friability of tablet cores which will be coated and individual tablet weights, are not included in the specification.

Certain tests conducted during the manufacturing process, where the acceptance criterion is identical to or tighter than the release requirement, (e.g., pH of a solution) may be sufficient to satisfy specification requirements when the test is included in the specification. However, this approach should be validated to show that test results or product performance characteristics do not change from the in-process stage to finished product.

D. Design and Development Considerations

The experience and data accumulated during the development of a new drug substance or product should form the basis for the setting of specifications. It may be possible to propose excluding or replacing certain tests on this basis. Some examples are:

- Microbiological testing for drug substances and solid dosage forms which have been shown during development not to support microbial viability or growth (see Decision Trees 6 and 8).
- Extractables from product containers where it has been reproducibly shown that either no extractables are found in the drug product or the levels meet accepted standards for safety.
- Particle size testing may fall into this category, may be performed as an in-process test, or may be performed as a release test, depending on its relevance to product performance.
- Dissolution testing for immediate release solid oral drug products made from highly water-soluble drug substances may be replaced by disintegration testing, if these products have been demonstrated during development to have consistently rapid drug-release characteristics [see Decision Trees 7(1) through 7(2)].

E. Limited Data Available at Filing

It is recognized that only a limited amount of data may be available at the time of filing, which can influence the process of setting acceptance criteria. As a result, it may be necessary to propose revised acceptance criteria as additional experience is gained with the manufacture of a particular drug substance or drug product (e.g., acceptance limits for a specific impurity). The basis for the acceptance criteria at the time of filing should necessarily focus on safety and efficacy.

When only limited data are available, the initially approved tests and acceptance criteria should be reviewed as more information is collected, with a view towards possible modification. This could involve loosening, as well as tightening, acceptance criteria as appropriate.

F. Parametric Release

Parametric release can be used as an operational alternative to routine release testing for the drug product in certain cases when approved by the regulatory authority. Sterility testing for terminally sterilized drug products is one example. In this case, the release of each batch is based on satisfactory results from monitoring specific parameters, for example, temperature, pressure, and time during the terminal sterilization phase(s) of drug product manufacturing. These parameters can generally be more accurately controlled and measured, so that they are more reliable in predicting sterility assurance than is end-product sterility testing. Appropriate laboratory tests (e.g., chemical or physical indicator) may be included in the parametric release program. It is important to note that the sterilization process should be adequately validated before parametric release is proposed, and maintenance of a validated state should be demonstrated by revalidation at established intervals. When parametric release is performed, the attribute which is indirectly controlled (e.g., sterility), together with a reference to the associated test procedure, still should be included in the specifications.

G. Alternative Procedures

Alternative procedures are those which may be used to measure an attribute when such procedures control the quality of the drug substance or drug product to an extent that is comparable or superior to the official procedure. Example: For tablets that have been shown not to degrade during manufacture, it may be permissible to use a spectrophotometric procedure for release as opposed to the official procedure, which is chromatographic. However, the chromatographic procedure should still be used to demonstrate compliance with the acceptance criteria during the shelf life of the product.

H. Pharmacopoeial Tests and Acceptance Criteria

References to certain procedures are found in pharmacopoeias in each region. Wherever they are appropriate, pharmacopoeial procedures should be utilized. Whereas differences in pharmacopoeial procedures and/or acceptance criteria have existed among the regions, a harmonized specification is possible only if the procedures and acceptance criteria defined are acceptable to regulatory authorities in all regions.

The full utility of this guideline is dependent on the successful completion of harmonization of pharmacopoeial procedures for several attributes commonly considered in the specification for new drug substances or new drug products. The Pharmacopoeial Discussion Group (PDG) of the European Pharmacopoeia, the Japanese Pharmacopoeia, and the United States Pharmacopeia has expressed a commitment to achieving harmonization of the procedures in a timely fashion.

Where harmonization has been achieved, an appropriate reference to the harmonized procedure and acceptance criteria is considered acceptable for a specification in all three regions. For example, after harmonization sterility data generated using the JP procedure, as well as the JP procedure itself and its acceptance criteria, are considered acceptable for registration in all three regions. To signify the harmonized status of these procedures, the pharmacopoeias have agreed to include a statement in their respective texts which indicates that the procedures and acceptance criteria from all three pharmacopoeias are considered equivalent and are, therefore, interchangeable.

Since the overall value of this guideline is linked to the extent of harmonization of the analytical procedures and acceptance criteria of the pharmacopoeias, it is agreed by the members of the Q6A expert working group that none of the three pharmacopoeias should change a harmonized monograph unilaterally. According to the PDG procedure for the revision of harmonized monographs and chapters, "no pharmacopoeia shall revise unilaterally any monograph or chapter after sign-off or after publication."

I. Evolving Technologies

New analytical technologies, and modifications to existing technology, are continually being developed. Such technologies should be used when they are considered to offer additional assurance of quality or are otherwise justified.

J. Impact of Drug Substance on Drug Product Specifications

In general, it should not be necessary to test the drug product for quality attributes uniquely associated with the drug substance. For example, it is normally not considered necessary to test the drug product for synthesis impurities, which are controlled in the drug substance and are not degradation products. Refer to the ICH guideline *Impurities in New Drug Products* for detailed information.

K. Reference Standard

A reference standard, or reference material, is a substance prepared for use as the standard in an assay, identification, or purity test. It should have a quality appropriate to its use. It is often characterized and evaluated for its intended purpose by additional procedures other than those used in routine testing. For new drug substance reference standards intended for use in assays, the impurities should be adequately identified and/or controlled, and purity should be measured by a quantitative procedure.

III. GUIDELINES

A. Specifications: Definition and Justification

1. Definition of Specifications

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests

described. It establishes the set of criteria to which a new drug substance or new drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance and/or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

It is possible that, in addition to release tests, a specification may list in-process tests as defined below, periodic (skip) tests, and other tests, which are not always conducted on a batch-by-batch basis. In such cases, the applicant should specify which tests are routinely conducted batch-by-batch and which tests are not, with an indication and justification of the actual testing frequency. In this situation, the drug substance and/or drug product should meet the acceptance criteria if tested.

It should be noted that changes in the specification after approval of the application may need prior approval by the regulatory authority.

2. Justification of Specifications

When a specification is first proposed, justification should be presented for each procedure and each acceptance criterion included. The justification should refer to relevant development data, pharmacopoeial standards, test data for drug substances and drug products used in toxicology and clinical studies, and results from accelerated and long-term stability studies, as appropriate. Additionally, a reasonable range of expected analytical and manufacturing variability should be considered. It is important to consider all of this information.

Approaches other than those set forth in this guideline may be applicable and acceptable. The applicant should justify alternative approaches. Such justification should be based on data derived from the new drug substance synthesis and/or the new drug product manufacturing process. This justification may consider theoretical tolerances for a given procedure or acceptance criterion, but the actual results obtained should form the primary basis for whatever approach is taken.

Test results from stability and scale-up/validation batches, with emphasis on the primary stability batches, should be considered in setting and justifying specifications. If multiple manufacturing sites are planned, it may be valuable to consider data from these sites in establishing the initial tests and acceptance criteria. This is particularly true when there is limited initial experience with the manufacture of the drug substance or drug product at any particular site. If data from a single representative manufacturing site are used in setting tests and acceptance criteria, product manufactured at all sites should still comply with these criteria.

Presentation of test results in graphic format may be helpful in justifying individual acceptance criteria, particularly for assay values and impurity levels. Data from development work should be included in such a presentation, along with stability data available for new drug substance or new drug product batches manufactured by the proposed commercial processes. Justification for proposing exclusion of a test from the specification should be based on development data and on process validation data (where appropriate).

B. Universal Tests/Criteria

Implementation of the recommendations in the following section should take into account the ICH guidelines *Text on Validation of Analytical Procedures* and *Validation of Analytical Procedures: Methodology.*

1. New Drug Substances

The following tests and acceptance criteria are considered generally applicable to all new drug substances.

(a) *Description*: A qualitative statement about the state (e.g., solid, liquid) and color of the new drug substance. If any of these characteristics change during storage, this change should be investigated and appropriate action taken.

(b) *Identification*: Identification testing should optimally be able to discriminate between compounds of closely related structure which are likely to be present. Identification tests should be specific for the new drug substance, for example, infrared spectroscopy. Identification solely by a single chromatographic retention time, for example, is not regarded as being specific. However, the use of two chromatographic procedures, where the separation is based on different principles or a combination of tests into a single procedure, such as HPLC/UV diode array, HPLC/MS, or GC/MS, is generally acceptable. If the new drug substance is a salt, identification testing should be specific for the individual ions. An identification test that is specific for the salt itself should suffice.

New drug substances, which are optically active may also need specific identification testing or performance of a chiral assay. Please refer to 3.3.1.d) in this guideline for further discussion of this topic.

(c) *Assay*: A specific, stability-indicating procedure should be included to determine the content of the new drug substance. In many cases, it is possible to employ the same procedure (e.g., HPLC) for both assay of the new drug substance and quantitation of impurities.

In cases where use of a nonspecific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. For example, where titration is adopted to assay the drug substance, the combination of the assay and a suitable test for impurities should be used.

(d) *Impurities*: Organic and inorganic impurities and residual solvents are included in this category. Refer to the ICH guidelines *Impurities in New Drug Substances* and *Residual Solvents in Pharmaceuticals* for detailed information.

Decision Tree 1 addresses the extrapolation of meaningful limits on impurities from the body of data generated during development. At the time of filing, it is unlikely that sufficient data will be available to assess process consistency. Therefore, it is considered inappropriate to establish acceptance criteria, which tightly encompass the batch data at the time of filing (see Section 2.5).

2. New Drug Products

The following tests and acceptance criteria are considered generally applicable to all new drug products:

(a) *Description*: A qualitative description of the dosage form should be provided (e.g., size, shape, and color). If any of these characteristics change during manufacture or storage, this change should be investigated and appropriate action taken. The acceptance criteria should include the final acceptable appearance. If color changes during storage, a quantitative procedure may be appropriate.

(b) *Identification*: Identification testing should establish the identity of the new drug substance(s) in the new drug product and should be able to discriminate between compounds of closely related structure which are likely to be present. Identity tests should be specific for the new drug substance, for example, infrared spectroscopy. Identification solely by a single chromatographic retention time, for example, is not regarded as being specific. However, the use of two chromatographic procedures, where the separation is based on different principles, or combination of tests into a single procedure, such as HPLC/UV diode array, HPLC/MS, or GC/MS, is generally acceptable.

(c) *Assay*: A specific, stability-indicating assay to determine strength (content) should be included for all new drug products. In many cases, it is possible to employ the same procedure (e.g., HPLC) for both assay of the new drug substance and quantitation of impurities. Results of content uniformity testing for new drug products can be used for quantitation of drug product strength, if the methods used for content uniformity are also appropriate as assays.

In cases where use of a nonspecific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. For example, where titration is adopted to assay the drug substance for release, the combination of the assay and a suitable test for impurities can be used. A specific procedure should be used when there is evidence of excipient interference with the nonspecific assay.

(d) *Impurities*: Organic and inorganic impurities (degradation products) and residual solvents are included in this category. Refer to the ICH guidelines *Impurities in New Drug Products* and *Residual Solvents in Pharmaceuticals* for detailed information.

Organic impurities arising from degradation of the new drug substance and impurities that arise during the manufacturing process for the drug product should be monitored in the new drug product. Acceptance limits should be stated for individual specified degradation products, which may include both identified and unidentified degradation products as appropriate, and total degradation products. Process impurities from the new drug substance synthesis are normally controlled during drug substance testing and therefore are not included in the total impurities limit. However, when a synthesis impurity is also a degradation product, its level should be monitored and included in the total degradation product limit. When it has been conclusively demonstrated via appropriate analytical methodology that the drug substance does not degrade in the specific formulation, and under the specific storage conditions proposed in the new drug application, degradation product testing may be reduced or eliminated upon approval by the regulatory authorities.

Decision Tree 2 addresses the extrapolation of meaningful limits on degradation products from the body of data generated during development. At the time of filing, it is unlikely that sufficient data will be available to assess process consistency. Therefore, it is considered inappropriate to establish acceptance criteria which tightly encompass the batch data at the time of filing (see Section 2.5).

C. Specific Tests/Criteria

In addition to the universal tests listed above, the following tests may be considered on a case by case basis for drug substances and/or drug products. Individual tests/criteria should be included in the specification when the tests have an impact on the quality of the drug substance and drug product for batch control. Tests other than those listed below may be needed in particular situations or as new information becomes available.

1. New Drug Substances

(a) *Physicochemical properties*: These are properties such as pH of an aqueous solution, melting point/range, and refractive index. The procedures used for the measurement of these properties are usually unique and do not need much elaboration, for example, capillary melting point, Abbé refractometry. The tests performed in this category should be determined by the physical nature of the new drug substance and by its intended use.

(b) *Particle size*: For some new drug substances intended for use in solid or suspension drug products, particle size can have a significant effect on dissolution rates, bioavailability, and/or stability. In such instances, testing for particle size distribution should be carried out using an appropriate procedure, and acceptance criteria should be provided.

Decision Tree 3 provides additional guidance on when particle size testing should be considered.

(c) *Polymorphic forms*: Some new drug substances exist in different crystalline forms, which differ in their physical properties. Polymorphism may also include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms. Differences in these forms could, in some cases, affect the quality or performance of the new drug products. In cases where differences exist which have been shown to affect drug product performance, bioavailability, or stability, then the appropriate solid state should be specified.

Physicochemical measurements and techniques are commonly used to determine whether multiple forms exist. Examples of these procedures are: Melting point (including hot-stage microscopy), solid state IR, X-ray powder diffraction, thermal analysis procedures (such as DSC, TGA, and DTA), Raman spectroscopy, optical microscopy, and solid-state NMR.

Decision Trees 4(1) through 4(3) provide additional guidance on when, and how, polymorphic forms should be monitored and controlled.

Note: These decision trees should be followed sequentially. Trees 1 and 2 consider whether polymorphism is exhibited by the drug substance and whether the different polymorphic forms can affect performance of the drug product. Tree 3 should only be applied when polymorphism has been demonstrated for the drug substance and shown to affect these properties. Tree 3 considers the potential for change in polymorphic forms in the drug product and whether such a change has any effect on product performance.

It is generally technically very difficult to measure polymorphic changes in drug products. A surrogate test (e.g., dissolution) [see Decision Tree 4(3)] can generally be used to monitor product performance, and polymorph content should only be used as a test and acceptance criterion of last resort.

(d) *Tests for chiral new drug substances*: Where a new drug substance is predominantly one enantiomer, the opposite enantiomer is excluded from the qualification and identification thresholds given in the ICH guidelines on *Impurities in New Drug Substances* and *Impurities in New Drug Products* because of practical difficulties in quantifying it at those levels. However, that impurity in the chiral new drug substance and the resulting new drug product(s) should otherwise be treated according to the principles established in those guidelines.

Decision Tree 5 summarizes when and if chiral identity tests, impurity tests, and assays may be needed for both new drug substances and new drug products, according to the following concepts:

Drug substance: *Impurities.* For chiral drug substances, which are developed as a single enantiomer, control of the other enantiomer should be considered in the same manner as for other impurities. However, technical limitations may preclude the same limits of quantification or qualification from being applied. Assurance of control also could be given by appropriate testing of a starting material or intermediate, with suitable justification.

Assay. An enantioselective determination of the drug substance should be part of the specification. It is considered acceptable for this to be achieved either through use of a chiral assay procedure or by the combination of an achiral assay together with appropriate methods of controlling the enantiomeric impurity.

Identity. For a drug substance developed as a single enantiomer, the identity test(s) should be capable of distinguishing both enantiomers and the racemic mixture. For a racemic drug substance, there are generally two situations where a stereospecific identity test is appropriate for release/acceptance testing: (1) where there is a significant possibility that the enantiomer might be substituted for the racemate, or (2) when there is evidence that preferential crystallization may lead to unintentional production of a nonracemic mixture.

Drug product: Degradation products. Control of the other enantiomer in a drug product is considered necessary unless racemization has been shown to be insignificant during manufacture of the dosage form and on storage.

Assay: An achiral assay may be sufficient where racemization has been shown to be insignificant during manufacture of the dosage form and on storage. Otherwise a chiral assay should be used, or alternatively, the combination of an achiral assay plus a validated procedure to control the presence of the opposite enantiomer may be used.

Identity: A stereospecific identity test is not generally needed in the drug product release specification. When racemization is insignificant during manufacture of the dosage form and on storage, stereospecific identity testing is more appropriately addressed as part of the drug substance specification. When racemization in the dosage form is a concern, chiral assay or enantiomeric impurity testing of the drug product will serve to verify identity.

(e) *Water content*: This test is important in cases where the new drug substance is known to be hygroscopic or degraded by moisture or when the drug substance is known to be a stoichiometric hydrate. The acceptance criteria may be justified with data on the effects

of hydration or moisture absorption. In some cases, a loss on drying procedure may be considered adequate; however, a detection procedure that is specific for water (e.g., Karl Fischer titration) is preferred.

(f) *Inorganic impurities*: The need for inclusion of tests and acceptance criteria for inorganic impurities (e.g., catalysts) should be studied during development and based on knowledge of the manufacturing process. Procedures and acceptance criteria for sulfated ash/residue on ignition should follow pharmacopoeial precedents; other inorganic impurities may be determined by other appropriate procedures, for example, atomic absorption spectroscopy.

(g) *Microbial limits*: There may be a need to specify the total count of aerobic microorganisms, the total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus*, *Escherichia coli*, *Salmonella*, *Pseudomonas aeruginosa*). These should be suitably determined using pharmacopoeial procedures. The type of microbial test(s) and acceptance criteria should be based on the nature of the drug substance, method of manufacture, and the intended use of the drug product. For example, sterility testing may be appropriate for drug substances manufactured as sterile, and endotoxin testing may be appropriate for drug substances used to formulate an injectable drug product.

Decision Tree 6 provides additional guidance on when microbial limits should be included.

2. New Drug Products

Additional tests and acceptance criteria generally should be included for particular new drug products. The following selection presents a representative sample of both the drug products and the types of tests and acceptance criteria, which may be appropriate. The specific dosage forms addressed include solid oral drug products, liquid oral drug products, and parenterals (small and large volume). Application of the concepts in this guideline to other dosage forms is encouraged. Note that issues related to optically active drug substances and to solid-state considerations for drug products are discussed in Part 3.3.1. of this guideline.

a. General Considerations

The following tests are applicable to tablets (coated and uncoated) and hard capsules. One or more of these tests may also be applicable to soft capsules and granules.

(a) *Dissolution*: The specification for solid oral dosage forms normally includes a test to measure release of drug substance from the drug product. Single-point measurements are normally considered to be suitable for immediate-release dosage forms. For modified-release dosage forms, appropriate test conditions and sampling procedures should be established. For example, multiple time point sampling should be performed for extended-release dosage forms, and two-stage testing (using different media in succession or in parallel, as appropriate) may be appropriate for delayed-release dosage forms. In these cases, it is important to consider the populations of individuals who will be taking the drug product (e.g., achlorhydric elderly) when designing the tests and acceptance criteria. In some cases [see Section 3.3.2.1 b) Disintegration], dissolution testing may be replaced by disintegration testing [see Decision Tree 7 (1)].

For immediate-release drug products where changes in dissolution rate have been demonstrated to significantly affect bioavailability, it is desirable to develop test conditions which can distinguish batches with unacceptable bioavailability. If changes in formulation or process variables significantly affect dissolution and such changes are not controlled by another aspect of the specification, it may also be appropriate to adopt dissolution test conditions which can distinguish these changes [see Decision Tree 7(2)].

Where dissolution significantly affects bioavailability, the acceptance criteria should be set to reject batches with *unacceptable* bioavailability. Otherwise, test conditions and acceptance criteria should be established which pass clinically acceptable batches [see Decision Tree 7(2)]. For extended-release drug products, in vitro/in vivo correlation may be used to establish acceptance criteria when human bioavailability data are available for formulations exhibiting different release rates. Where such data are not available, and drug release cannot be shown to be independent of in vitro test conditions, then acceptance criteria should be established on the basis of available batch data. Normally, the permitted variability in mean release rate at any given time point should not exceed a total numerical difference of ±10% of the labeled content of drug substance (i.e., a total variability of 20%: A requirement of 50% ± 10% thus means an acceptable range from 40% to 60%), unless a wider range is supported by a bioequivalency study [see Decision Tree 7(3)].

(b) *Disintegration*: For rapidly dissolving (dissolution >80% in 15 minutes at pH 1.2, 4.0, and 6.8) products containing drugs which are highly soluble throughout the physiological range (dose/solubility volume <250 mL from pH 1.2 to 6.8), disintegration may be substituted for dissolution. Disintegration testing is most appropriate when a relationship to dissolution has been established or when disintegration is shown to be more discriminating than dissolution. In such cases, dissolution testing may not be necessary. It is expected that development information will be provided to support the robustness of the formulation and manufacturing process with respect to the selection of dissolution vs. disintegration testing [see Decision Tree 7(1)].

(c) *Hardness/friability*: It is normally appropriate to perform hardness and/or friability testing as an in-process control (see Section 2.3). Under these circumstances, it is normally not necessary to include these attributes in the specification. If the characteristics of hardness and friability have a critical impact on drug product quality (e.g., chewable tablets), acceptance criteria should be included in the specification.

(d) *Uniformity of dosage units*: This term includes both the mass of the dosage form and the content of the active substance in the dosage form; a pharmacopoeial procedure should be used. In general, the specification should include one or the other but not both. If appropriate, these tests may be performed in-process; the acceptance criteria should be included in the specification. When weight variation is applied for new drug products exceeding the threshold value to allow testing uniformity by weight variation, applicants should verify during drug development that the homogeneity of the product is adequate.

(e) *Water content*: A test for water content should be included when appropriate. The acceptance criteria may be justified with data on the effects of hydration or water absorption on the drug product. In some cases, a loss on drying procedure may be considered adequate; however, a detection procedure which is specific for water (e.g., Karl Fischer titration) is preferred.

(f) *Microbial limits*: Microbial limit testing is seen as an attribute of Good Manufacturing Practice, as well as of quality assurance. In general, it is advisable to test the drug product unless its components are tested before manufacture and the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination or proliferation. It should be noted that, whereas this guideline does not directly address excipients, the principles discussed here may be applicable to excipients as well as to new drug products. Skip testing may be an appropriate approach in both cases where permissible. (See Decision Tree 6 for microbial testing of excipients.)

Acceptance criteria should be set for the total count of aerobic microorganisms, the total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., *S. aureus*, *E. coli*, *Salmonella*, *Pseudomonas aeruginosa*). These should be determined by suitable procedures, using pharmacopoeial procedures, and at a sampling frequency or time point in manufacture which is justified by data and experience. The type of microbial test(s) and acceptance criteria should be based on the nature of the drug substance, method of manufacture, and the intended use of the drug product. With acceptable scientific justification, it should be possible to propose no microbial limit testing for solid oral dosage forms.

Decision Tree 8 provides additional guidance on the use of microbial limits testing.

b. Oral Liquids

One or more of the following specific tests will normally be applicable to oral liquids and to powders intended for reconstitution as oral liquids.

(a) *Uniformity of dosage units*: This term includes both the mass of the dosage form and the content of the active substance in the dosage form; a pharmacopoeial procedure should be used. In general, the specification should include one or the other but not both. When weight variation is applied for new drug products exceeding the threshold value to allow testing uniformity by weight variation, applicants should verify during drug development that the homogeneity of the product is adequate. If appropriate, tests may be performed in-process; however, the acceptance criteria should be included in the specification. This concept may be applied to both single-dose and multiple-dose packages.

The dosage unit is considered to be the typical dose taken by the patient. If the actual unit dose, as taken by the patient, is controlled, it may either be measured directly or calculated, based on the total measured weight or volume of drug divided by the total number of doses expected. If dispensing equipment (such as medicine droppers or dropper tips for bottles) is an integral part of the packaging, this equipment should be used to measure the dose. Otherwise, a standard volume measure should be used. The dispensing equipment to be used is normally determined during development.

For powders for reconstitution, uniformity of mass testing is generally considered acceptable.

(b) *pH*: Acceptance criteria for pH should be provided where applicable and the proposed range justified.

(c) *Microbial limits*: Microbial limit testing is seen as an attribute of Good Manufacturing Practice, as well as of quality assurance. In general, it is advisable to test the drug product unless its components are tested before manufacture and the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination or proliferation. It should be noted that, whereas this guideline does not directly address excipients, the principles discussed here may be applicable to excipients as well as to new drug products. Skip testing may be an appropriate approach in both cases where permissible. With acceptable scientific justification, it may be possible to propose no microbial limit testing for powders intended for reconstitution as oral liquids.

Acceptance criteria should be set for the total count of aerobic microorganisms, total count of yeasts and molds, and the absence of specific objectionable bacteria

(e.g., *S. aureus*, *E. coli*, *Salmonella*, *Pseudomonas aeruginosa*). These should be determined by suitable procedures, using pharmacopoeial procedures, and at a sampling frequency or time point in manufacture which is justified by data and experience.

Decision Tree 8 provides additional guidance on the use of microbial limits testing.

(d) *Antimicrobial preservative content*: For oral liquids needing an antimicrobial preservative, acceptance criteria for preservative content should be established. Acceptance criteria for preservative content should be based upon the levels of antimicrobial preservative necessary to maintain microbiological quality of the product at all stages throughout its proposed usage and shelf life. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using a pharmacopoeial antimicrobial preservative effectiveness test.

Testing for antimicrobial preservative content should normally be performed at release. Under certain circumstances, in-process testing may suffice in lieu of release testing. When antimicrobial preservative content testing is performed as an in-process test, the acceptance criteria should remain part of the specification.

Antimicrobial preservative effectiveness should be demonstrated during development, during scale-up, and throughout the shelf life (e.g., in stability testing: See the ICH guideline, *Stability Testing of New Drug Substances and Products*), although chemical testing for preservative content is the attribute normally included in the specification.

(e) *Antioxidant preservative content*: Release testing for antioxidant content should normally be performed. Under certain circumstances, where justified by developmental and stability data, shelf-life testing may be unnecessary, and in-process testing may suffice in lieu of release testing where permitted. When antioxidant content testing is performed as an in-process test, the acceptance criteria should remain part of the specification. If only release testing is performed, this decision should be reinvestigated whenever either the manufacturing procedure or the container/closure system changes.

(f) *Extractables*: Generally, where development and stability data show evidence that extractables from the container/closure systems are consistently below levels that are demonstrated to be acceptable and safe, elimination of this test can normally be accepted. This should be reinvestigated if the container/closure system or formulation changes.

Where data demonstrate the need, tests and acceptance criteria for extractables from the container/closure system components (e.g., rubber stopper, cap liner, plastic bottle, etc.) are considered appropriate for oral solutions packaged in non-glass systems or in glass containers with non-glass closures. The container/closure components should be listed and data collected for these components as early in the development process as possible.

(g) *Alcohol content*: Where it is declared quantitatively on the label in accordance with pertinent regulations, the alcohol content should be specified. It may be assayed or calculated.

(h) *Dissolution*: In addition to the attributes recommended immediately above, it may be appropriate (e.g., insoluble drug substance) to include dissolution testing and acceptance criteria for oral suspensions and dry powder products for resuspension. Dissolution testing should be performed at release. This test may be performed as an in-process test when justified by product development data. The testing apparatus, media, and conditions should be pharmacopoeial, if possible, or otherwise justified. Dissolution procedures using either pharmacopoeial or non-pharmacopoeial apparatus and conditions should be validated.

Single-point measurements are normally considered suitable for immediate-release dosage forms. Multiple-point sampling, at appropriate intervals, should be performed for modified-release dosage forms. Acceptance criteria should be set based on the observed range of variation and should take into account the dissolution profiles of the batches that showed acceptable performance in vivo. Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure.

(i) *Particle size distribution*: Quantitative acceptance criteria and a procedure for determination of particle size distribution may be appropriate for oral suspensions. Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure for these formulations.

Particle size distribution testing should be performed at release. It may be performed as an in-process test when justified by product development data. If these products have been demonstrated during development to have consistently rapid drug-release characteristics, exclusion of a particle size distribution test from the specification may be proposed.

Particle size distribution testing may also be proposed in place of dissolution testing; justification should be provided. The acceptance criteria should include acceptable particle size distribution in terms of the percent of total particles in given size ranges. The mean, upper, and/or lower particle size limits should be well defined.

Acceptance criteria should be set based on the observed range of variation and should take into account the dissolution profiles of the batches that

showed acceptable performance in vivo, as well as the intended use of the product. The potential for particle growth should be investigated during product development; the acceptance criteria should take the results of these studies into account.

(j) *Redispersibility*: For oral suspensions, which settle on storage (produce sediment), acceptance criteria for redispersibility may be appropriate. Shaking may be an appropriate procedure.

The procedure (mechanical or manual) should be indicated. Time required to achieve resuspension by the indicated procedure should be clearly defined. Data generated during product development may be sufficient to justify skip lot testing, or elimination of this attribute from the specification may be proposed.

(k) *Rheological properties*: For relatively viscous solutions or suspensions, it may be appropriate to include rheological properties (viscosity/specific gravity) in the specification. The test and acceptance criteria should be stated. Data generated during product development may be sufficient to justify skip lot testing, or elimination of this attribute from the specification may be proposed.

(l) *Reconstitution time*: Acceptance criteria for reconstitution time should be provided for dry powder products, which require reconstitution. The choice of diluent should be justified. Data generated during product development may be sufficient to justify skip lot testing, or elimination of this attribute from the specification may be proposed.

(m) *Water content*: For oral products requiring reconstitution, a test and acceptance criterion for water content should be proposed when appropriate. Loss on drying is generally considered sufficient if the effect of absorbed moisture vs. water of hydration has been adequately characterized during the development of the product. In certain cases, a more specific procedure (e.g., Karl Fischer titration) may be preferable.

c. Parenteral Drug Products

The following tests may be applicable to parenteral drug products.

(a) *Uniformity of dosage units*: This term includes both the mass of the dosage form and the content of the active substance in the dosage form; a pharmacopoeial procedure should be used. In general, the specification should one or the other but not both and is applicable to powders for reconstitution. When weight variation is applied for new drug products exceeding the threshold value to allow testing uniformity by weight variation, applicants should verify during drug development that the homogeneity of the product is adequate.

If appropriate (see Section 2.3), these tests may be performed in-process; the acceptance criteria should be included in the specification. This test may be applied to both single-dose and multiple-dose packages.

For powders for reconstitution, uniformity of mass testing is generally considered acceptable.

(b) *pH*: Acceptance criteria for pH should be provided where applicable and the proposed range justified.

(c) *Sterility*: All parenteral products should have a test procedure and acceptance criterion for evaluation of sterility. Where data generated during development and validation justify parametric release, this approach may be proposed for terminally sterilized drug products (see Section 2.6).

(d) *Endotoxins/pyrogens*: A test procedure and acceptance criterion for endotoxins, using a procedure such as the limulus amoebocyte lysate test, should be included in the specification. Pyrogenicity testing may be proposed as an alternative to endotoxin testing where justified.

(e) *Particulate matter*: Parenteral products should have appropriate acceptance criteria for particulate matter. This will normally include acceptance criteria for visible particulates and/or clarity of solution, as well as for subvisible particulates as appropriate.

(f) *Water content*: For nonaqueous parenterals, and for parenteral products for reconstitution, a test procedure and acceptance criterion for water content should be proposed when appropriate. Loss on drying is generally considered sufficient for parenteral products, if the effect of absorbed moisture vs. water of hydration has been adequately characterized during development. In certain cases a more specific procedure (e.g., Karl Fischer titration) may be preferred.

(g) *Antimicrobial preservative content*: For parenteral products needing an antimicrobial preservative, acceptance criteria for preservative content should be established. Acceptance criteria for preservative content should be based upon the levels of antimicrobial preservative necessary to maintain microbiological quality of the product at all stages throughout its proposed usage and shelf life. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using a pharmacopoeial antimicrobial preservative effectiveness test.

Testing for antimicrobial preservative content should normally be performed at release. Under certain circumstances, in-process testing may suffice in lieu of release testing where permitted. When antimicrobial preservative content testing is performed as an in-process test, the acceptance criteria should remain part of the specification.

Antimicrobial preservative effectiveness should be demonstrated during development, during scaleup, and throughout the shelf life (e.g., in stability testing: See the ICH guideline, *Stability Testing*

of New Drug Substances and Products), although chemical testing for preservative content is the attribute normally included in the specification.

(h) *Antioxidant preservative content*: Release testing for antioxidant content should normally be performed. Under certain circumstances, where justified by developmental and stability data, shelf-life testing may be unnecessary and in-process testing may suffice in lieu of release testing. When antioxidant content testing is performed as an in-process test, the acceptance criteria should remain part of the specification. If only release testing is performed, this decision should be reinvestigated whenever either the manufacturing procedure or the container/closure system changes.

(i) *Extractables*: Control of extractables from container/closure systems is considered significantly more important for parenteral products than for oral liquids. However, where development and stability data show evidence that extractables are consistently below the levels that are demonstrated to be acceptable and safe, elimination of this test can normally be accepted. This should be reinvestigated if the container/closure system or formulation changes.

Where data demonstrate the need, acceptance criteria for extractables from the container/closure components are considered appropriate for parenteral products packaged in non-glass systems or in glass containers with elastomeric closures. This testing may be performed at release only, where justified by data obtained during development. The container/closure system components (e.g., rubber stopper, etc.) should be listed, and data collected for these components as early in the development process as possible.

(j) *Functionality testing of delivery systems*: Parenteral formulations packaged in prefilled syringes, autoinjector cartridges, or the equivalent should have test procedures and acceptance criteria related to the functionality of the delivery system. These may include control of syringeability, pressure, and seal integrity (leakage), and/or parameters such as tip cap removal force, piston release force, piston travel force, and power injector function force. Under certain circumstances these tests may be performed in process. Data generated during product development may be sufficient to justify skip lot testing or elimination of some or all attributes from the specification.

(k) *Osmolarity*: When the tonicity of a product is declared in its labeling, appropriate control of its osmolarity should be performed. Data generated during development and validation may be sufficient to justify performance of this procedure as an in-process control, skip lot testing, or direct calculation of this attribute.

(l) *Particle size distribution*: Quantitative acceptance criteria and a procedure for determination of particle size distribution may be appropriate for injectable suspensions. Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure.

Particle size distribution testing should be performed at release. It may be performed as an in-process test when justified by product development data. If the product has been demonstrated during development to have consistently rapid drug release characteristics, exclusion of particle size controls from the specification may be proposed.

Particle size distribution testing may also be proposed in place of dissolution testing, when development studies demonstrate that particle size is the primary factor influencing dissolution; justification should be provided. The acceptance criteria should include acceptable particle size distribution in terms of the percent of total particles in given size ranges. The mean, upper, and/or lower particle size limits should be well defined.

Acceptance criteria should be set based on the observed range of variation and should take into account the dissolution profiles of the batches that showed acceptable performance in vivo and the intended use of the product. The potential for particle growth should be investigated during product development; the acceptance criteria should take the results of these studies into account.

(m) *Redispersibility*: For injectable suspensions, which settle on storage (produce sediment), acceptance criteria for redispersibility may be appropriate. Shaking may be an appropriate procedure. The procedure (mechanical or manual) should be indicated. Time required to achieve resuspension by the indicated procedure should be clearly defined. Data generated during product development may be sufficient to justify skip lot testing, or elimination of this attribute from the specification may be proposed.

(n) *Reconstitution time*: Acceptance criteria for reconstitution time should be provided for all parenteral products which require reconstitution. The choice of diluent should be justified. Data generated during product development and process validation may be sufficient to justify skip lot testing or elimination of this attribute from the specification for rapidly dissolving products.

GLOSSARY

The following definitions are presented for the purpose of this guideline.

Acceptance Criteria: Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.

Chiral: Not superimposable with its mirror image, as applied to molecules, conformations, and macroscopic

objects, such as crystals. The term has been extended to samples of substances whose molecules are chiral, even if the macroscopic assembly of such molecules is racemic.

Combination Product: A drug product which contains more than one drug substance.

Degradation Product: A molecule resulting from a chemical change in the drug molecule brought about over time and/or by the action of, for example, light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Also called decomposition product.

Delayed Release: Release of a drug (or drugs) at a time other than immediately following oral administration.

Enantiomers: Compounds with the same molecular formula as the drug substance which differ in the spatial arrangement of atoms within the molecule and are nonsuperimposable mirror images.

Extended Release: Products which are formulated to make the drug available over an extended period after administration.

Highly Water-Soluble Drugs: Drugs with a dose/solubility volume of less than or equal to 250 mL over a pH range of 1.2 to 6.8. (e.g., Compound A has as its lowest solubility at 37°C ± 0.5°C, 1.0 mg/mL at pH 6.8, and is available in 100-, 200-, and 400-mg strengths. This drug would be considered a low solubility drug as its dose/solubility volume is greater than 250 mL (400 mg/1.0 mg/mL = 400 mL).

Immediate Release: Allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug.

Impurity: (1) Any component of the new drug substance which is not the chemical entity defined as the new drug substance. (2) Any component of the drug product which is not the chemical entity defined as the drug substance or an excipient in the drug product.

Identified Impurity: An impurity for which a structural characterization has been achieved.

In-Process Tests: Tests which may be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal battery of tests which are conducted prior to release.

Modified Release: Dosage forms whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. Modified release solid oral dosage forms include both delayed and extended release drug products.

New Drug Product: A pharmaceutical product type, for example, tablet, capsule, solution, cream, etc., which has not previously been registered in a region or Member State and which contains a drug ingredient generally, but not necessarily, in association with excipients.

New Drug Substance: The designated therapeutic moiety which has not previously been registered in a region or Member State (also referred to as a new molecular entity or new chemical entity). It may be a complex, simple ester, or salt of a previously approved drug substance.

Polymorphism: The occurrence of different crystalline forms of the same drug substance. This may include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms.

Quality: The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity.

Racemate: A composite (solid, liquid, gaseous, or in solution) of equimolar quantities of two enantiomeric species. It is devoid of optical activity.

Rapidly Dissolving Products: An immediate release solid oral drug product is considered rapidly dissolving when not less than 80% of the label amount of the drug substance dissolves within 15 minutes in each of the following media: (1) pH 1.2, (2) pH 4.0, and (3) pH 6.8.

Reagent: A substance, other than a starting material or solvent, which is used in the manufacture of a new drug substance.

Solvent: An inorganic or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of a new drug substance or the manufacture of a new drug product.

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

Specific Test: A test which is considered to be applicable to particular new drug substances or particular new drug products depending on their specific properties and/or intended use.

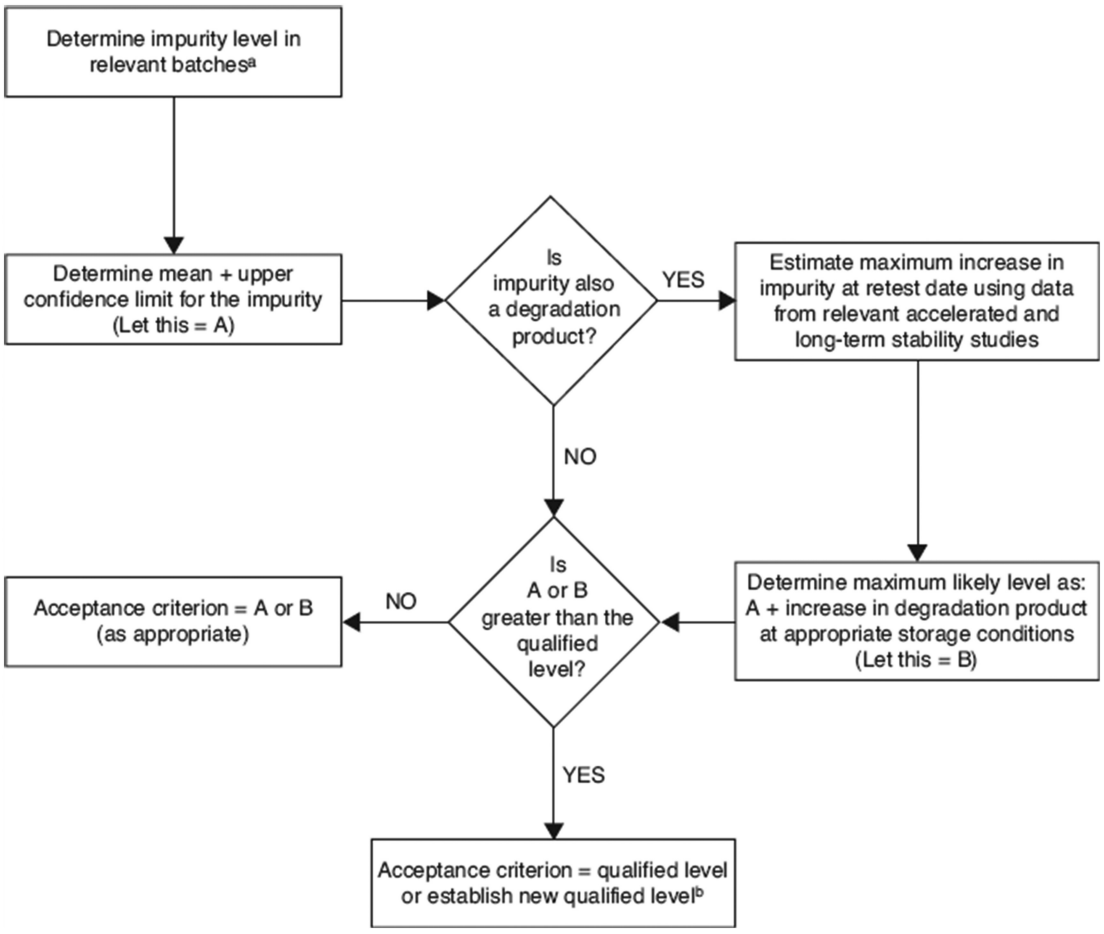
Specified Impurity: An identified or unidentified impurity that is selected for inclusion in the new drug substance or new drug product specification and is individually listed and limited in order to assure the quality of the new drug substance or new drug product.

Unidentified Impurity: An impurity which is defined solely by qualitative analytical properties, (e.g., chromatographic retention time).

Universal Test: A test which is considered to be potentially applicable to all new drug substances or all new drug products, for example, appearance, identification, assay, and impurity tests.

IV. ATTACHMENTS

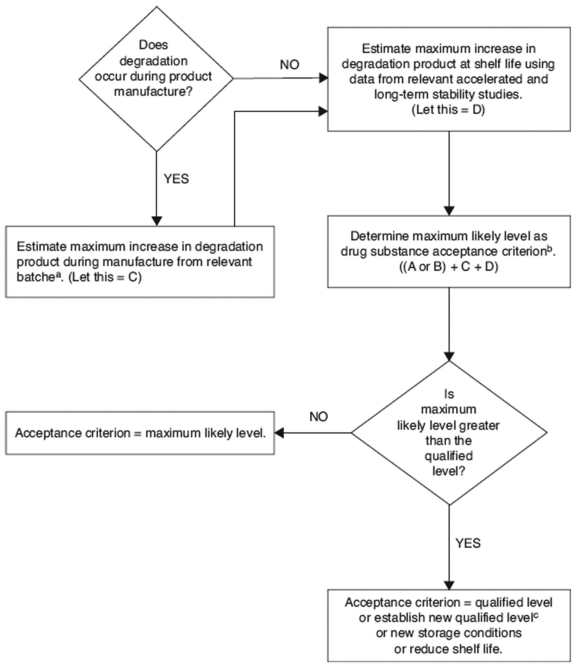
Decision Tree #1 Establishing Acceptance Criterion for a Specified Impurity in a New Drug Substance



[a] Relevant batches are those from development, pilot, and scale-up studies.
[b] Refer to ICH guideline on *Impurities in New Drug Substances.*

Definition: Upper confidence limit = three times the standard deviation of batch analysis data.

Decision Tree #2 Establishing Acceptance Criterion for a Degradation Product in a New Drug Product

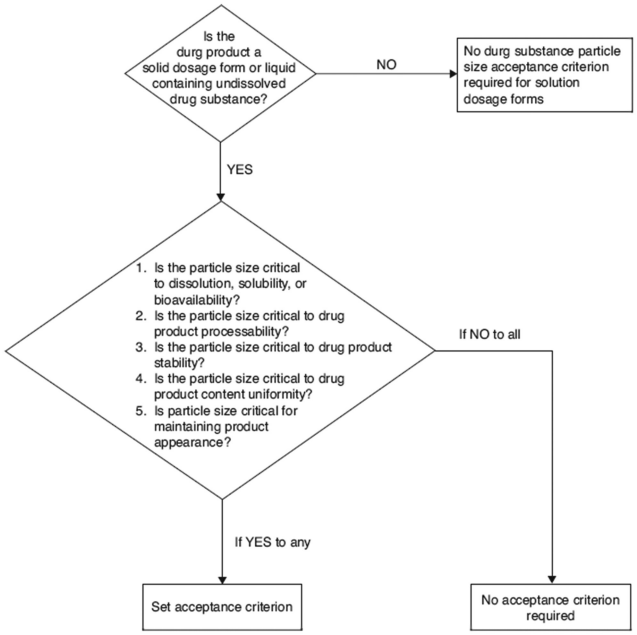


[a] Relevant batches are those from development, pilot, and scale-up studies.

[b] Refer to Decision Tree 1 for information regarding A and B.

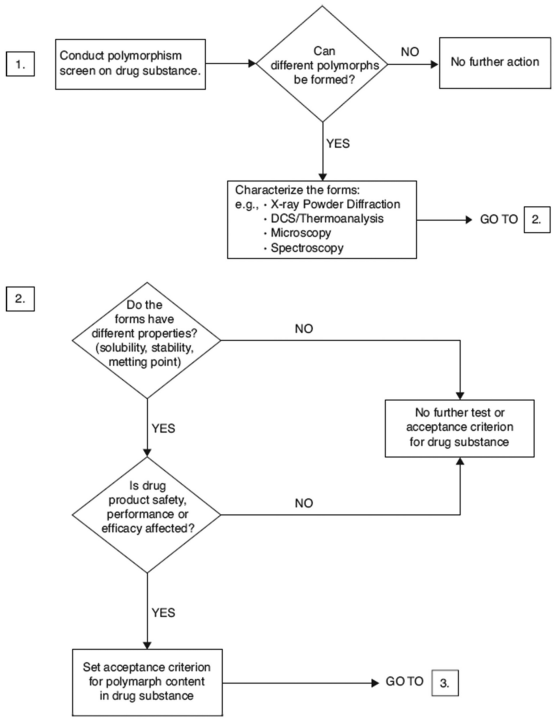
[c] Refer to ICH guideline on *Impurities in New Drug Products*.

Decision Tree #3 Setting Acceptance Criteria for Drug Substance Particle Size Distribution



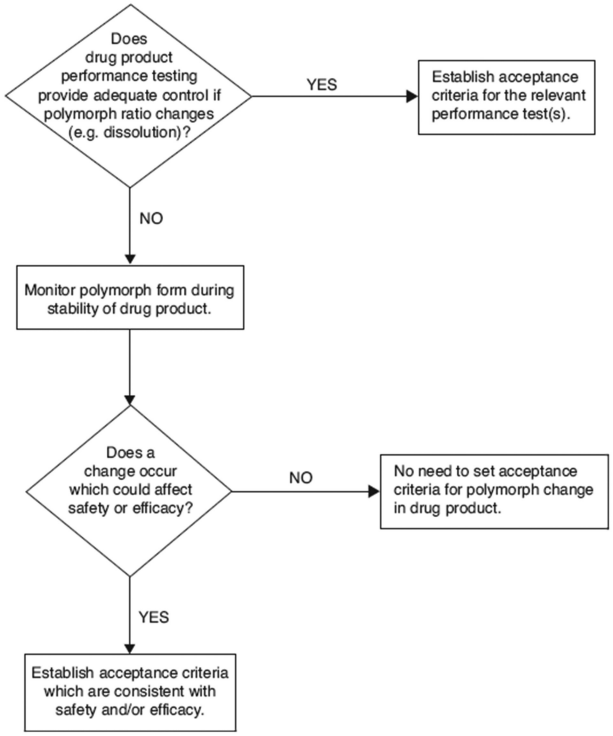
Decision Tree #4 Investigating the Need to set Acceptance Criteria for Polymorphism in Drug Substances and Drug Products

Drug Substances

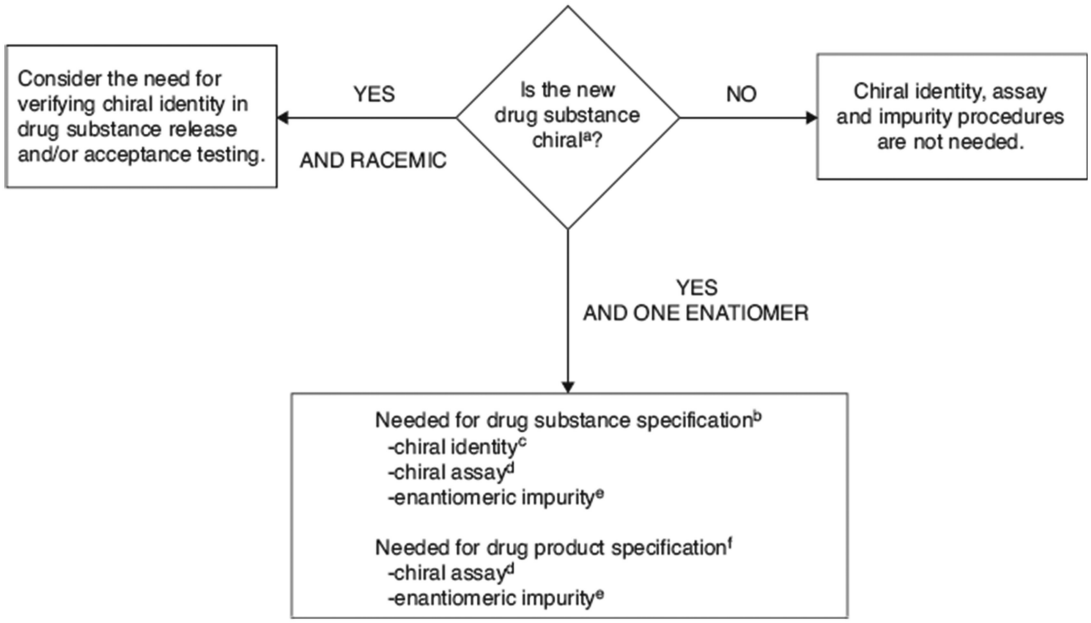


Drug Product—Solid Dosage Form or Liquid Containing Undissolved Drug Substance

N.B.: Undertake the following processes only technically possible to measure polymorph content in the drug product.



Decision Tree #5 Establishing Identity, Assay, and Enantiomeric Impurity Procedures for Chiral New Drug Substances and New Drug Products Containing Chiral Drug Substances



[a] Chiral substances of natural origin are not addressed in this guideline.

[b] As with other impurities arising in and from raw materials used in drug substance synthesis, control of chiral quality could be established alternatively by applying limits to appropriate starting materials or intermediates when justified from developmental studies. This essentially will be the case when there are multiple chiral centers (e.g., three or more) or when control as a step prior to production of the final drug substance is desirable.

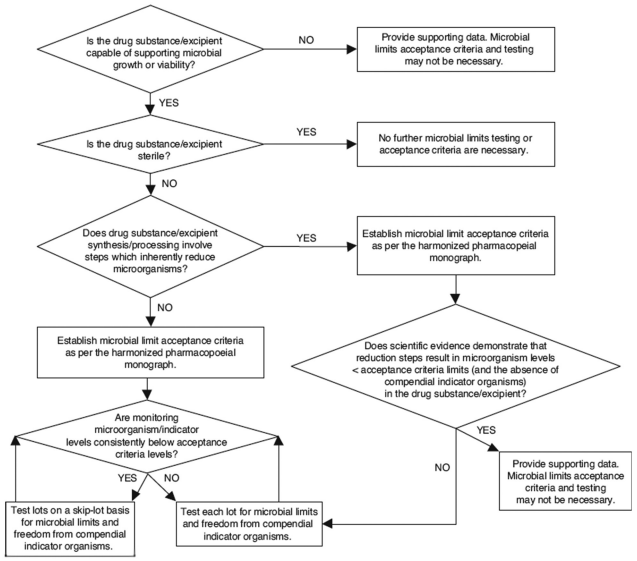
[c] A chiral assay or an enantiomeric impurity procedure may be acceptable in lieu of a chiral identity procedure.

[d] An achiral assay combined with a method for controlling the opposite enantiomer is acceptable in lieu of a chiral assay.

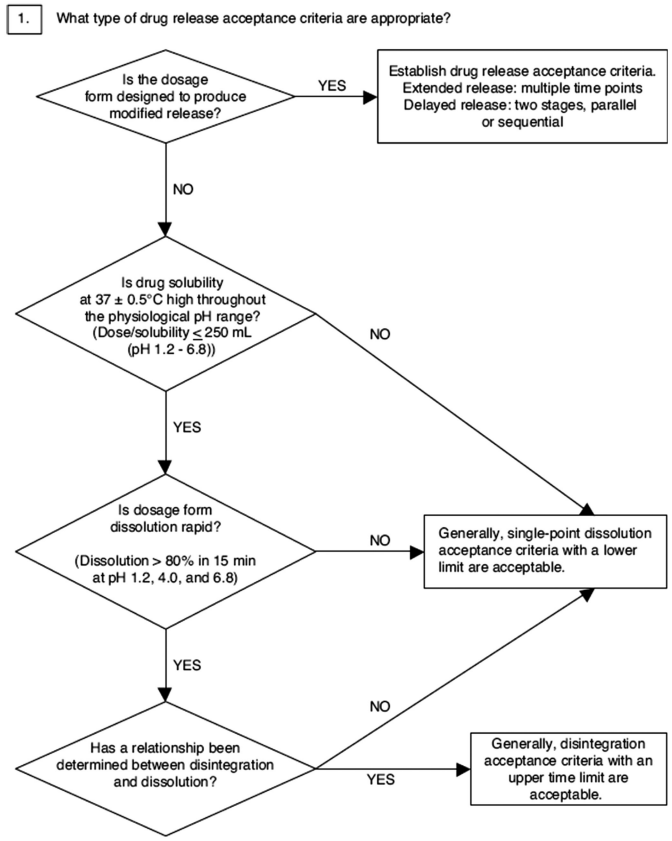
[e] The level of the opposite enantiomer of the drug substance may be derived from chiral assay data or from a separate procedure.

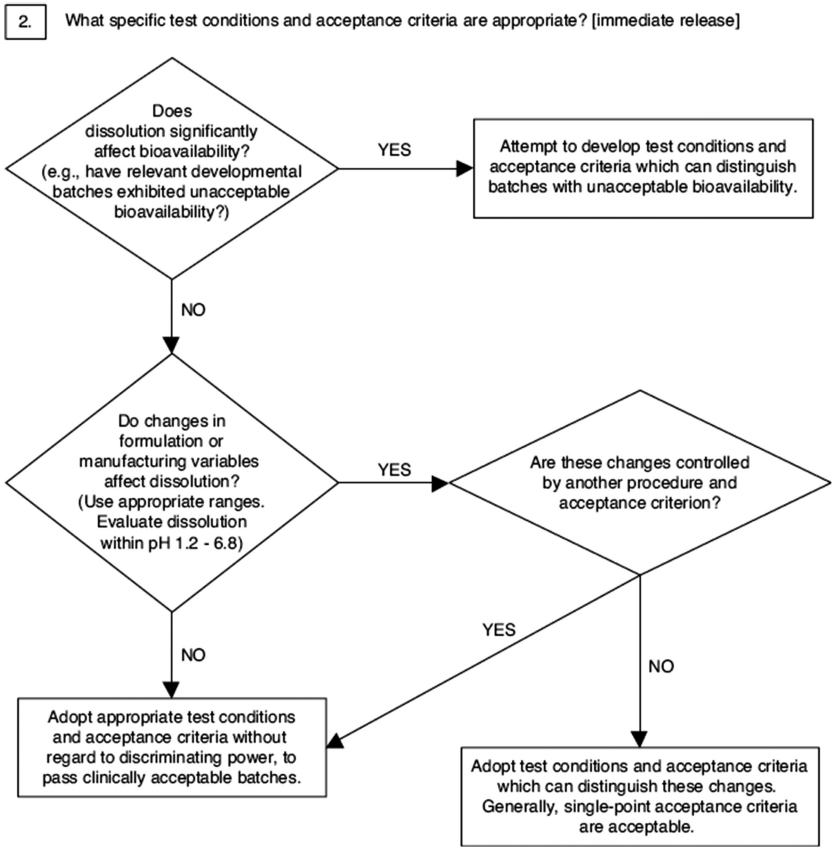
[f] Stereospecific testing of drug product may not be necessary if racerization has been demonstrated to be insignificant during drug product manufacture and during storage of the finished dosage form.

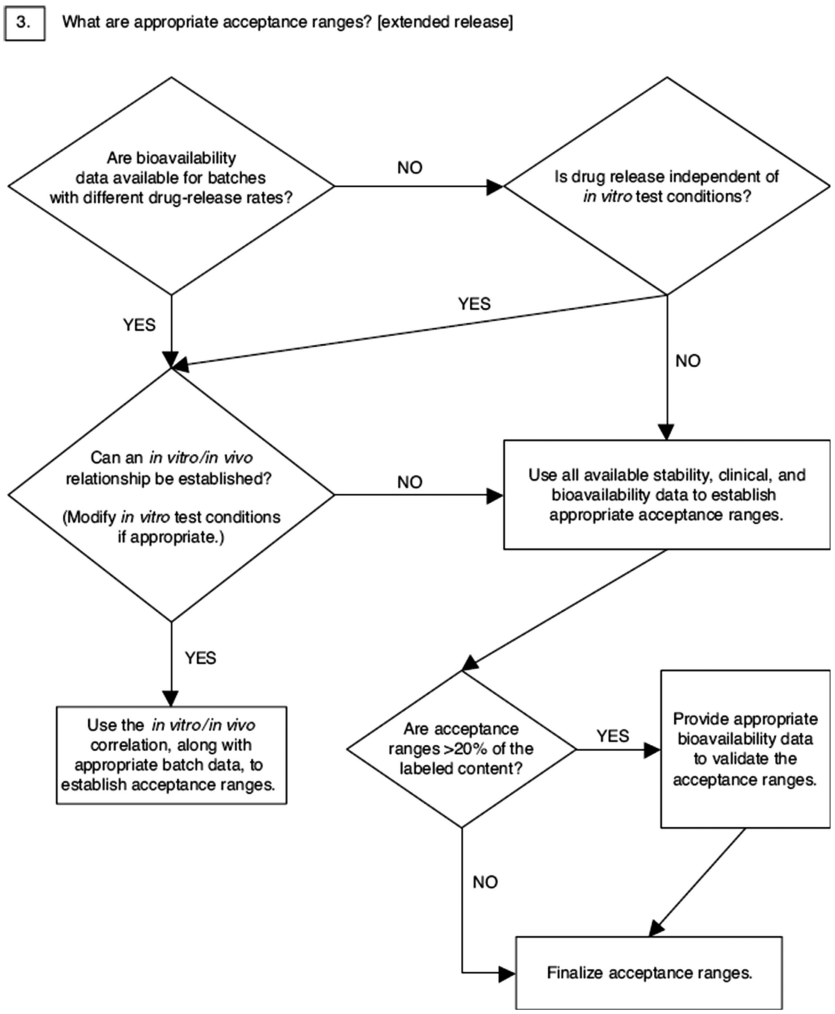
Decision Tree #6 Microbiological Quality Attributes of Drug Substance and Excipients



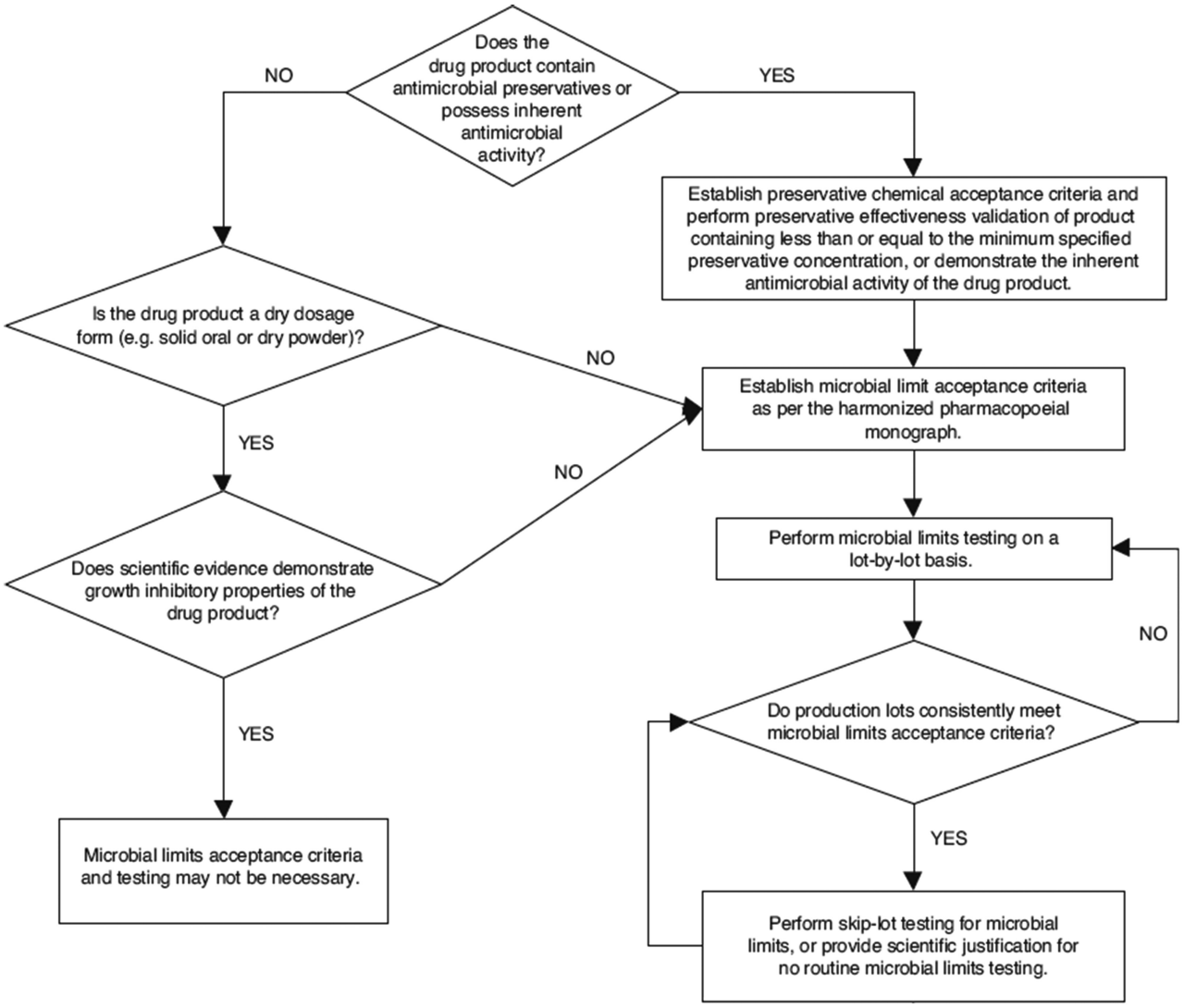
Decision Trees #7 Setting Acceptance Criteria for Drug Product Dissolution






3. What are appropriate acceptance ranges? [extended release]
Are bioavailability data available for batches with different drug-release rates?
NO
Is drug release independent of *in vitro* test conditions?
YES
YES
NO
Can an *in vitro/in vivo* relationship be established? (Modify *in vitro* test conditions if appropriate.)
NO
Use all available stability, clinical, and bioavailability data to establish appropriate acceptance ranges.
YES
Use the *in vitro/in vivo* correlation, along with appropriate batch data, to establish acceptance ranges.
Are acceptance ranges >20% of the labeled content?
YES
Provide appropriate bioavailability data to validate the acceptance ranges.
NO
Finalize acceptance ranges.

Decision Tree #8 Microbiological Attributes of Nonsterile Drug Products



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11 Topical Testing of Transdermal Drug Products

To fully evaluate the equivalence of a transdermal product for an abbreviated new drug application to a reference-listed drug, skin irritation and sensitization should be assessed because the condition of the skin may affect the absorption of a drug from a transdermal system. More severe skin irritation may affect the efficacy or safety of the product.

Transdermal products have properties that may lead to skin irritation or sensitization. The delivery system, or the system in conjunction with the drug substance, may cause these reactions. In the development of transdermal products, dermatologic adverse events are evaluated primarily with animal studies and safety evaluations in the context of large clinical trials generally associated with the submission of new drug applications. Separate skin irritation and skin sensitization studies also are used for this purpose. These latter studies are designed to detect irritation and sensitization under conditions of maximal stress and may be used during the assessment of transdermal drug products for abbreviated new drug applications.

I. STUDY DESIGNS

Recommended designs for skin irritation and skin sensitization studies for the comparative evaluation of transdermal drug products for an abbreviated new drug application are delineated below. Other proposals for studies may be suggested, but potential applicants are advised to consult the Office of Generic Drugs about alternative study designs before the initiation of such a study.

A. Recommendations for a Cumulative Skin Irritation Study

1. Sample Size

The sample size should be 30 subjects.

2. Exclusion Criteria

Dermatologic disease that might interfere with the evaluation of test site reaction should be grounds for exclusion.

3. Duration of Study

The study should last for 22 days.

4. Study Design

The study should be a randomized, controlled, repeat patch test study that compares the test patch with the innovator patch. Placebo patches (transdermal patch without active drug substance) or high- and low-irritancy controls (e.g., sodium lauryl sulfate 0.1% and 0.9% saline) can be included as additional test arms.

5. Patch Application

Each subject applies one of each of the patches to be tested. Test sites should be randomized among patients. Patches should be applied for 23 hours (±1 hour) daily for 21 days to the same skin site. At each patch removal, the site should be evaluated for reaction and the patch reapplied.

Application of a test patch should be discontinued at a site if predefined serious reactions occur at the site of repeated applications. Application at a different site may subsequently be initiated.

6. Evaluations

Scoring of skin reactions and patch adherence should be performed by a trained and blinded observer at each patch removal, using an appropriate scale.

Dermal reactions should be scored on a scale that describes the amount of erythema, edema, and other features indicative of irritations. (See Appendix A for an example of a scoring system that can be used.) The percentage adherence of the transdermal patches should be assessed using a five-point scale (see Appendix B).

7. Data Presentation and Analysis

Individual daily observations should be provided, as well as a tabulation that presents the percentage of subjects with each grade of skin reaction and degree of patch adherence on each study day. The mean cumulative irritation score, the total cumulative irritation score, and the number of days until sufficient irritation occurred to preclude patch application for all the study subjects should be calculated for each test product, and a statistical analysis of the comparative results should be performed (see Appendix C).

B. Recommendations for a Skin Sensitization Study (Modified Draize Test)

1. Sample Size

Two hundred subjects should be sampled.

2. Exclusion Criteria

Exclusion criteria include

a. Dermatologic disease that might interfere with the evaluation of the test site reactions and
b. Use of systemic or topical analgesics or antihistamines within 72 hours of study enrollment or systemic or topical corticosteroids within 3 weeks of study enrollment

3. Duration of Study

The study should last for 6 weeks.

4. Study Design

The study should be a randomized, controlled study on three test products: The test transdermal patch, the innovator patch, and the placebo patch (transdermal patch without the active drug substance).

5. Patch Application

Test sites should be randomized among patients. The study is divided into three sequential periods.

a. Induction Phase

Applications of the test materials should be made to the same skin sites three times weekly for 3 weeks, for a total of nine applications. The patches should remain in place for 48 hours on weekdays and for 72 hours on weekends. Scoring of skin reactions and patch adherence should be performed by a trained and blinded observer at each patch removal, using an appropriate scale.

Dermal reactions should be scored on a scale that describes the amount of erythema, edema, and other features indicative of irritation. (See Appendix A for an example of a scoring system that can be used.) The percentage adherence of the transdermal patches should be assessed using a five-point scale (see Appendix B).

b. Rest Phase

The induction phase is followed by a rest phase of 2 weeks, during which no applications are made.

c. Challenge Phase

The patches should be applied to new skin sites for 48 hours. Evaluation of skin reactions should be made by a trained blinded observer at 30 minutes and at 24, 48, and 72 hours after patch removal. (See Appendix A for an example of a scoring system that can be used.)

6. Data Presentation and Analysis

The individual daily observations should be provided, as well as a tabulation of the percentage of subjects with each grade of skin reaction and degree of patch adherence on each study day. The mean cumulative irritation score and the total cumulative irritation score for all the study subjects should be calculated for each test product, and a statistical analysis of the comparative results should be performed.

A narrative description of each reaction in the challenge phase should be provided, together with the opinion of the investigator as to whether such reactions are felt to be indicative of contact sensitization.

C. Combined Studies

Alternatively, the cumulative skin irritation study and the skin sensitization study can be combined into a single study. The study design would be identical to that described for the skin sensitization study (see Section I.B), except that patch application during the induction phase should be daily for 23 hours (±1 hour) each day over 21 days.

APPENDIX A: SKIN IRRITATION SCORING SYSTEMS

The following scoring system for irritation or sensitization reactions is included as an example of a scoring system that can be used for these studies. Other validated scoring systems can be used in quantifying skin reactions. The inclusion of this system should not be interpreted as an endorsement of the system by the agency. It is provided as an example only.

1. Dermal response:
   0 = no evidence of irritation
   1 = minimal erythema, barely perceptible
   2 = definite erythema, readily visible; minimal edema or minimal papular response
   3 = erythema and papules
   4 = definite edema
   5 = erythema, edema, and papules
   6 = vesicular eruption
   7 = strong reaction spreading beyond test site
2. Other effects:
   A = slight glazed appearance
   B = marked glazing
   C = glazing with peeling and cracking
   D = glazing with fissures
   E = film of dried serous exudate covering all or part of the patch site
   F = small petechial erosions or scabs

APPENDIX B: ADHESION SCORE

The following scoring system is included as an example of a scoring system that can be used for this type of study. Other validated scoring systems may be equally effective in quantifying comparative adhesion of transdermal systems. The inclusion of this system is not to be interpreted as an endorsement of the system by the agency. It is provided as an example only.

An estimate of the adherence of the transdermal system will be rated as follows:

0 ≥90% adhered (essentially no lift off the skin)
1 ≥75% to <90% adhered (some edges only lifting off the skin)
2 ≥50% to <75% adhered (less than half of the system lifting off the skin)
3 ≥50% adhered but not detached (more than half the system lifting off the skin without falling off)
4 = patch detached (patch completely off the skin)

APPENDIX C: STATISTICS

To be considered equivalent for a particular response, the average response for the generic (μ_T) should be between 80% and 125% of the average response for the innovator (μ_R). It is recommended that the response of the generic be equivalent to or better than the innovator. This implies a one-sided test.

For a variable for which low scores are better, such as mean irritation score or total cumulative irritation score, the hypotheses would be

$$H_0 : \mu_T / \mu_R > 1.25$$

$$H_1 : \mu_T / \mu_R \geq 1.25$$

which (assuming that $\mu_R > 0$) implies

$$H_0 : \mu_T - 1.25\mu_R \geq 0$$

$$H_1 : \mu_T - 1.25\mu_R \geq 0$$

The null hypothesis H_0 will be rejected when the upper limit of the 90% confidence interval (that is, the 95% upper confidence bound) for the quantity $\mu_T - 1.25\mu_R$ is less than or equal to zero.

For a variable for which high values are better, such as time to removal score, the hypotheses would be

$$H_0 : \mu_T / \mu_R < 0.80$$

$$H_1 : \mu_T / \mu_R \geq 0.80$$

which (assuming that $\mu_R > 0$) implies

$$H_0 : \mu_T - 0.80\mu_R < 0$$

$$H_0 : \mu_T - 0.80\mu_R \geq 0$$

The null hypothesis H_0 will be rejected in this case when the lower limit of the 90% confidence interval (i.e., the 95% lower confidence bound) for the quantity $\mu_T - 0.80\mu_R$ is greater than or equal to zero.

In either case, if the null hypothesis H_0 is rejected, the generic should be considered equivalent to or better than the innovator.

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12 Impurities Profiling
Drug Substance

I. PREAMBLE

This document is intended to provide guidance for registration applications on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in a region or member state. It is not intended to apply to new drug substances used during the clinical research stage of development. The following types of drug substances are not covered in this guideline: Biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation product and semisynthetic products derived therefrom, herbal products, and crude products of animal or plant origin.

Impurities in new drug substances are addressed from the following two perspectives:

Chemistry Aspects include classification and identification of impurities, report generation, listing of impurities in specifications, and a brief discussion of analytical procedures.

Safety Aspects include specific guidance for qualifying those impurities that were not present, or were present at substantially lower levels, in batches of a new drug substance used in safety and clinical studies.

II. CLASSIFICATION OF IMPURITIES

Impurities can be classified into the following categories:

- Organic impurities (process and drug related)
- Inorganic impurities
- Residual solvents

Organic impurities can arise during the manufacturing process and/or storage of the new drug substance. They can be identified or unidentified, volatile or nonvolatile, and include

- Starting materials
- Byproducts
- Intermediates
- Degradation products
- Reagents, ligands, and catalysts

Inorganic impurities can result from the manufacturing process. They are normally known and identified and include

- Reagents, ligands, and catalysts
- Heavy metals or other residual metals
- Inorganic salts
- Other materials (e.g., filter aids, charcoal)

Solvents are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a new drug substance. Since these are generally of known toxicity, the selection of appropriate controls is easily accomplished (see ICH guideline Q3C on residual solvents).

Excluded from this document are (1) extraneous contaminants that should not occur in new drug substances and are more appropriately addressed as GMP issues, (2) polymorphic forms, and (3) enantiomeric impurities.

III. RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

A. Organic Impurities

The applicant should summarize the actual and potential impurities most likely to arise during the synthesis, purification, and storage of the new drug substance. This summary should be based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the new drug substance, and possible degradation products. This discussion can be limited to those impurities that might reasonably be expected based on knowledge of the chemical reactions and conditions involved.

In addition, the applicant should summarize the laboratory studies conducted to detect impurities in the new drug substance. This summary should include test results of batches manufactured during the development process and batches from the proposed commercial process, as well as the results of stress testing (see ICH guideline Q1A on stability) used to identify potential impurities arising during storage. The impurity profile of the drug substance batches intended for marketing should be compared with those used in development and any differences discussed.

The studies conducted to characterize the structure of actual impurities present in the new drug substance at a level greater than (>) the identification threshold given in Attachment 1 (e.g., calculated using the response factor of the drug substance) should be described. Note that any impurity at a level greater than (>) the identification threshold in any batch manufactured by the proposed commercial process should be identified. In addition, any degradation product observed in stability studies at recommended storage conditions at a level greater than (>) the identification threshold

should be identified. When identification of an impurity is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the application. Where attempts have been made to identify impurities present at levels of not more than (<) the identification thresholds, it is useful also to report the results of these studies.

Identification of impurities present at an apparent level of not more than (≤) the identification threshold is generally not considered necessary. However, analytical procedures should be developed for those potential impurities that are expected to be unusually potent, producing toxic or pharmacological effects at a level not more than (≤) the identification threshold. All impurities should be qualified as described later in this guideline.

B. Inorganic Impurities

Inorganic impurities are normally detected and quantified using pharmacopoeial or other appropriate procedures. Carryover of catalysts to the new drug substance should be evaluated during development. The need for inclusion or exclusion of inorganic impurities in the new drug substance specification should be discussed. Acceptance criteria should be based on pharmacopoeial standards or known safety data.

C. Solvents

The control of residues of the solvents used in the manufacturing process for the new drug substance should be discussed and presented according to the ICH Q3C *Guideline for Residual Solvents.*

IV. ANALYTICAL PROCEDURES

The registration application should include documented evidence that the analytical procedures are validated and suitable for the detection and quantification of impurities (see ICH Q2A and Q2B guidelines for analytical validation). Technical factors (e.g., manufacturing capability and control methodology) can be considered as part of the justification for selection of alternative thresholds based on manufacturing experience with the proposed commercial process. The use of two decimal places for thresholds (see Attachment 1) does not necessarily reflect the precision of the analytical procedure used for routine quality control purposes. Thus, the use of lower precision techniques (e.g., thin-layer chromatography) can be acceptable where justified and appropriately validated. Differences in the analytical procedures used during development and those proposed for the commercial product should be discussed in the registration application.

The quantitation limit for the analytical procedure should be not more than (≤) the reporting threshold.

Organic impurity levels can be measured by a variety of techniques, including those that compare an analytical response for an impurity to that of an appropriate reference standard or to the response of the new drug substance itself. Reference standards used in the analytical procedures for control of impurities should be evaluated and characterized according to their intended uses. The drug substance can be used as a standard to estimate the levels of impurities. In cases where the response factors of the drug substance and the relevant impurity are not close, this practice can still be appropriate, provided a correction factor is applied or the impurities are, in fact, being overestimated. Acceptance criteria and analytical procedures used to estimate identified or unidentified impurities can be based on analytical assumptions (e.g., equivalent detector response). These assumptions should be discussed in the registration application.

V. REPORTING IMPURITY CONTENT OF BATCHES

Analytical results should be provided in the application for all batches of the new drug substance used for clinical, safety, and stability testing, as well as for batches representative of the proposed commercial process. Quantitative results should be presented numerically and not in general terms such as "complies," "meets limit," etc. Any impurity at a level greater than (>) the reporting threshold (see Attachment 1) and total impurities observed in these batches of the new drug substance should be reported with the analytical procedures indicated. Below 1.0%, the results should be reported to two decimal places (e.g., 0.06%, 0.13%); at and above 1.0%, the results should be reported to one decimal place (e.g., 1.3%). Results should be rounded using conventional rules (see Attachment 2). A tabulation (e.g., spreadsheet) of the data is recommended. Impurities should be designated by code number or by an appropriate descriptor, for example, retention time. If a higher reporting threshold is proposed, it should be fully justified. All impurities at a level greater than (>) the reporting threshold should be summed and reported as total impurities.

When analytical procedures change during development, reported results should be linked to the procedure used, with appropriate validation information provided. Representative chromatograms should be provided. Chromatograms of representative batches from analytical validation studies showing separation and detectability of impurities (e.g., on spiked samples), along with any other impurity tests routinely performed, can serve as the representative impurity profiles. The applicant should ensure that complete impurity profiles (e.g., chromatograms) of individual batches are available, if requested.

A tabulation should be provided that links the specific new drug substance batch to each safety study and each clinical study in which the new drug substance has been used.

For each batch of the new drug substance, the report should include

- Batch identity and size
- Date of manufacture
- Site of manufacture
- Manufacturing process
- Impurity content, individual and total
- Use of batches
- Reference to analytical procedure used

VI. LISTING OF IMPURITIES IN SPECIFICATIONS

The specification for a new drug substance should include a list of impurities. Stability studies, chemical development studies, and routine batch analyses can be used to predict those impurities likely to occur in the commercial product. The selection of impurities in the new drug substance specification should be based on the impurities found in batches manufactured by the proposed commercial process. Those individual impurities with specific acceptance criteria included in the specification for the new drug substance are referred to as "specified impurities" in this guideline. Specified impurities can be identified or unidentified.

A rationale for the inclusion or exclusion of impurities in the specification should be presented. This rationale should include a discussion of the impurity profiles observed in the safety and clinical development batches, together with a consideration of the impurity profile of batches manufactured by the proposed commercial process. Specified identified impurities should be included along with specified unidentified impurities estimated to be present at a level greater than (>) the identification threshold given in Attachment 1. For impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation/detection limit of the analytical procedures should be commensurate with the level at which the impurities should be controlled. For unidentified impurities, the procedure used and assumptions made in establishing the level of the impurity should be clearly stated. Specified, unidentified impurities should be referred to by an appropriate qualitative analytical descriptive label (e.g., "unidentified A," "unidentified with relative retention of 0.9"). A general acceptance criterion of not more than (≤) the identification threshold (Attachment 1) for any unspecified impurity and an acceptance criterion for total impurities should be included.

Acceptance criteria should be set no higher than the level that can be justified by safety data and should be consistent with the level achievable by the manufacturing process and the analytical capability. Where there is no safety concern, impurity acceptance criteria should be based on data generated on batches of the new drug substance manufactured by the proposed commercial process, allowing sufficient latitude to deal with normal manufacturing and analytical variation and the stability characteristics of the new drug substance. Although normal manufacturing variations are expected, significant variation in batch-to-batch impurity levels can indicate that the manufacturing process of the new drug substance is not adequately controlled and validated (see ICH Q6A guideline on specifications, Decision Tree No. 1, for establishing an acceptance criterion for a specified impurity in a new drug substance). The use of two decimal places for thresholds (see Attachment 1) does not necessarily indicate the precision of the acceptance criteria for specified impurities and total impurities.

In summary, the new drug substance specification should include, where applicable, the following list of impurities:

Organic Impurities
- Each specified identified impurity
- Each specified unidentified impurity
- Any unspecified impurity with an acceptance criterion of not more than (≤) the identification threshold
- Total impurities

Residual Solvents

Inorganic Impurities

VII. QUALIFICATION OF IMPURITIES

Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified. The applicant should provide a rationale for establishing impurity acceptance criterion that includes safety considerations. The level of any impurity present in a new drug substance that has been adequately tested in safety and/or clinical studies would be considered qualified. Impurities that are also significant metabolites present in animal and/or human studies are generally considered qualified. A level of a qualified impurity higher than that present in a new drug substance can also be justified based on an analysis of the actual amount of impurity administered in previous relevant safety studies.

If data are unavailable to qualify the proposed acceptance criterion of an impurity, studies to obtain such data can be appropriate when the usual qualification thresholds given in Attachment 1 are exceeded.

Higher or lower thresholds for qualification of impurities can be appropriate for some individual drugs based on scientific rationale and level of concern, including drug class effects and clinical experience. For example, qualification can be especially important when there is evidence that such impurities in certain drugs or therapeutic classes have previously been associated with adverse reactions in patients. In these instances, a lower qualification threshold can be appropriate. Conversely, a higher qualification threshold can be appropriate for individual drugs when the level of concern for safety is less than usual based on similar considerations (e.g., patient population, drug class effects, clinical considerations). Proposals for alternative thresholds would be considered on a case-by-case basis.

The "Decision Tree for Identification and Qualification" (Attachment 3) describes considerations for the qualification of impurities when thresholds are exceeded. In some cases, decreasing the level of impurity to not more than the threshold can be simpler than providing safety data. Alternatively, adequate data could be available in the scientific literature to qualify an impurity. If neither is the case, additional safety testing should be considered. The studies considered appropriate to qualify an impurity will depend on a number of factors, including the patient population, daily dose, and route and duration of drug administration. Such studies can be conducted on the new drug substance containing the impurities to be controlled, although studies using isolated impurities can sometimes be appropriate.

Although this guideline is not intended to apply during the clinical research stage of development, in the later stages of development the thresholds in this guideline can be useful in evaluating new impurities observed in drug substance batches prepared by the proposed commercial process. Any new impurity observed in later stages of development should be identified if its level is greater than (>) the identification threshold given in Attachment 1 (see the "Decision Tree for Identification and Qualification" in Attachment 3). Similarly, the qualification of the impurity should be considered if its level is greater than (>) the qualification threshold given in Attachment 1. Safety assessment studies to qualify an impurity should compare the new drug substance containing a representative amount of the new impurity with previously qualified material. Safety assessment studies using a sample of the isolated impurity can also be considered.

GLOSSARY

Chemical Development Studies: Studies conducted to scale up, optimize, and validate the manufacturing process for a new drug substance.

Enantiomeric Impurity: A compound with the same molecular formula as the drug substance that differs in the spatial arrangement of atoms within the molecule and is a nonsuperimposable mirror image.

Extraneous Contaminant: An impurity arising from any source extraneous to the manufacturing process.

Herbal Products: Medicinal products containing, exclusively, plant material and/or vegetable drug preparations as active ingredients. In some traditions, materials of inorganic or animal origin can also be present.

Identified Impurity: An impurity for which a structural characterization has been achieved.

Identification Threshold: A limit above (>) which an impurity should be identified.

Impurity: Any component of the new drug substance that is not the chemical entity defined as the new drug substance.

Impurity Profile: A description of the identified and unidentified impurities present in a new drug substance.

Intermediate: A material produced during steps of the synthesis of a new drug substance that undergoes further chemical transformation before it becomes a new drug substance.

Ligand: An agent with a strong affinity to a metal ion.

New Drug Substance: The designated therapeutic moiety that has not been previously registered in a region or member state (also referred to as a new molecular entity or new chemical entity). It can be a complex, simple ester, or salt of a previously approved drug substance.

Polymorphic Forms: Different crystalline forms of the same drug substance. These can include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms.

Potential Impurity: An impurity that theoretically can arise during manufacture or storage. It may or may not actually appear in the new drug substance.

Qualification: The process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

Qualification Threshold: A limit above (>) which an impurity should be qualified.

Reagent: A substance other than a starting material, intermediate, or solvent that is used in the manufacture of a new drug substance.

Reporting Threshold: A limit above (>) which an impurity should be reported. Reporting threshold is the same as reporting level in Q2B.

Solvent: An inorganic or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of a new drug substance.

Specified Impurity: An impurity that is individually listed and limited with a specific acceptance criterion in the new drug substance specification. A specified impurity can be either identified or unidentified.

Starting Material: A material used in the synthesis of a new drug substance that is incorporated as an element into the structure of an intermediate and/or of the new drug substance. Starting materials are normally commercially available and of defined chemical and physical properties and structure.

Unidentified Impurity: An impurity for which a structural characterization has not been achieved and that is defined solely by qualitative analytical properties (e.g., chromatographic retention time).

Unspecified Impurity: An impurity that is limited by a general acceptance criterion, but not individually listed with its own specific acceptance criterion, in the new drug substance specification.

ATTACHMENT 1: THRESHOLDS

Maximum Daily Dose[a]	Reporting Threshold[b,c]	Identification Threshold[c]	Qualification Threshold[c]
≤2 g/day	0.05%	0.10% or 1.0 mg/day intake (whichever is lower)	0.15% or 1.0 mg/day intake (whichever is lower)
>2 g/day	0.03%	0.05%	0.05%

[a] The amount of drug substance administered per day.

[b] Higher reporting thresholds should be scientifically justified.

[c] Lower thresholds can be appropriate if the impurity is unusually toxic.

ATTACHMENT 2: ILLUSTRATION OF REPORTING IMPURITY RESULTS FOR IDENTIFICATION AND QUALIFICATION IN AN APPLICATION

The attachment is only illustrative and is not intended to serve as template for how results on impurities should be presented in an application file. Normally raw data are not presented.

Example 1: 0.5 g Maximum Daily Dose

Reporting threshold = 0.05%
Identification threshold = 0.10%
Qualification threshold = 0.15%

			Action	
"Raw" Result (%)	**Reported Result (%) Reporting Threshold = 0.05%**	**Calculated Total Daily Intake (TDI) (mg) of the Impurity (Rounded Result in mg)**	**Identification (Threshold 0.10% Exceeded?)**	**Qualification (Threshold 0.15% Exceeded?)**
0.044	Not reported	0.2	None	None
0.0963	0.10	0.5	None	None
0.12	0.12[a]	0.6	Yes	None[a]
0.1649	0.16[a]	0.8	Yes	Yes[a]

Example 2: 0.8 g Maximum Daily Dose

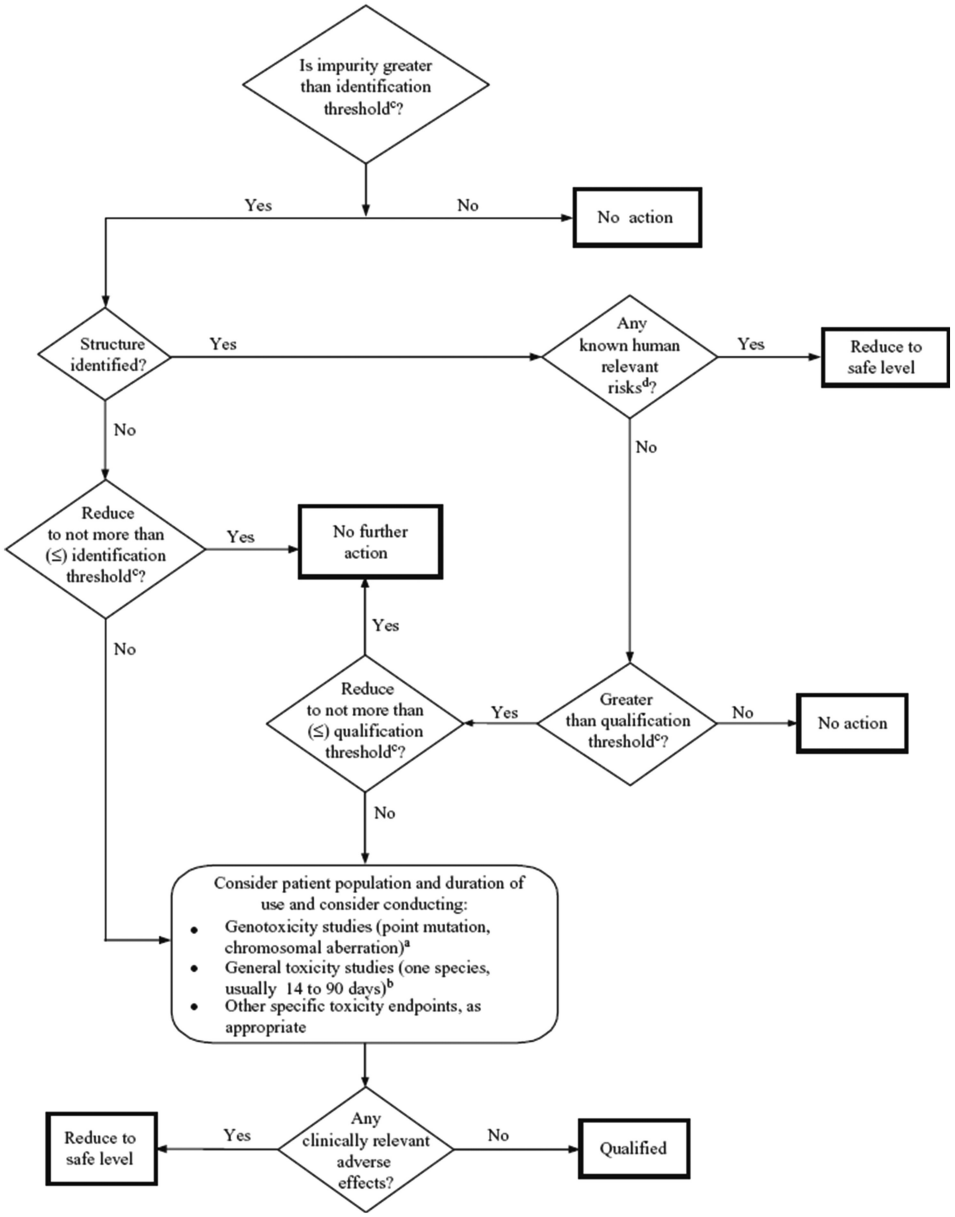
Reporting threshold = 0.05%
Identification threshold = 0.10%
Qualification threshold = 1.0 mg TDI

			Action	
"Raw" Result (%)	**Reported Result (%) Reporting Threshold = 0.05%**	**Calculated Total Daily Intake (TDI) (mg) of the Impurity (Rounded Result in mg)**	**Identification (Threshold 0.10% Exceeded?)**	**Qualification (Threshold 1.0 mg TDI Exceeded?)**
0.066	0.07	0.6	None	None
0.124	0.12	1.0	Yes	None[a,b]
0.143	0.14	1.1	Yes	Yes[a]

[a] After identification, if the response factor is determined to differ significantly from the original assumptions, it may be appropriate to remeasure the actual amount of the impurity present and reevaluate against the qualification threshold (see Attachment 1).

[b] To verify if a threshold is exceeded, a reported result has to be evaluated against the thresholds as follows: When the threshold is described in %, the reported result rounded to the same decimal place as the threshold should be compared directly to the threshold. When the threshold is described in TDI, the reported result should be converted to TDI, rounded to the same decimal place as the threshold, and compared to the threshold. For example, the amount of impurity at 0.12% level corresponds to a TDI of 0.96 mg (absolute amount), which is then rounded up to 1.0 mg; so the qualification threshold expressed in TDI (1.0 mg) is not exceeded.

ATTACHMENT 3: DECISION TREE FOR IDENTIFICATION AND QUALIFICATION



[a] If considered desirable, a minimum screen (e.g., genotoxic potential) should be conducted. A study to detect point mutations and to detect chromosomal aberrations, both in vitro, is considered an appropriate minimum screen.

[b] If general toxicity studies are desirable, one or more studies should be designed to allow comparison of unqualified to qualified material. The study duration should be based on available relevant information and performed in the species most likely to maximize the potential to detect the toxicity of an impurity. On a case-by-case basis, single-dose studies can be appropriate, especially for single-dose drugs. In general, a minimum duration of 14 days and a maximum duration of 90 days would be considered appropriate.

[c] Lower thresholds can be appropriate if the impurity is unusually toxic.

[d] For example, do known safety data for this impurity or its structural class preclude human exposure at the concentration present?

13 Impurities in New Drug Products

I. INTRODUCTION

A. Objective of the Guideline

This document provides guidance for registration applications on the content and qualification of impurities in new drug products produced from chemically synthesized new drug substances not previously registered in a region or member state.

B. Background

This guideline is complementary to the ICH Q3A(R) guideline *Impurities in New Drug Substances*, which should be consulted for basic principles. The ICH Q3C guideline *Residual Solvents* should also be consulted, if appropriate.

C. Scope of the Guideline

This guideline addresses only those impurities in new drug products classified as degradation products of the drug substance or reaction products of the drug substance with an excipient and/or immediate container closure system (collectively referred to as "degradation products" in this guideline). Generally, impurities present in the new drug substance need not be monitored or specified in the new drug product unless they are also degradation products (see ICH Q6A guideline on specifications).

Impurities arising from excipients present in the new drug product or extracted or leached from the container closure system are not covered by this guideline. This guideline also does not apply to new drug products used during the clinical research stages of development. The following types of products are not covered in this guideline: Biological/biotechnological products, peptides, oligonucleotides, radiopharmaceuticals, fermentation products and semisynthetic products derived therefrom, herbal products, and crude products of animal or plant origin. Also excluded from this document are (1) extraneous contaminants that should not occur in new drug products and are more appropriately addressed as good manufacturing practice (GMP) issues, (2) polymorphic forms, and (3) enantiomeric impurities.

II. RATIONALE FOR THE REPORTING AND CONTROL OF DEGRADATION PRODUCTS

The applicant should summarize the degradation products observed during manufacture and/or stability studies of the new drug product. This summary should be based on sound scientific appraisal of potential degradation pathways in the new drug product and impurities arising from the interaction with excipients and/or the immediate container closure system. In addition, the applicant should summarize any laboratory studies conducted to detect degradation products in the new drug product. This summary should also include test results of batches manufactured during the development process and batches representative of the proposed commercial process. A rationale should be provided for exclusion of those impurities that are not degradation products (e.g., process impurities from the drug substance and impurities arising from excipients). The impurity profiles of the batches representative of the proposed commercial process should be compared with the profiles of batches used in development and any differences discussed.

Any degradation product observed in stability studies conducted at the recommended storage condition should be identified when present at a level greater than (>) the identification thresholds given in Attachment 1. When identification of a degradation product is not feasible, a summary of the laboratory studies demonstrating the unsuccessful efforts to identify it should be included in the registration application.

Degradation products present at a level of not more than (≤) the identification threshold generally would not need to be identified. However, analytical procedures should be developed for those degradation products that are suspected to be unusually potent, producing toxic or significant pharmacological effects at levels not more than (≤) the identification threshold. In unusual circumstances, technical factors (e.g., manufacturing capability, a low drug substance to excipient ratio, or the use of excipients that are crude products of animal or plant origin) can be considered as part of the justification for selection of alternative thresholds based upon manufacturing experience with the proposed commercial process.

III. ANALYTICAL PROCEDURES

The registration application should include documented evidence that the analytical procedures have been validated and are suitable for the detection and quantitation of degradation products (see ICH Q2A and Q2B guidelines on analytical validation). In particular, analytical procedures should be validated to demonstrate specificity for the specified and unspecified degradation products. As appropriate, this validation should include samples stored under relevant stress conditions: Light, heat, humidity, acid/base hydrolysis, and oxidation. When an analytical procedure reveals the presence of other peaks in addition to those of the degradation products (e.g., the drug substance, impurities arising from the synthesis of the drug substance, excipients and impurities arising from the excipients), these peaks should be labeled in the chromatograms and their origin(s) discussed in the validation documentation.

The quantitation limit for the analytical procedure should be not more than (≤) the reporting threshold.

Degradation product levels can be measured by a variety of techniques, including those that compare an analytical response for a degradation product to that of an appropriate reference standard or to the response of the new drug substance itself. Reference standards used in the analytical procedures for control of degradation products should be evaluated and characterized according to their intended uses. The drug substance can be used to estimate the levels of degradation products. In cases where the response factors are not close, this practice can still be used if a correction factor is applied or the degradation products are, in fact, being overestimated. Acceptance criteria and analytical procedures, used to estimate identified or unidentified degradation products, are often based on analytical assumptions (e.g., equivalent detector response). These assumptions should be discussed in the registration application.

Differences between the analytical procedures used during development and those proposed for the commercial product should also be discussed.

IV. REPORTING DEGRADATION PRODUCTS CONTENT OF BATCHES

Analytical results should be provided in the registration application for all relevant batches of the new drug product used for clinical, safety, and stability testing, as well as batches that are representative of the proposed commercial process. Quantitative results should be presented numerically and not in general terms such as "complies," "meets limit," etc. Any degradation product at a level greater than (>) the reporting threshold (see Attachment 1), and total degradation products observed in the relevant batches of the new drug product, should be reported with the analytical procedures indicated. Below 1.0%, the results should be reported to the number of decimal places (e.g., 0.06%) in the applicable reporting threshold; at and above 1.0%, the results should be reported to one decimal place (e.g., 1.3%). Results should be rounded using conventional rules (see Attachment 2). A tabulation (e.g., spreadsheet) of the data is recommended. Degradation products should be designated by code number or by an appropriate descriptor, for example, retention time. If a higher reporting threshold is proposed, it should be fully justified. All degradation products at a level greater than (>) the reporting threshold should be summed and reported as total degradation products.

Chromatograms with peaks labeled (or equivalent data if other analytical procedures are used) from representative batches, including chromatograms from analytical procedure validation studies and from long-term and accelerated stability studies, should be provided. The applicant should ensure that complete degradation product profiles (e.g., chromatograms) of individual batches are available, if requested.

For each batch of the new drug product described in the registration application, the documentation should include

- Batch identity, strength, and size
- Date of manufacture
- Site of manufacture
- Manufacturing process
- Immediate container closure
- Degradation product content, individual and total
- Use of batch (e.g., clinical studies, stability studies)
- Reference to analytical procedure used
- Batch number of the drug substance used in the new drug product
- Storage conditions for stability studies

V. LISTING OF DEGRADATION PRODUCTS IN SPECIFICATIONS

The specification for a new drug product should include a list of degradation products expected to occur during manufacture of the commercial product and under recommended storage conditions. Stability studies, knowledge of degradation pathways, product development studies, and laboratory studies should be used to characterize the degradation profile. The selection of degradation products in the new drug product specification should be based on the degradation products found in batches manufactured by the proposed commercial process. Those individual degradation products with specific acceptance criteria included in the specification for the new drug product are referred to as "specified degradation products" in this guideline. Specified degradation products can be identified or unidentified. A rationale for the inclusion or exclusion of degradation products in the specification should be presented. This rationale should include a discussion of the degradation profiles observed in the safety and clinical development batches and in stability studies, together with a consideration of the degradation profile of batches manufactured by the proposed commercial process. Specified identified degradation products should be included along with specified unidentified degradation products estimated to be present at a level greater than (>) the identification threshold given in Attachment 1. For degradation products known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation/detection limit of the analytical procedures should be commensurate with the level at which the degradation products should be controlled. For unidentified degradation products, the procedure used and assumptions made in establishing the level of the degradation product should be clearly stated. Specified unidentified degradation products should be referred to by an appropriate qualitative analytical descriptive label (e.g., "unidentified A," "unidentified with relative retention of 0.9"). A general acceptance criterion of not more than (≤) the identification threshold (Attachment 1) for any unspecified degradation product and an acceptance criterion for total degradation products should also be included.

For a given degradation product, its acceptance criterion should be established by taking into account its acceptance criterion in the drug substance (if applicable), its qualified

level, its increase during stability studies, and the proposed shelf life and recommended storage conditions for the new drug product. Furthermore, each acceptance criterion should be set no higher than the qualified level of the given degradation product.

Where there is no safety concern, degradation product acceptance criteria should be based on data generated from batches of the new drug product manufactured by the proposed commercial process, allowing sufficient latitude to deal with normal manufacturing and analytical variation and the stability characteristics of the new drug product. Although normal manufacturing variations are expected, significant variation in batch-to-batch degradation product levels can indicate that the manufacturing process of the new drug product is not adequately controlled and validated (see ICH Q6A guideline on specifications, Decision Tree No. 2, for establishing an acceptance criterion for a specified degradation product in a new drug product).

In this guideline, the use of two decimal places for thresholds (see Attachment 1) does not necessarily indicate the precision of the acceptance criteria for specified degradation products and total degradation products.

In summary, the new drug product specification should include, where applicable, the following list of degradation products:

- Each specified identified degradation product
- Each specified unidentified degradation product
- Any unspecified degradation product with an acceptance criterion of not more than (≤) the identification threshold
- Total degradation products

VI. QUALIFICATION OF DEGRADATION PRODUCTS

Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual degradation product or a given degradation profile at the level(s) specified. The applicant should provide a rationale for establishing degradation product acceptance criteria that includes safety considerations. The level of any degradation product present in a new drug product that has been adequately tested in safety and/or clinical studies would be considered qualified. Therefore, it is useful to include any available information on the actual content of degradation products in the relevant batches at the time of use in safety and/or clinical studies. Degradation products that are also significant metabolites present in animal and/or human studies are generally considered qualified. Degradation products could be considered qualified at levels higher than those administered in safety studies based on a comparison between actual doses given in the safety studies and the intended dose of the new drug product. Justification of such higher levels should include consideration of factors such as (1) the amount of degradation product administered in previous safety and/or clinical studies and found to be safe, (2) the increase in the amount of the degradation product, and (3) other safety factors, as appropriate.

If the qualification thresholds given in Attachment 1 are exceeded and data are unavailable to qualify the proposed acceptance criterion of a degradation product, additional studies to obtain such data can be appropriate (see Attachment 3).

Higher or lower thresholds for qualification of degradation products can be appropriate for some individual new drug products based on scientific rationale and level of concern, including drug class effects and clinical experience. For example, qualification can be especially important when there is evidence that such degradation products in certain new drug products or therapeutic classes have previously been associated with adverse reactions in patients. In these instances, a lower qualification threshold can be appropriate. Conversely, a higher qualification threshold can be appropriate for individual new drug products when the level of concern for safety is less than usual based on similar considerations (e.g., patient population, drug class effects, and clinical considerations). Proposals for alternative thresholds would be considered on a case-by-case basis.

The "Decision Tree for Identification and Qualification of a Degradation Product" (Attachment 3) describes considerations for the qualification of degradation products when thresholds are exceeded. In some cases, reducing the level of degradation product (e.g., use of a more protective container closure or modified storage conditions) to not more than (≤) the threshold can be simpler than providing safety data. Alternatively, adequate data could be available in the scientific literature to qualify a degradation product. If neither is the case, additional safety testing should be considered. The studies considered appropriate to qualify a degradation product will depend on a number of factors, including the patient population, daily dose, and route and duration of new drug product administration. Such studies can be conducted on the new drug product or substance containing the degradation products to be controlled, although studies using isolated degradation products can sometimes be appropriate.

Although this guideline is not intended to apply during the clinical research stage of development, in the later stages of development the thresholds in this guideline can be useful in evaluating new degradation products observed in new drug product batches prepared by the proposed commercial process. Any new degradation product observed in later stages of development should be identified (see the "Decision Tree for Identification and Qualification of a Degradation Product" in Attachment 3) if its level is greater than (>) the identification threshold given in Attachment 1. Similarly, qualification of the degradation product should be considered if its level is greater than (>) the qualification threshold given in Attachment 1.

Safety studies should provide a comparison of results of safety testing of the new drug product or drug substance containing a representative level of the degradation product with previously qualified material, although studies using the isolated degradation products can also be considered.

GLOSSARY

Degradation Product: An impurity resulting from a chemical change in the drug substance brought about during manufacture and/or storage of the new drug product by the effect of, for example, light, temperature, pH, water, or by reaction with an excipient and/or the immediate container closure system.

Degradation Profile: A description of the degradation products observed in the drug substance or drug product.

Development Studies: Studies conducted to scale up, optimize, and validate the manufacturing process for a drug product.

Identification Threshold: A limit above (>) which a degradation product should be identified.

Identified Degradation Product: A degradation product for which a structural characterization has been achieved.

Impurity: Any component of the new drug product that is not the drug substance or an excipient in the drug product.

Impurity Profile: A description of the identified and unidentified impurities present in a drug product.

New Drug Substance: The designated therapeutic moiety that has not been previously registered in a region or member state (also referred to as a new molecular entity or new chemical entity). It can be a complex, simple ester, or salt of a previously approved substance.

Qualification: The process of acquiring and evaluating data that establishes the biological safety of an individual degradation product or a given degradation profile at the level(s) specified.

Qualification Threshold: A limit above (>) which a degradation product should be qualified.

Reporting Threshold: A limit above (>) which a degradation product should be reported.

Specified Degradation Product: A degradation product that is individually listed and limited with a specific acceptance criterion in the new drug product specification. A specified degradation product can be either identified or unidentified.

Unidentified Degradation Product: A degradation product for which a structural characterization has not been achieved and that is defined solely by qualitative analytical properties (e.g., chromatographic retention time).

Unspecified Degradation Product: A degradation product that is limited by a general acceptance criterion, but not individually listed with its own specific acceptance criterion, in the new drug product specification.

ATTACHMENT 1: THRESHOLDS FOR DEGRADATION PRODUCTS IN NEW DRUG PRODUCTS

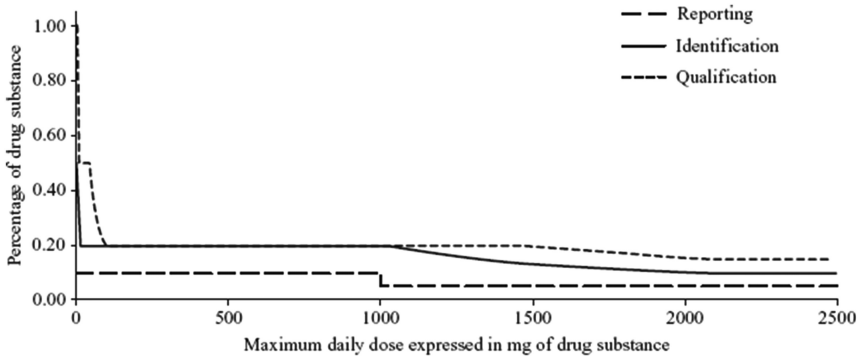
Maximum Daily Dose[a]	Threshold[b,c]
Reporting thresholds	
≤1 g	0.1%
>1 g	0.05%
Identification thresholds	
<1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg–10 mg	0.5% or 20 µg TDI, whichever is lower
>10 mg–2 g	0.2% or 2 mg TDI, whichever is lower
>2 g	0.10%
Qualification thresholds	
<10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg–100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg–2 g	0.2% or 3 mg TDI, whichever is lower
>2 g	0.15%

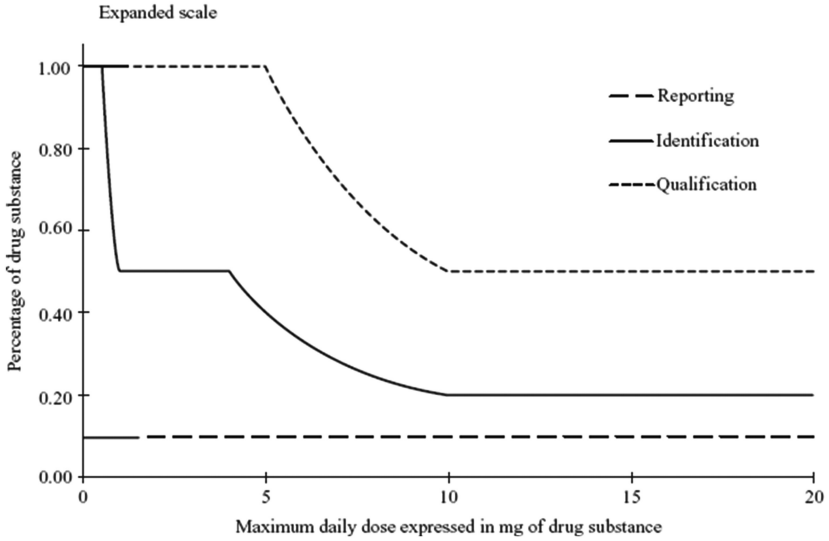
[a] The amount of drug substance administered per day.

[b] Thresholds for degradation products are expressed either as a percentage of the drug substance or as total daily intake (TDI) of the degradation product. Lower thresholds can be appropriate if the degradation product is unusually toxic.

[c] Higher thresholds should be scientifically justified.

Illustration of Thresholds for Reporting, Identification, and Qualification of Degradation Products in New Drug Products as a Function of Maximum Daily Dose[a]





[a] Note: Actual threshold values should be taken from the preceding table in this attachment.

ATTACHMENT 2: ILLUSTRATION OF REPORTING DEGRADATION PRODUCT RESULTS FOR IDENTIFICATION AND QUALIFICATION IN AN APPLICATION

The attachment is only illustrative and is not intended to serve as a template of how results on degradation products should be presented in an application file. Normally raw data are not provided.

Example 1: 50 mg Maximum Daily Dose

Reporting threshold: 0.1%
Identification threshold: 0.2%
Qualification threshold: 200 µg

"Raw" Result (%)	Reported Result (%) Reporting Threshold = 0.05%	Total Daily Intake (TDI) of the Degradation Product (Rounded Result in µg)	Identification Threshold 0.2% Exceeded?	Action Qualification Threshold 200 µg TDI Exceeded?
0.04	Not reported	20	None	None
0.2143	0.2	100	None	None
0.349	0.3[a]	150	Yes	None[a]
0.550	0.6[a]	300	Yes	Yes[a]

Example 2:1.9 g Maximum Daily Dose

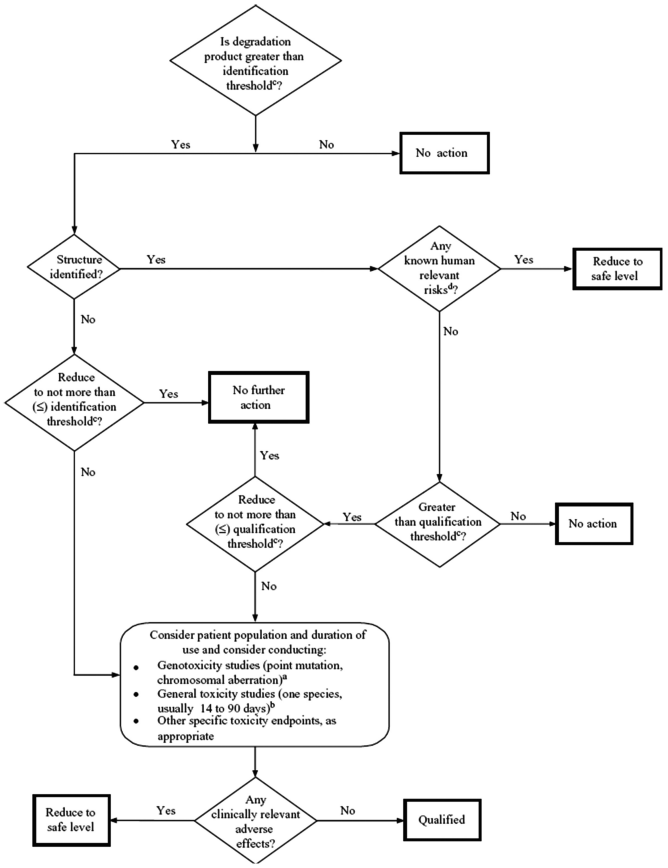
Reporting threshold: 0.05%
Identification threshold: 2 mg
Qualification threshold: 3 mg

"Raw" Result (%)	Reported Result (%) Reporting Threshold = 0.05%	Total Daily Intake (TDI) of the Degradation Product (Rounded Result in mg)	Identification Threshold 2 mg TDI Exceeded?	Action Qualification Threshold 3 mg TDI Exceeded?
0.049	Not reported	1	None	None
0.079	0.08	2	None	None
0.183	0.18[a]	3	Yes	None[a,b]
0.192	0.19[a]	4	Yes	Yes[a]

[a] After identification, if the response factor is determined to differ significantly from the original assumptions, it can be appropriate to remeasure the actual amount of the degradation product present and reevaluate against the qualification threshold (see Attachment 1).

[b] To verify if a threshold is exceeded, a reported result has to be evaluated against the thresholds as follows: When the threshold is described in %, the reported result rounded to the same decimal place as the threshold should be compared directly to the threshold. When the threshold is described in TDI, the reported result should be converted to TDI, rounded to the same decimal place as the threshold, and compared to the threshold, for example, an amount of 0.18% degradation level corresponds to a TDI of 3.4 mg impurity (absolute amount), which is then rounded down to 3 mg; so the qualification threshold expressed in TDI (3 mg) is not exceeded.

ATTACHMENT 3: DECISION TREE FOR IDENTIFICATION AND QUALIFICATION OF A DEGRADATION PRODUCT



[a] If considered desirable, a minimum screen (e.g., genotoxic potential) should be conducted. A study to detect point mutations and to detect chromosomal aberrations, both in vitro, is considered an appropriate minimum screen.

[b] If general toxicity studies are desirable, one or more studies should be designed to allow comparison of unqualified to qualified material. The study duration should be based on available relevant information and performed in the species most likely to maximize the potential to detect the toxicity of a degradation product. On a case-by-case basis, single-dose studies can be appropriate, especially for single-dose drugs. In general, a minimum duration of 14 days and a maximum duration of 90 days would be considered appropriate.

[c] Lower thresholds can be appropriate if the degradation product is unusually toxic.

[d] For example, do known safety data for this degradation product or its structural class preclude human exposure at the concentration present?

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14 Formulation Factors in Semisolid Dosage Forms

The subjects covered here are generally applicable to all forms of topical drug products, including those that are intended to be sterile. The topics given below address several problem areas that may be encountered in the production of semisolid drug products (including transdermal products) including their potency, active ingredient uniformity, physical characteristics, microbial purity, and chemical purity.

I. POTENCY UNIFORMITY

Active ingredient solubility and particle size are generally important ingredient characteristics that need to be controlled to ensure potency uniformity in many topical drug products such as emulsions, creams, and ointments. Crystalline form is also important where the active ingredient is dispersed as a solid phase in either the oil or water phase of an emulsion, cream, or ointment.

It is important that active ingredient solubility in the carrier vehicle be known and quantified at the manufacturing step in which the ingredient is added to the liquid phase. The development data should adequately demonstrate such solubility and its validation.

Substances that are very soluble, as is frequently the case with ointments, would be expected to present less of a problem than if the drug substance were to be suspended, as is the case with creams. If the drug substance is soluble, then potency uniformity would be based largely on adequate distribution of the component throughout the mix.

If the active ingredient is insoluble in the vehicle, then in addition to ensuring uniformity of distribution in the mix, potency uniformity depends on control of particle size and use of a validated mixing process. Particle size can also affect the activity of the drug substance because the smaller the particle size, the greater its surface area, which may influence its activity. Particle size also affects the degree to which the product may be physically irritating when applied; in general, smaller particles are less irritating.

Production controls should be implemented that account for the solubility characteristics of the drug substance; inadequate controls can adversely affect product potency, efficacy, and safety. For example, in one instance, residual water remaining in the manufacturing vessel, used to produce an ophthalmic ointment, resulted in partial solubilization and subsequent recrystallization of the drug substance; the substance recrystallized in a larger particle size than expected and thereby raised questions about the product efficacy.

In addition to ingredient solubility and particle size, other physical characteristics and specifications for both ingredients and finished products are important.

II. EQUIPMENT AND PRODUCTION CONTROL

A. Mixers

There are many different kinds of mixers used in the manufacture of topical products. It is important that the design of a given mixer is appropriate for the type of topical product being mixed. One important aspect of mixer design is how well the internal walls of the mixer are scraped during the mixing process. This can present some problems with stainless steel mixers because scraper blades should be flexible enough to remove interior material, yet not rigid enough to damage the mixer itself. In general, good design of a stainless-steel mixer includes blades that are made of some hard plastic, such as Teflon®, which facilitates scrapping of the mixer walls without damaging the mixer.

If the internal walls of the mixer are not adequately scraped during mixing and the residual material becomes part of the batch, the result may be nonuniformity. Such nonuniformity may occur, for example, if operators use handheld spatulas to scrape the walls of the mixer.

Another mixer design concern is the presence of "dead spots" where quantities of the formula are stationary and not subject to mixing. Where such dead spots exist, there should be adequate procedures for recirculation or nonuse of the cream or ointment removed from the dead spots in the tank.

B. Filling and Packaging

Suspension products often require constant mixing of the bulk suspension during filling to maintain uniformity. When validating a suspension manufacturing process, determine how to ensure that the product remains homogeneous during the filling process and establish the data that support the adequacy of the firm's process. When the batch size is large and the bulk suspension is in large tanks, determine how the low levels of bulk suspension near the end of the filling process are handled. If the bulk suspension drops below a level, can this be adequately mixed? This question must be answered. If the residual material is transferred to a smaller tank, how is the consistency in hand mixing assured? The adequacy of the process for dealing with residual material should be demonstrated.

C. Process Temperature Control

Typically, heat is applied in the manufacture of topical products to facilitate mixing or filling operations. Heat may also be generated by the action of high-energy mixers. It is important

to control the temperature within spec parameters, not only to facilitate those operations but also to ensure that product stability is not adversely affected. Excessive temperatures may cause physical or chemical degradation of the drug product, vehicle, active ingredient or ingredients, or preservatives. Furthermore, excessive temperatures may cause insoluble ingredients to dissolve, reprecipitate, or change particle size or crystalline form.

Temperature control is also important where microbial quality of the product is a concern. The processing of topical products at higher temperatures can destroy some of the objectionable microorganisms that may be present. However, elevated temperatures may also promote incubation of microorganisms.

Temperature uniformity within a mixer should be controlled. In addressing temperature uniformity, one should consider the complex interaction among vat size, mixer speed, blade design, viscosity of contents, and rate of heat transfer. Where temperature control is critical, use of recording thermometers to continuously monitor and document temperature measurements is preferred to frequent manual checks. Where temperature control is not critical, it may be adequate to manually monitor and document temperatures periodically by use of handheld thermometers.

III. CLEANING VALIDATION

It is current good manufacturing practice for a manufacturer to establish and follow written standard operating procedures to clean production equipment in a manner that precludes contamination of current and future batches. This is especially critical where contamination may present direct safety concerns, as with a potent drug such as a steroid (e.g., cortisone, and estrogen), antibiotic, or sulfa drug, where there are hypersensitivity concerns.

The insolubility of some excipients and active substance used in the manufacture of topical products makes some equipment, such as mixing vessels, pipes, and plastic hoses, difficult to clean. Often piping and transfer lines are inaccessible to direct physical cleaning. Some firms address this problem by dedicating lines and hoses to specific products or product classes.

It is therefore important that the following considerations be adequately addressed in a cleaning validation protocol and in the procedures that are established for production batches.

A. Detailed Cleaning Procedures

Cleaning procedures should be detailed and provide specific understandable instructions. The procedure should identify equipment, cleaning methods, solvents and detergents approved for use, inspection and release mechanisms, and documentation. For some of the more complex systems, such as clean-in-place systems, it is usually necessary both to provide a level of detail that includes drawings and to provide provision to label valves. The time that may elapse from completion of a manufacturing operation to initiation of equipment cleaning should also be stated where excessive delay may affect the adequacy of the established cleaning procedure. For example, residual product may dry and become more difficult to clean.

B. Sampling Plan for Contaminants

As part of the validation of the cleaning method, the cleaned surface is sampled for the presence of residues. Sampling should be made by an appropriate method, selected on the basis of factors such as equipment and solubility of residues. For example, representative swabbing of surfaces is often used, especially in areas that are hard to clean or where the residue is relatively insoluble. Analysis of rinse solutions for residues has also been shown to be of value where the residue is soluble or difficult to access for direct swabbing. Both methods are useful when there is a direct measurement of the residual substance. However, it is unacceptable to test rinse solutions (such as purified water) for conformance to the purity specifications for those solutions instead of testing directly for the presence of possible residues.

C. Equipment Residue Limits

Because of improved technology, analytical methods are becoming much more sensitive and capable of determining very low levels of residues. Thus, it is important to establish appropriate limits on levels of post-equipment-cleaning residues. Such limits must be safe, practical, achievable, and verifiable and must ensure that residues remaining in the equipment will not cause the quality of subsequent batches to be altered beyond established product specifications. The rationale for residue limits should be established. Because surface residues will not be uniform, it should be recognized that a detected residue level may not represent the maximum amount that may be present. This is particularly true when surface sampling by swabs is performed on equipment.

IV. MICROBIOLOGICAL

A. Controls (Nonsterile Topicals)

The extent of microbiological controls needed for a given topical product will depend on the nature of the product, the use of the product, and the potential hazard to users posed by microbial contamination. This concept is reflected in the current good manufacturing practice regulations at 21 CFR 211.113(a) (Control of Microbiological Contamination) and in the U.S. Pharmacopeia (USP). It is therefore vital that manufacturers assess the health hazard of all organisms isolated from the product.

1. Deionized Water Systems for Purified Water

The microbiological control of deionized water systems used to produce purified water is important. Deionizers are usually excellent breeding areas for microorganisms. The microbial population tends to increase as the length of time between

deionizer service periods increases. Other factors that influence microbial growth include flow rates, temperature, surface area of resin beds, and, of course, the microbial quality of the feed water. These factors should be considered in assessing the suitability of deionizing systems where microbial integrity of the product incorporating the purified water is significant. There should be a suitable routine water monitoring program and a program of other controls as necessary.

It is not necessary to assess and monitor the suitability of a deionizer by relying solely on representations of the deionizer manufacturer. Specifically, product quality could be compromised if a deionizer is serviced at intervals based not on validation studies but, rather, on the "recharge" indicator built into the unit. Unfortunately, such indicators are not triggered by microbial population but, rather, are typically triggered by measures of electrical conductivity or resistance. If a unit is infrequently used, sufficient time could elapse between recharging and sanitizing to allow the microbial population to increase significantly.

Pre-use validation of deionizing systems used to produce purified water should include consideration of such factors as microbial quality of feed water (and residual chlorine levels of feed water where applicable), surface area of ion-exchange resin beds, temperature range of water during processing, operational range of flow rates, recirculation systems to minimize intermittent use and low flow, frequency of use, quality of regenerant chemicals, and frequency and method of sanitization.

A monitoring program used to control deionizing systems should include established water quality and conductivity monitoring intervals, measurement of conditions and quality at significant stages through the deionizer (influent, post-cation, post-anion, post-mixed bed, etc.), microbial conditions of the bed, and specific methods of microbial testing. Frequency of monitoring should be based on the firm's experience with the systems.

Other methods of controlling deionizing systems include establishment of water-quality specifications and corresponding action levels, remedial action when microbial levels are exceeded, documentation of regeneration, and a description of sanitization and sterilization procedures for piping, filters, and so forth.

2. Microbiological Specifications and Test Methods

Microbiological specifications and microbial test methods for each topical product should be well-established to ensure that they are consistent with any described in the relevant application or USP. In general, product specifications should cover the total number of organisms permitted, as well as specific organisms that must not be present. These specifications must be based on use of specified sampling and analytical procedures. Where appropriate, the specifications should describe action levels where additional sampling or speciation of organisms is necessary.

Manufacturers must demonstrate that the test methods and specifications are appropriate for their intended purpose. Where possible, firms should use methods that isolate and identify organisms that may present a hazard to the user under the intended use. It should be noted that the USP does not state methods that are specific for water-insoluble topical products.

One test deficiency to be aware of is inadequate dispersement of a cream or ointment on microbial test plates. Firms may claim to follow USP procedures, yet in actual practice they may not disperse product over the test plate, resulting in inhibited growth as a result of concentrated preservative in the non-dispersed inoculate. The spread technique is critical, and the firm should document that the personnel performing the technique have been adequately trained and are capable of performing the task. Validation of the spread-plate technique is particularly important when the product has a potential antimicrobial affect.

In assessing the significance of microbial contamination of a topical product, both the identification of the isolated organisms and the number of organisms found are significant. For example, the presence of a high number of organisms may indicate that the manufacturing process, component quality, or container integrity may be deficient. Although high numbers of nonpathogenic organisms may not pose a health hazard, they may affect product efficacy and physical/chemical stability. Inconsistent batch-to-batch microbial levels may indicate some process or control failure in the batch. The batch release evaluation should extend to both organism identification and numbers and, if limits are exceeded, there should be an investigation into the cause.

B. Preservative Activity

Manufacturing controls necessary to maintain the anti-microbiological effectiveness of preservatives should be evaluated. For example, for those products that separate on standing, there should be data available that show the continued effectiveness of the preservative throughout the product's shelf life.

For preservative-containing products, finished product testing must ensure that the specified level of preservative is present before release. In addition, preservative effectiveness must be monitored as part of the final ongoing stability program. This can be accomplished through analysis for the level of preservative previously shown to be effective or through appropriate microbiological challenge at testing intervals.

For concepts relating to sterility assurance and bioburden controls on the manufacture of sterile topicals, see the *Guideline on Sterile Drug Products Produced by Aseptic Processing.*

V. CHANGE CONTROL

As with other dosage forms, it is important to carefully control how changes are made in the production of topical products. The procedures should be able to support changes that represent departures from approved and validated manufacturing processes. There should be written change control procedures that have been reviewed and approved by the quality-control unit. The procedures should provide for full description of

the proposed change, the purpose of the change, and controls to ensure that the change will not adversely alter product safety and efficacy. Factors to consider include potency or bioactivity, uniformity, particle size (if the active ingredient is suspended), viscosity, chemical and physical stability, and microbiological quality.

Of particular concern are the effects that formulation and process changes may have on the therapeutic activity and uniformity of the product. For example, changes in vehicle can affect absorption, and processing changes can alter the solubility and microbiological quality of the product.

VI. TRANSDERMAL TOPICAL PRODUCTS

The manufacturing of topical transdermal products (patches) has many problems in scale-up and validation. Problems analogous to production of topical creams or ointments include uniformity of the drug substance and particle size in the bulk gel or ointment. Uniformity and particle size are particularly significant when the drug substance is suspended or partially suspended in the vehicle. Viscosity also needs control because it can affect the absorption of the drug; the dissolution test is important in this regard. Other areas that need special inspectional attention are assembly and packaging of the patch, including adhesion, package integrity (regarding pinholes), and controls to ensure that a dose is present in each unit.

Because of the many quality parameters that must be considered in the manufacture and control of a transdermal dosage form, scale-up may be considerably more difficult than for many other dosage forms. Therefore, special attention should be given to evaluating the adequacy of the process validation efforts. As with other dosage forms, process validation must be based on multiple lots, typically at least three consecutive successful batches. Summary data should be augmented by comparison with selected data contained in supporting batch records, particularly where the data appear unusually uniform or disparate. Given the complexities associated with this dosage form, the tolerances or variances may be broader than for other dosage forms. In addition, batches may not be entirely problem free. Nevertheless, there should be adequate rationale for the tolerances and production experiences, based on appropriate developmental efforts and investigation of problems.

A. General Considerations

In general, semisolid dosage forms are complex formulations having complex structural elements. Often they are composed of two phases (oil and water), one of which is a continuous (external) phase, and the other of which is a dispersed (internal) phase. The active ingredient is often dissolved in one phase, although occasionally the drug is not fully soluble in the system and is dispersed in one or both phases, thus creating a three-phase system. The physical properties of the dosage form depend on various factors, including the size of the dispersed particles, the interfacial tension between the phases, the partition coefficient of the active ingredient between the phases, and the product rheology. These factors combine to determine the release characteristics of the drug as well as other characteristics, such as viscosity.

For a true solution, the order in which solutes are added to the solvent is usually unimportant. The same cannot be said for dispersed formulations, however, because depending on at which phase a particulate substance is added, dispersed matter can distribute differently. In a typical manufacturing process, the critical points are generally the initial separation of a one-phase system into two phases and the point at which the active ingredient is added. Because the solubility of each added ingredient is important for determining whether a mixture is visually a single homogeneous phase, such data, possibly supported by optical microscopy, should usually be available for review. This is particularly important for solutes added to the formulation at a concentration near or exceeding that of their solubility at any temperature to which the product may be exposed. Variations in the manufacturing procedure that occur after either of these events are likely to be critical to the characteristics of the finished product. This is especially true of any process intended to increase the degree of dispersion through reducing droplet or particle size (e.g., homogenization). Aging of the finished bulk formulation before packaging is critical and should be specifically addressed in process validation studies.

B. The Role of In Vitro Release Testing

The key parameter for any drug product is its efficacy as demonstrated in controlled clinical trials. The time and expense associated with such trials make them unsuitable as routine quality control methods. Therefore, in vitro surrogate tests are often used to ensure that product quality and performance are maintained over time and in the presence of change. A variety of physical and chemical tests commonly performed on semisolid products and their components (e.g., solubility, particle size and crystalline form of the active component, viscosity, and homogeneity of the product) have historically provided reasonable evidence of consistent performance. More recently, in vitro release testing has shown promise as a means to comprehensively ensure consistent delivery of the active component or components from semisolid products. An in vitro release rate can reflect the combined effect of several physical and chemical parameters, including solubility and particle size of the active ingredient and rheological properties of the dosage form. In most cases, in vitro release rate is a useful test to assess product sameness between pre-change and post-change products. However, there may be instances in which it is not suitable for this purpose. In such cases, other physical and chemical tests to be used as measures of sameness should be proposed and discussed with the agency. With any test, the metrics and statistical approaches to documentation of "sameness" in quality attributes should be considered. The evidence available at this time for the in vitro–in vivo correlation of release tests for semisolid dosage forms is not as convincing as that for in vitro dissolution as a surrogate for in vivo bioavailability of solid oral dosage forms. Therefore,

the FDA's current position concerning in vitro release testing is as follows:

a. In vitro release testing is a useful test to assess product sameness under certain scale-up and post-approval changes for semisolid products.
b. The development and validation of an in vitro release test are not required for approval of an NDA, ANDA, or AADA, nor is the in vitro release test required as a routine batch-to-batch quality control test.
c. In vitro release testing alone is not a surrogate test for in vivo bioavailability or bioequivalence.
d. The in vitro release rate should not be used for comparing different formulations across manufacturers.

In vitro release is one of several standard methods that can be used to characterize performance characteristics of a finished topical dosage form, that is, semisolids such as creams, gels, and ointments. Important changes in the characteristics of a drug product formula or the thermodynamic properties of the drug or drugs it contains should show up as a difference in drug release. Release is theoretically proportional to the square root of time when the formulation in question is in control of the release process because the release is from a receding boundary. In vitro release method for topical dosage forms is based on an open chamber diffusion cell system such as a Franz cell system, fitted usually with a synthetic membrane. The test product is placed on the upper side of the membrane in the open donor chamber of the diffusion cell, and a sampling fluid is placed on the other side of the membrane in a receptor cell. Diffusion of drug from the topical product to and across the membrane is monitored by assay of sequentially collected samples of the receptor fluid. The in vitro release methodology should be appropriately validated. Sample collection can be automated. Aliquots removed from the receptor phase can be analyzed for drug content by high-pressure liquid chromatography or other analytical methodology. A plot of the amount of drug released per unit area (mcg/cm) against the square root of time yields a straight line, the slope of which represents the release rate. This release rate measure is formulation specific and can be used to monitor product quality. The release rate of the biobatch or currently manufactured batch should be compared with the release rate of the product prepared after a change, as defined in this guidance.

C. In Vivo Bioequivalence Studies

The design of in vivo bioequivalence studies for semisolid dosage forms varies depending on the pharmacological activity of the drug and dosage form. A brief general discussion of such tests follows. The objective is to document the bioequivalence of the drug product for which the manufacture has been changed, as defined in this guidance, compared with the drug product manufactured before the change or with the reference-listed drug. The study design is dependent on the nature of the active drug. The bioequivalence study can be a comparative skin-blanching study as in glucocorticoids (FDA, 1995) or a comparative clinical trial or any other appropriate validated bioequivalence study (e.g., dermatopharmacokinetic study) for the topical dermatological drug product. The assay methodology selected should ensure specificity, accuracy, interday and intraday precision, linearity of standard curves, and adequate sensitivity, recovery, and stability of the samples under the storage and handling conditions associated with the analytical method.

VII. CHEWING GUM

Chewing gum can deliver either pharmaceuticals or nutrients and are known as medicated chewing gum (MCG) and non-MCG. MCG is supposed to act as an extended release dosage form that provides a continuous release of medicine contained. The first MCG was launched in 1924 in United States of America which was called Aspergum®, but an admission of chewing gum as a drug delivery system did not advance until nicotine chewing gum was released at the market. The most important patent on the use of chewing gum involves delivery of bitter drugs by incorporating a release of carbon dioxide that anesthetizes taste buds (US Patent 4639368A, 1985, Niazi inventor). There is a monograph in European Pharmacopoeia (EP) that defines MCG, but the term "chewing gum" was first listed in guidelines as a pharmaceutical dosage form in 1991 and approved by the commission of European communities.

Table 14.1 lists a few examples of the types of MCG marketed.

The ability of chewing gums to release active ingredients into the oral cavity, their steady and rapid action, and capability of both systemic and local delivery make it appropriate for extensive use in food and pharmaceutical industries. Advantages of medicated chewing gums as drug delivery system include:

- Increased rate of effectiveness rather than other oral delivery systems
- Removal of gum at any time, therefore termination of drug delivery
- Reduced risk of overdosing if it's whole swallowed
- Requires no water to drink
- Protection of the susceptible drugs contained from chemical or enzymatic attack in gastrointestinal (GI) tract
- Both systemic and local drug delivery
- High acceptance by children and teenagers
- Low first-pass effect so reduced dose is formulated in chewing gum compared to other oral delivery systems
- Good for rapid delivery
- Fewer side effects
- Reduced risk of intolerance to gastric mucosa
- Good stability against light, oxygen, and moisture[20]
- Annihilation of xerostomia and help tasting and swallowing in people with dry mouth
- Reduced pains and difficulties in swallowing following tonsillectomy

TABLE 14.1
Therapeutic Use and Examples of MCGs

Component	Function and Proportion	Example
Water-Soluble Bulk Portion		
Bulk Sweeteners		
Sugar sweeteners	30–60%, saccharide-coating components	Sucrose, dextrose, maltose, dextrin, dried invert sugar, fructose, levulose, galactose, corn syrup
Sugarless sweeteners		Sorbitol, mannitol, xylitol, hydrogenated starch hvdrolysate, maltitol
High-intensity artificial sweetener	0.02–8%	Sucralose, aspartame, salts of acesulfarne, alitame, saccharin
Flavoring agent	0.01–1%	Essential oils, synthetic flavors, mixture (citrus oils, fruit essences, peppermint oil, spearmint oil, clove oil, oil of wintergreen and anise)
Softener (plasticizer)	0.5–15%, regulating the cohesiveness and modifying the texture	Glycerin, lecithin, aqueous sweetener solutions, sorbitol, hydrogenated starch hydrolysate, corn syrup, tallow, cocoa butter, glycerol monostearate, glycerol triacetate, fatty acid (palmitic, stearic, olic…)
Emulsifier	15–45%, dispersing immiscible compounds	Mono-, di-, tri-, stearyl acetate, lactylic esters
Colorants (FD&C type dye and lake)	0.1%	Fruit and vegetable extracts, titanium oxide
Antioxidant	0.02% of the gum base	Ascorbic acid, tocopherol, butylhydroxytoluene
Anti-tack agent	0.2–0.6%, something that helps chewing gum not adhere to denture fillings and natural teeth	Slip-agent can be used for this purpose which may be comprised of a-cellulose and vegetable proteins Alkaline metal phosphate, malto dextrin
Anti-caking agent	0.5–2%, preventing agglomeration	Precipitated silicon dioxide, solid carbon dioxide
Water-Insoluble Gum Base		
Elastomers		
Natural	15–45%, provides elasticity and cohesiveness	Smoked or liquid latex, guayule, jelutong, lechi-caspi, perilio, sorva, rosadinha, chicle, massaranduba balata, massaranduba chocolate, nispero
Synthetic		Polyisobutylene, isobutylene, -isoprene copolymer, styrene-butadiene copolymers, polyvinyl acetate
Rubber/fat/resin phase (elastomeric plasticizer)	15%, softening elastomeric material	Estrugums: Glycerol esters, pentaerythritol esters of rosins (hydrogenated dimerized and polymerized rosins) Synthetic: Terpene resins
Filler/texturizer	Up to 50%, modifying the texture of gum base	Magnesium and calcium carbonate, ground limestone, silicate types, clay, alumina, talc, titanium oxide, mono-, di-, tri-calcium phosphate, cellulose polymers
Wax (the base may be wax-free)		

- Improves work performance and cognitive function
- Fast bowel recovery after GI surgery
- Reduced hypoglycemic shocks in people taking anti-diabetic drugs
- Stimulates alertness through increased blood flow to brain
- Helps reduce food cravings

Disadvantages of medicated chewing gums:

- Disappearing of drug in oral cavity following salivary dilution
- Different release profiles because of chewing style differences
- Short time of administration due to eating, speaking, and drinking
- Allergic reaction to artificial sweeteners
- Continuous stress on jaws that may cause temporo-mandibular joint disorder
- Teeth decay through being coated by sugar
- Masseter problems
- Stomach irritations, aches, gastric ulcer through continuous swallowing of saliva and even flatulence because of presence of sorbitol in some formulations
- Risk of choking by swallowing gum in under-aged children

Composition

Medicated chewing gums are gums made with a tasteless masticatory gum base that consists of natural or synthetic elastomers. They include excipients such as fillers, softeners, and

sweetening and flavoring agents. Natural gum bases include chicle and smoked natural rubber and are permitted in formulations by the FDA, but modern gum bases are mostly synthetic in origin and approved bases include styrene-butadiene rubber, polyethylene, and polyvinylacetate. Gum base usually forms about 40% of the gum but can comprise up to 65% and is a complex mixture, insoluble in saliva, comprising mainly of elastomer, plasticizers, waxes, lipids, and emulsifiers (see Table 14.2). It will also contain an adjuvant such as talc to modify the texture of the gum and low quantities of additional excipients including colorants and antioxidants such as butylated hydroxyanisole. Elastomers control the gummy texture while the plasticizers and texture agents regulate the cohesiveness of the product. The lipid and waxes melt in the mouth to provide a cooling, lubricating feeling while the juicy feel of the gum texture is from the emulsifiers. The choice and formulation of gum base will affect the release of active ingredient and the texture, stability, and method of manufacture of the product.

The remaining ingredients in the chewing gum itself include drug, sweeteners, softeners, and flavoring and coloring agents. A typical chewing gum formulation is shown in Table 14.3. The sugar is for sweetening the product while the corn syrup keeps the gum fresh and flexible. Softeners or fillers are included to help blend the ingredients and retain moisture. Sugar-free gum has sorbitol, mannitol, aspartame, or saccharin instead of sugar. Optimized chewing gum formulations will require tailoring for each individual product. For example, nicotine-containing gums are formulated with the nicotine within an ion-exchange resin and pH-modifying carbonates and/or bicarbonates to increase the percentage of the drug in its free base form in saliva.

Manufacture of Chewing Gum

The majority of chewing gum delivery systems today are manufactured using conventional gum processes. The gum base is softened or melted and placed in a kettle mixer where sweeteners, syrups, active ingredients, and other excipients are added at a defined time. The gum is then sent to a series of rollers that form it into a thin, wide ribbon. During this process, a light coating of an anti-sticking agent can be added (e.g., magnesium stearate, calcium carbonate, or finely powdered sugar or sugar substitute). Finally, the gum is cut to the desired size and cooled at a carefully controlled temperature and humidity.

As the heating process involved in conventional methods may limit the applicability of the process for formulation of thermally labile drugs, directly compressible, free-flowing powdered gums such as Pharmagum (SPI Pharma) and MedGumBase (Gumbase Co) have been proposed to simplify the process. These formulations can be compacted into a gum tablet using a conventional tablet press and have the potential to simplify the manufacture, facilitating inclusion of a wider range of drugs.

Fusion Method

The first step of a typical process for manufacturing chewing gum is to melt and soften the gum base at about 60°C and place it in a kettle mixer, in which blades soften the base; then other ingredients such as sugar, glycerin, sweeteners, and taste-masking agent are added to the softened base, lately the flavoring agent is added in the mixing procedure at 40°C, then cooling and rolling steps would be done, and the rolled chewing gum would then be cut into pieces of desired shapes and sizes. To make a coated gum tablet, a coating agent should be sprayed to form a uniform surface.

The second type of this method is somewhat different: The primary step of preparation is to set up a mixer (the mixer could be sigma blade or other types of mixers); if a sugar-containing gum is needed, the first step is to add corn syrup to the mixer, and then finely powdered sugar is added gradually. Sugar, used in this step, could be powdered sucrose, dextrose, fructose, corn syrup solids, or combination of them.

After adding these sweeteners, plasticizers are added to modify the texture and regulate the cohesiveness. Glycerin is the most preferable plasticizer used. Other components specified in Table 14.3 could be added to the matrix according to required characteristics, such as fillers, colorants, and flavorings. But it is recommended that flavors be added to the matrix at the end of procedures when the gum base is totally and completely homogenized because most flavors are relatively volatile.

After matrix preparation and completely mixing, the commercially prepared particles of gum base are added to the chamber all at once.

One other method to provide a chewing gum with desired taste, color, and flavor is to mix gum base with favorable and

TABLE 14.2
Typical Formulation of Gum Base

Ingredient	Weight (%)	Example
Elastomer	10	Styrene-butadiene rubber
Plasticizer	30	Rosin esters
Texture agent/filler	35	Calcium carbonate
Wax	15	Paraffin wax
Lipid	7	Soya oil
Emulsifier	3	Lecithin
Miscellaneous	1	Colorant, antioxidant

TABLE 14.3
Example Chewing Gum Formulations

Ingredient (%)	Sugar Gum	Sugar-Free Gum
Gum base	19.4	25.0
Corn syrup	19.8	—
Sorbitol, 70%	—	15.0
Sugar	59.7	—
Glycerin	0.5	6.5
Sorbitol	—	52.3
Flavor	0.6	1.2

suitable sweeteners, corn syrups, starches, flavoring agents, and colorants and then refrigerate and cool it by a freezer apparatus or by contacting with a coolant like carbon dioxide to a temperature below −15°C. This is then crushed and pulverized with a cutter or grinding apparatus to obtain minute particles; then these finely ground particles are heated to a temperature which makes them adhere to each other and form a slick and uniform bulk with consistent texture and low specific gravity. If the fragments are such that they do not self-adhere, low pressure would be applied manually or mechanically before they are warmed to the normal room temperature to thereby promote self-adhesion.

The cooling and grinding steps can be combined by cooling the grinding apparatus. After the grinding step, we can let the coolant (if used) evaporate and disappear from our desired composition.

The minute particles may be coated by edible substances or premixed with powdery materials.

For tableting, compressing punches may be needed, but an anti-adherent agent should be applied to avoid sticking to surfaces of punches.

Direct Compression

A new technology to make a chewing gum tablet is direct compression and tableting with a high-speed standard machine. As explained in a patent, this way of forming chewing gum tablets provides a quickly dissociable chewing gum, but after a few seconds of chewing, particles adhere together to form a uniform and homogenous mass. In this method, we need a granulating agent, most preferably sorbitol which can also act as a sweetener. A lubricant such as magnesium stearate, talc, stearic acid, hydrogenated vegetable oils, and sodium stearyl fumarate is added to formulation before tableting. The first step of this method is dry mixing of gum base, granulating agent, and at least one processing material; then the active ingredient, sweeteners, and other necessary ingredients are added to the formulation in a free-flowing form; then the chewing gum is directly compressed into tablets. In the first step, the temperature should not rise higher than the melting point of the gum base. After obtaining a uniform and slick mass, the temperature would be lowered to add other ingredients.

Evaluation Tests

Content uniformity

Ten MCGs are selected randomly then their contents are measured; if each single content is between 85% and 115% of average content, it will comply with the test, but if one single preparation is out of this range the preparation will not comply with the test.[1]

Mass uniformity

Twenty MCGs are selected randomly and weighed; not more than two single masses should vary from the average mass.

Dissolution test

Mastication devices are designed to simulate human chewing behavior.

Release of Drug

Factors affecting the release of medicament from chewing gum can be divided into three groups: The physicochemical properties of the drug, the gum properties, and chew-related factors, including rate and frequency. Drugs can be incorporated into gums as solids or liquids. For most pharmaceuticals, aqueous solubility of the drug will be a major factor affecting the release rate. In order for drugs to be released, the gum would need to become hydrated; the drugs can then dissolve and diffuse through the gum base under the action of chewing.

For treatment of local conditions, a release period less than 1 h may be desirable, but a faster release may be required if a rapid onset of action is required for a systemically absorbed formulation. There are a number of strategies that can be undertaken in order to achieve the desired release rate. Decreasing the amount of the gum base will enhance the release of lipophilic drugs and addition of excipients designed to promote release can also be considered. Release can be sustained using, for example, ion-exchange resins as described for nicotine-containing gums. Changes in gum texture as a consequence of changes in excipient levels provide a further challenge to controlling the release of drugs. A quantitative measure of gum texture during the process is possible using texture analysis techniques.

15 Pediatric Research Equity Act (PREA) Compliance

INTRODUCTION

PREA amends the Federal Food, Drug, and Cosmetic Act (the Act) by adding Section 505B (21 U.S.C. 355B). PREA requires the conduct of pediatric studies for certain drug and biological products.[2] Specifically, PREA requires new drug applications (NDAs) and biologics licensing applications (BLAs) (or supplements to applications) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral [see Section 505B(a) of the Act]. It also authorizes FDA to require holders of applications for previously approved marketed drugs and biological products who are not seeking approval for one of the changes enumerated above (hereinafter "marketed drugs and biological products") to submit a pediatric assessment under certain circumstances [see Section 505B(b) of the Act].

Although PREA applies to both new applications (or supplements to applications) and already marketed drugs and biological products, this guidance will only provide recommendations on NDAs and BLAs (or supplements to an already approved application) for drugs and biological products under Section 505B(a) of the Act. Issues under Section 505B(b) of the Act related to already marketed drug and biological products for which the sponsor is not seeking one of the enumerated changes may be addressed in future guidance.

This guidance addresses the pediatric assessment,[3] the pediatric plan (see Section V.A), waivers and deferrals, compliance issues, and pediatric exclusivity provisions.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended but not required.

I. BACKGROUND

On December 3, 2003, the Pediatric Research Equity Act (PREA) was signed into law. PREA is the most recent of more than a decade of legislative and regulatory attempts to address the lack of pediatric use information in drug product labeling. In PREA, Congress codified many of the elements of the Pediatric Rule, a final rule issued by FDA on December 2, 1998 (63 FR 66632) and suspended by court order on October 17, 2002.[4]

Under the Pediatric Rule, approval actions taken or applications submitted on or after April 1, 1999, for changes in active ingredient, indication, dosage form, dosing regimen, or route of administration were required to include pediatric assessments for indications for which sponsors were receiving or seeking approval in adults, unless the requirement was waived or deferred.

The Pediatric Rule was designed to work in conjunction with the *pediatric exclusivity* provision of Section 505A of the Act (21 U.S.C. 355a), an incentive signed into law to encourage sponsors or holders of approved applications to voluntarily perform the pediatric studies described in a Written Request[5] issued by FDA, in order to qualify for an additional 6 months of marketing exclusivity.

On January 4, 2002, the Best Pharmaceuticals for Children Act (BPCA) (Public Law 107-109) was enacted. The BPCA reauthorized and amended the pediatric exclusivity incentive program of Section 505A and created new mechanisms for funding pediatric studies that sponsors or holders of approved applications declined to conduct voluntarily. On April 24, 2002, FDA issued an advance notice of proposed rulemaking (ANPRM) soliciting comments on the most appropriate ways to update the Pediatric Rule in a manner consistent with other mechanisms for obtaining studies created by the BPCA.

On October 17, 2002, the U.S. District Court for the District of Columbia held that FDA had exceeded its statutory authority when issuing the Pediatric Rule, and the court suspended its implementation and enjoined its enforcement [*Association of Am. Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204 (D. D.C. 2002)]. When the Court enjoined FDA from enforcing the Pediatric Rule in October 2002, the ANPRM was also rendered obsolete.

As noted above, PREA codified elements of the suspended Pediatric Rule and attempted to fill gaps left by the Pediatric Rule's suspension.

II. OVERVIEW—REQUIREMENTS OF PREA

A. PREA Statutory Requirements

PREA requires all applications (or supplements to an application) submitted under Section 505 of the Act (21 U.S.C. 355) or Section 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral (Section 505B(a) of the Act). It also authorizes FDA to require holders of approved NDAs

and BLAs for marketed drugs and biological products to conduct pediatric studies under certain circumstances (Section 505B(b) of the Act).

In general, PREA applies only to those drugs and biological products developed for diseases and/or conditions that occur in both the adult and pediatric populations. Products intended for pediatric-specific indications will be subject to the requirements of PREA only if they are initially developed for a subset of the relevant pediatric population.

B. Scope of Requirements

1. Applications Affected by PREA

Because Section 4(b) of PREA makes the legislation retroactive, all approved applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration submitted on or after April 1, 1999 (including those approved when the Pediatric Rule was suspended), are subject to PREA. Under PREA, holders of such approved applications that did not previously include pediatric assessments, waivers, or deferrals must submit their pediatric assessments or requests for waiver or deferral [Section 4(b)(2)(B) of PREA]. If a waiver request is denied and/or studies are deferred, FDA will require the applicable studies as post-marketing studies. (For additional information on applicable deferral dates, see Section IV.B and Attachment C.)

2. Orphan Drugs

PREA states, "Unless the Secretary requires otherwise by regulation, this section does not apply to any drug for an indication for which orphan designation has been granted under section 526." FDA has not issued regulations applying PREA to orphan-designated indications. Thus, submission of a pediatric assessment is not required for an application to market a product for an orphan-designated indication, and waivers are not needed at this time. However, if only one indication for a product has orphan designation, a pediatric assessment may still be required for any applications to market that same product for the non-orphan indication(s).

3. Generic Drugs Under 505(j) of the Act [21 U.S.C. 355(j)]

Because PREA applies only to applications (or supplements to applications) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, and because an abbreviated new drug application (ANDA) submitted under Section 505(j) of the Act for a duplicate version of a previously approved drug product does not involve such changes, PREA does not impose pediatric assessment requirements on ANDAs for generic drugs. However, ANDAs submitted under an approved suitability petition under Section 505(j)(2)(C) of the Act for changes in dosage form, route of administration, or new active ingredient in combination products are subject to the pediatric assessment requirements that PREA imposes. If clinical studies are required under PREA for a product submitted under an approved suitability petition and a waiver is not granted, that application is no longer eligible for approval under an ANDA.

Because PREA is retroactive, all approved and pending ANDAs submitted on or after April 1, 1999 (when the Pediatric Rule became effective) and prior to December 3, 2003 (when PREA was enacted) under suitability petitions for changes in dosage form, route of administration, or active ingredient in combination products are subject to PREA. Although some ANDAs submitted under suitability petitions after April 1, 1999, and prior to December 3, 2003, would not have been approved as ANDAs had PREA been in effect at the time of approval, PREA's retroactivity does not require FDA to revoke those previous approvals. Instead, as with NDAs and BLAs, holders of approved and pending ANDAs submitted under suitability petitions between April 1, 1999 and December 3, 2003, who have not already obtained waivers, must submit post-approval pediatric studies or a request for a waiver or deferral of the pediatric assessment requirement [Section 505B(a)(2) of the Act]. If a waiver request is denied for a product already submitted or approved in an ANDA based upon a suitability petition during this time frame, FDA will require the applicable studies as post-marketing studies.

III. THE PEDIATRIC ASSESSMENT

A. What Is the Pediatric Assessment? [Section 505B(a)(2) of the Act]

Under PREA, the pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required and other data that are adequate to:

- Assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations
- Support dosing and administration for each pediatric subpopulation for which the drug or the biological product has been assessed to be safe and effective

B. When to Submit the Pediatric Assessment in Compliance with PREA

Under PREA, a pediatric assessment must be submitted at the time an application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration is submitted to the Agency, unless the requirement for the assessment has been deferred or waived. If a deferral has been granted, the pediatric assessment will be due on or before the date specified by the Agency [Section 505B(a)(3) of the Act].

As noted above, PREA is retroactive and requires pediatric assessments for all applications submitted between April 1, 1999, and the present. To address potential gaps in pediatric information for applications approved between April 1, 1999, and the present resulting from, among other things, the suspension of the Pediatric Rule in October 2002, PREA

provides for waivers or deferrals in cases where pediatric study requirements were never addressed and for extensions of certain deferrals issued previously under the Pediatric Rule (see Attachment C for chart of deferral dates under PREA).

If an application previously was granted a waiver of pediatric studies under the Pediatric Rule, the waiver will continue to apply under PREA [Section 4(b)(2)(A) of PREA].

C. What Types of Data Are Submitted as Part of the Pediatric Assessment?

The data submitted under PREA will depend on the nature of the application, what is known about the product in pediatric populations, and the underlying disease or condition being treated. PREA does not require applicants to conduct separate safety and effectiveness studies in pediatric patients in every case. PREA states:

> If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies. [Section 505B(a)(2)(B)(i) of the Act]

If extrapolation from adult effectiveness data is inappropriate, adequate and well-controlled efficacy studies in the pediatric population may nevertheless be required. Additional information, such as dosing and safety data, could also be important to support pediatric labeling decisions.

PREA further provides, "A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group" [Section 505B(a)(2)(B)(ii) of the Act].

Whether or not pediatric studies in more than one age group are necessary depends on expected therapeutic benefit and use in each age group and on whether safety and effectiveness data from one age group can be extrapolated to other age groups. As with the use of adult data, the extrapolation may be supplemented with data to define dosing and safety for the relevant age groups.

Applicants should contact the appropriate review division to discuss the types of pediatric studies needed to complete their pediatric assessments.

IV. THE PEDIATRIC PLAN AND SUBMISSIONS

A. When to Develop a Pediatric Plan

A pediatric plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that the applicant plans to conduct. The plan should also address the development of an age-appropriate formulation. Furthermore, it should address whether and, if so, under what grounds, the applicant plans to request a waiver of deferral under PREA. Applicants are encouraged to submit their pediatric plans to the Agency as early as possible in the drug development process and to discuss these plans with the Agency at critical points in the development process for a particular drug or biologic.

Early consultation and discussions are particularly important for products intended for life- threatening or severely debilitating illnesses. For these products, FDA encourages applicants to discuss the pediatric plan at pre-investigational new drug (pre-IND) meetings and end-of-phase meetings. For products for life-threatening diseases, the review division will provide its best judgment at the end-of-phase-1 meetings on whether pediatric studies will be required under PREA and, if so, whether the submission will be deferred until after approval. In general, studies of drugs or biological products for diseases that are life-threatening or severely debilitating in pediatric patients and that lack adequate therapy could begin earlier than studies of other products because the urgency of the need for the products may justify early trials despite the relative lack of safety and effectiveness information.

For products that are not intended for treatment of life-threatening or severely debilitating illnesses, applicants are encouraged to submit and discuss the pediatric plan no later than the end-of-phase-2 meeting. Information to support any planned request for a waiver or deferral of pediatric studies also should be submitted as part of the background package for this meeting. The review division will provide its best judgment about (1) the pediatric assessment that will be required for the product, (2) whether its submission can be deferred, and (3) if deferred, the date studies will be due. In addition, if relevant, FDA encourages applicants to include a discussion of their intent to qualify for and the studies needed to earn pediatric exclusivity (see Section VIII for a discussion of PREA and pediatric exclusivity).

When a decision to waive or defer pediatric studies is made at key meetings, the minutes from those meetings reflecting the decision generally will be provided to applicants for their records. Alternatively, a separate letter may be sent to the applicant conveying FDA's decision to either waive or defer the pediatric assessment. If a deferral of studies is granted at the time of the meeting, a due date for submission generally will also be included in the meeting minutes or separate letter.

B. What Ages to Cover in a Pediatric Plan

PREA requires, unless waived or deferred, the submission of a pediatric assessment for certain applications for the claimed indications in all relevant pediatric populations. As discussed in Section VI, PREA authorized FDA to waive assessments when: 1) the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and 2) is not likely to be used in a substantial number of pediatric patients [Section 505B(a)(4)(A)(iii) of the Act]. Thus, PREA requires the pediatric assessment to evaluate safety and effectiveness for the claimed indication(s) for each age group in which the drug or biological product is expected to provide a meaningful therapeutic benefit over existing therapies for pediatric patients or is likely to be used in a substantial number7 of pediatric patients.

Under PREA, a drug or biological product is considered to represent a *meaningful therapeutic benefit* over existing therapies if FDA estimates that (1) "if approved, the drug or biological product would represent a significant improvement in the treatment, diagnosis, or prevention of disease, compared with marketed products adequately labeled for that use in the relevant pediatric population," or (2) "the drug or biological product is in a class of products or for an indication for which there is a need for additional options" [Section 505B(c) of the Act].

Improvement over marketed products might be demonstrated by showing (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) enhancement of compliance; or (4) safety and effectiveness in a new subpopulation for which marketed products are not currently labeled.

The BPCA defines "pediatric studies" or "studies" to include studies in all "pediatric age groups (including neonates in appropriate cases)" in which a drug is anticipated to be used [Section 505A(a) of the Act]. For purposes of satisfying the requirements of PREA, the appropriate age ranges to be studied may vary, depending on the pharmacology of the drug or biological product, the manifestations of the disease in various age groups, and the ability to measure the response to therapy. In general, however, the pediatric population includes patients age "birth to 16 years, including age groups often called neonates, infants, children, and adolescents" [21 CFR 201.57(f)(9)].

The complex medical state of neonates and infants makes it critical to evaluate drugs specifically for their use. The Agency is also aware that trials in neonates and infants pose special ethical issues. FDA generally will require studies in neonates and infants under PREA if the drug represents an important advancement and use in these age groups for the approved indication is anticipated. However, it is possible that partial waivers for these specific age groups might be appropriate under certain circumstances when "necessary studies are impossible or highly impracticable," or when "there is evidence strongly suggesting that the drug or biologic product would be ineffective or unsafe in that age group" [Section 505B(a)(4)(B)(i) and (ii) of the Act].

C. Must the Sponsor Develop a Pediatric Formulation?

PREA requires pediatric assessments to be gathered "using appropriate formulations for each age group for which the assessment is required" [Section 505B(a)(2)(A) of the Act]. Under PREA, applicants must submit requests for approval of the pediatric formulation used in their pediatric studies, and failure to submit such a request may render the product misbranded [Section 505B(d) of the Act]. FDA interprets the language "request for approval of a pediatric formulation" to mean that applicants must submit an application or supplemental application for any not previously approved formulation(s) used to conduct their pediatric studies. Where appropriate, applicants may need to begin the development of a pediatric formulation before initiation of pediatric clinical trials.

PREA does, however, specifically authorize FDA to waive the requirement for pediatric studies in one or more age groups requiring a pediatric formulation if the applicant certifies and FDA finds that "the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed" [Section 505B(a)(4)(B)(iv) of the Act].

This exception is limited to the pediatric groups requiring that formulation [Section 505B(a)(4)(C)]. FDA believes that this partial waiver provision will generally apply to situations where the applicant can demonstrate that unusually difficult technological problems prevented the development of a pediatric formulation. In certain cases, the Agency may seek appropriate external expert opinion (e.g., from an advisory committee) to assess whether a waiver should be granted (see Sections VI.A and B for more detailed information on waivers).

D. When to Initiate Pediatric Studies

As discussed in Section V.A, applicants may initiate pediatric studies of drugs and biologics for life-threatening diseases for which adequate treatment is not available earlier in development than might occur for less serious diseases. The medical need for these products may justify early pediatric trials despite a relative lack of safety and effectiveness data. In some cases, pediatric studies of a drug or biological product for a life-threatening disease may begin as early as phase 1 or phase 2, when the initial safety data in adults become available.

The Agency recognizes that in certain cases scientific and ethical considerations will dictate that pediatric studies should not begin until after approval of the drug or biological product for use in adults—for example, where a product has not shown any benefit over other adequately labeled products in the class, the therapeutic benefit is likely to be low, or the risks of exposing pediatric patients to the new product may not be justified until after the product's safety profile is well established in adults after initial marketing.

The Agency recommends that for products with a narrow therapeutic index, the nature of the disease in the pediatric population to be studied and the context in which the drug will be used should factor into the decision on when to initiate the studies in the affected pediatric patient population. For example, studies for an oncology drug product with a narrow therapeutic index might be conducted in children with a life-threatening cancer at an earlier stage in the drug development process than studies for a new aminoglycoside antimicrobial used to treat acute pyelonephritis infections in children. In the latter case, there are several therapeutic options available, so the investigational drug would likely be studied in children after the approval in adults for this condition.

E. What Information Must Be Submitted to FDA

Pediatric studies of drugs conducted under an investigational new drug application (IND) are subject to the rules governing

INDs, including the content and format requirements of 21 CFR 312.23 and the IND safety and annual reporting requirements described in 21 CFR 312.32 and 312.33, respectively.

- When study reports are submitted as part of an application or supplement to an application, the content and format must meet the relevant general requirements for submission (see 21 CFR 314.50 for NDA requirements and 21 CFR 601.2 for BLA requirements).

V. WAIVERS AND DEFERRALS

A. What Is a Waiver?

PREA authorizes FDA to waive the requirement to submit the pediatric assessment, based on established criteria, for some or all pediatric age groups. FDA can grant a full or partial waiver of the requirements on its own initiative or at the request of an applicant. If an applicant requests a waiver, the applicant should provide written justification for the waiver and evidence to support the request.

B. How to Apply for a Waiver

1. Criteria for Full Waiver [Section 505B(a)(4)(A) of the Act]

On FDA's initiative or at the request of an applicant, FDA will grant a full waiver of the requirement to submit pediatric assessments if the applicant certifies and FDA finds one or more of the following:

(a) Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed) [Section 505B(a)(4)(A)(i) of the Act].

Another example is a drug or biological product for an indication that has extremely limited applicability to pediatric patients because the pathophysiology of these diseases occurs for the most part in the adult population. FDA would be likely to grant a waiver for studies on products developed for the treatment of these conditions without requiring applicants to provide additional evidence of impossibility or impracticality. For a list of adult-related conditions that may be candidates for a disease-specific waiver, see Attachment A, Sample Waiver Request Form.

(b) There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups [Section 505B(a)(4)(A)(ii) of the Act].

If a waiver is granted based upon evidence that the drug is unsafe or ineffective in pediatric populations, the applicant must include this information in the labeling for the drug or biological product [Section 505B(a)(4)(D) of the Act].

(c) The drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and (2) is not likely to be used in a substantial number of pediatric patients [Section 505B(a)(4)(A)(iii) of the Act].

2. Criteria for Partial Waiver [Section 505B(a)(4)(B) of the Act]

On its own initiative or at the request of an applicant, FDA will grant a partial waiver of the requirement to submit pediatric assessments for a drug or biological product with respect to a specific pediatric age group, if the applicant certifies and FDA finds evidence of one or more of the following:

(a) Necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed) [Section 505B(a)(4)(B)(i) of the Act].

(b) There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group [Section 505B(a)(4)(B)(ii) of the Act]. If a partial waiver is granted based on evidence that the drug is unsafe or ineffective in pediatric populations, the applicant must include this information in the labeling for the drug or biological product [Section 505B(a)(4)(D) of the Act].

(c) The drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group and (2) is not likely to be used by a substantial number of pediatric patients in that age group [Section 505B(a)(4)(B)(iii) of the Act].

(d) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed [Section 505B(a)(4)(B)(iv) of the Act]. If a waiver is granted on the basis that it is not possible to develop a pediatric formulation, the waiver shall cover only the pediatric groups requiring that formulation [Section 505B(a)(4)(C) of the Act].

3. Information in a Waiver Request

As noted in Section V, discussions with FDA on developing pediatric plans and initiating pediatric studies should occur early in the drug development process. If an applicant believes a full or partial waiver of the pediatric studies requirement is warranted, FDA strongly encourages the applicant to request the waiver at the earliest appropriate time. This guidance includes a sample Waiver Request to assist applicants in providing sufficient information for FDA to determine whether to grant a waiver request (Attachment A). However, the information necessary to support any particular waiver will be determined on a case-by-case basis.

To request a waiver, we recommend an applicant provide:

- Product name, applicant name, and indication
- Age group(s) included in waiver request

- Statutory reason(s) for requesting a waiver, including reference to the applicable statutory authority [i.e., one of 2(a)–(d) in Attachment A]
- Evidence that the request meets the statutory reason(s) for waiver of pediatric assessment requirements
- Applicant Certification

4. Waiver Decision

The Agency will grant a waiver request if FDA determines that any of the criteria for a waiver enumerated in the statute have been met. As noted above, if a full or partial waiver is granted "because there is evidence that a drug or biological product would be ineffective or unsafe in pediatric populations, this information shall be included in the labeling for the drug or biological product" [Section 505B(a)(4)(D) of the Act].

As discussed in Section V, for waivers agreed to at the end-of-phase-2 meetings, the meeting minutes will document the waiver of pediatric assessment requirements. Full or partial waiver documentation (meeting minutes or a letter from FDA) should be submitted in the Clinical Data Section of the NDA or BLA and noted in Form FDA-356h under the "Pediatric Use" part of item 8 and also under item 20, "Other." Under "Other," the applicant should identify the location (volume and page number) of the waiver documentation in the NDA or BLA submission.

Decisions to waive the requirement for submission of pediatric assessments that are made early in the pre-approval development period (e.g., end-of-phase-1 or end-of-phase-2 meetings) reflect the Agency's best judgment at that time. If, prior to approval, the Agency becomes aware of new or additional scientific information that affects the criteria on which the waiver decision was based, the Agency may reconsider its earlier decision. A waiver decision becomes final once issued in the approval letter for an NDA, BLA, or supplement.

C. What Is a Deferral?

A deferral acknowledges that a pediatric assessment is required but permits the applicant to submit the pediatric assessment after the submission of an NDA, BLA, or supplemental NDA or BLA. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all of the pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product for adult use [Section 505B(a)(3) of the Act].

D. How to Apply for a Deferral

1. Criteria for Deferral [Section 505B(a)(3) of the Act]

FDA may defer the timing of submission of some or all required pediatric studies if it finds one or more of the following:

- The drug or biological product is ready for approval for use in adults before pediatric studies are complete [Section 505B(a)(3)(A)(i) of the Act].
- Pediatric studies should be delayed until additional safety or effectiveness data have been collected [Section 505B(a)(3)(A)(ii) of the Act].

OR

- There is another appropriate reason for deferral [Section 505B(a)(3)(A)(iii) of the Act] (e.g., development of a pediatric formulation is not complete).

In addition, to obtain a deferral the applicant must submit certification of the reason(s) for deferring the assessments, a description of the planned or ongoing studies, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time [Section 505B(a)(3)(B)(i)–(iii) of the Act].

2. Information in a Deferral Request

FDA has provided a sample deferral request checklist to assist applicants in providing sufficient information for FDA to determine whether to grant a deferral request (Attachment B). To request a deferral, we recommend an applicant provide:

- Product name, applicant name, and indication
- Age group(s) included in deferral request
- Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request (e.g., studies have already been completed in other age groups and need not be deferred)
- Reason(s) for requesting a deferral
- Evidence justifying that the proposed product meets the criteria for deferral of the pediatric assessment requirement
- Description of planned or ongoing studies
- Evidence that planned or ongoing studies are proceeding
- Projected date for the submission of the pediatric assessment (deferral date)
- Applicant certification

3. Deferral Decision

The decision to defer and the deferral date will be determined on a case-by-case basis. Considerations used in determining whether and how long to defer submission of the pediatric assessment may include:

- The need for the drug or biologic in pediatric patients
- Availability of sufficient safety data to initiate pediatric trials
- The nature and extent of pediatric data needed to support pediatric labeling
- The existence of substantiated difficulties in enrolling patients
- Evidence of technical problems in developing pediatric formulations

As discussed in Section V.A, the meeting minutes or a separate letter will document the deferral of pediatric assessments agreed to at the end-of-phase-2 meetings. For a deferral granted during the pre-approval development period, it is possible that FDA may reevaluate the length of the deferral closer to the time of approval, taking into account any new information obtained while the product was in development and information reviewed in the NDA or BLA. The pediatric assessments deferred under PREA are required post-marketing studies subject to the annual status reporting and information disclosure provisions of 21 CFR 314.81(b)(2)(vii)(a) and (b) and 21 CFR 601.70.

VI. COMPLIANCE WITH PREA

If a pediatric assessment or a request for approval of a pediatric formulation is not submitted by an applicant in accordance with the statutory requirements, the drug or biological product may be considered misbranded solely because of that failure and subject to relevant enforcement action [Section 505B(d)(1) of the Act]. The failure to submit a pediatric assessment or request for waiver or deferral will not be the basis for withdrawing approval of a drug under Section 505(e) of the Act or the revocation of a license for a biological product under Section 351 of the PHSA [Section 505B(d)(2) of the Act]. However, the Agency could bring injunction or seizure proceedings if a product is found to be misbranded under these provisions.[8]

VII. PREA AND PEDIATRIC EXCLUSIVITY

It is the Agency's policy to offer applicants the opportunity to qualify for *pediatric exclusivity* under Section 505A of the Act for studies required and conducted under PREA. Under that policy, however, FDA will not issue a Written Request for or grant pediatric exclusivity for studies that have been submitted to the Agency before the Written Request is issued. Therefore, an applicant seeking to qualify for pediatric exclusivity should obtain a Written Request for studies from FDA before submitting the pediatric studies to satisfy PREA. [Note that for marketed drugs and biological products, the Agency is required to issue a Written Request prior to requiring studies under PREA (Section 505B(b)(3) of the Act).] To qualify for pediatric exclusivity, the pediatric studies conducted to satisfy the requirements of PREA must also satisfy all of the requirements for pediatric exclusivity under Section 505A of the Act [see Sections 505A(d) and 505A(h) of the Act].

In addition, there is a noteworthy distinction between the scope of the studies requested under the pediatric exclusivity provisions and what is required under PREA. For pediatric exclusivity under the Act, FDA's authority to issue a Written Request extends to the use of an active moiety for all indications that occur in the pediatric population, regardless of whether the indications have been previously approved in adults or approval for those indications is being sought in adults [see Section 505A(a), which refers only to "information relating to the use of a new drug in the pediatric population"]. Under PREA, on the other hand, a pediatric assessment is required only on those indications included in the pending application [Section 505B(a), which addresses "the safety and effectiveness of the drug or biological product for the claimed indications"]. To learn more about eligibility for pediatric exclusivity, applicants should consult the guidance for industry entitled *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*[9] or should contact the relevant review division.

VIII. ADDITIONAL INFORMATION

A. Additional Information Concerning PREA

General information about complying with PREA can be obtained from the Division of Pediatric Drug Development (DPDD), 301-594-7337 or 301-827-7777, e-mail pdit@cder.fda.gov.

Additional pediatric information is available at www.fda.gov/cder/pediatric.

Specific information about the types of pediatric studies that must be conducted and requirements for submission of assessments for your drug product can be obtained from the appropriate review division.

B. Additional Information Concerning Pediatric Exclusivity

General information and the latest statistical information regarding pediatric exclusivity are located at www.fda.gov/cder/pediatric. You can also refer to the guidance for industry on *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*.

ATTACHMENT A—SAMPLE WAIVER REQUEST

Product name:
IND/NDA/BLA number (as applicable):
Applicant:
Indications(s):

(NOTE: If drug is approved for or you are seeking approval for more than one indication, address the following for each indication.)

1. Identify pediatric age group(s) included in your waiver request.
2. With regard to each age group for which a waiver is sought, state the reason(s) for waiving pediatric assessment requirements with reference to applicable statutory authority (i.e., one of the options (a)–(d) listed below—choose all that apply):
   (a) Studies are impossible or highly impractical (because, for example, the number of pediatric patients is so small or geographically dispersed). If applicable, please check from the following list of adult-related conditions that may qualify the drug product for disease-specific waivers:

____ Age-related macular degeneration	____ Basal cell and squamous cell cancer
____ Alzheimer's disease	____ Breast cancer
____ Amyotrophic lateral sclerosis	____ Colorectal cancer
____ Arteriosclerosis	____ Endometrial cancer
____ Infertility	____ Hairy cell cancer
____ Menopause symptoms	____ Lung cancer (small cell and non-small cell)
____ Osteoarthritis	____ Oropharynx cancers (squamous cell)
____ Parkinson's disease	____ Ovarian cancer (non-germ cell)
	____ Pancreatic cancer
____ Other (please state and justify)	____ Prostate cancer
	____ Renal cell cancer
	____ Uterine cancer

(b) The product would be ineffective or unsafe in one or more of the pediatric age group(s) for which a waiver is being requested.
(c) The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
(d) Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. Please document previous attempts to make a pediatric formulation, and describe reason for failure.

3. Provide evidence that the statutory reason(s) for waiver of pediatric studies have been met [not necessary if a 2(a) category is checked].
4. Applicant certification.

ATTACHMENT B—SAMPLE DEFERRAL REQUEST

Product name:
IND/NDA/BLA number (as applicable):
Applicant:
Indications(s):

(NOTE: If drug is approved for or you are seeking approval for more than one indication, address the following for each indication.)

1. What pediatric age group(s) are included in your deferral request?
2. Reason(s) for requesting deferral of pediatric studies (address each age group separately and for each age group—choose all that apply):
   (a) Adult studies completed and ready for approval
   (b) Additional post-marketing safety data needed (describe)
   (c) Nature and extent of pediatric data needed (explain)
   (d) Evidence provided of technological problems with development of a pediatric formulation
   (e) Difficulty in enrolling pediatric patients (provide documentation)
   (f) Other (specify)
3. What pediatric age group(s) is/are not included in your deferral request?
4. Reason(s) for not including the pediatric age group(s) listed in number 3 in the deferral request (address each excluded age group separately and for each such age group—choose all that apply):
   (a) Adequate pediatric labeling exists
   (b) Studies completed in the specified age group
   (c) Requesting a waiver
   (d) Currently conducting pediatric studies that will be submitted with application
   (e) Other (specify)
5. Has a pediatric plan been submitted to the Agency?
   - If so, provide date submitted.
   - If not, provide projected date pediatric plan is to be submitted.
6. Suggested deferred date for submission of studies.

ATTACHMENT C—COMPLIANCE DATES FOR APPLICATIONS SUBJECT TO PREA

Categories of Application	Expected Date of Compliance
Application or supplement submitted between 4/1/99 and 12/3/03, no waiver or deferral was granted and no studies were submitted	Immediate unless FDA specifies later date
Application or supplement submitted between 4/1/99 and 10/17/02, studies were deferred to a date after 4/1/99, but no studies were submitted	Deferral date + 411 days
Application or supplement submitted between 10/17/02 and 12/3/03 and approved after 12/3/03, studies were deferred	Immediate unless later date is specified in deferral letter
Applications submitted after 12/3/03, studies were deferred	Date specified in deferral letter

16 Global Regulatory Guidance on Bioequivalence Testing

BACKGROUND

Although the current bioequivalence guidelines and recommendations of the major regional and national health authorities show a fair degree of consistency, a number of outstanding bioequivalence issues and concerns remain to be resolved. The most obvious of these controversial issues, such as the bioequivalence acceptance limits for NTI drugs and HVDs/HVDPs, the use of metabolites for bioequivalence assessment, conditions to grant biowaivers, are not always dealt with in the same way by the various health authorities. Global harmonization should therefore be the next logical step in the continuing process to improve the bioequivalence guidelines as a means to guarantee safe and efficacious drug products for the consumer in all parts of the world. Global harmonization efforts by the International Conference on Harmonization (ICH) and the WHO should be stepped up in collaboration with the regulatory agencies of the Western world as more nations throughout the world have come to rely on low-cost, good-quality multi-source (generic) pharmaceutical products to provide lower healthcare costs without sacrificing important public health goals. However, as pointed out above, consensus on a number of bioequivalence issues has not been reached at this point in time amongst international regulatory agencies. In addition, differing levels of commitment and resources by the various countries and regions constitute another formidable barrier that has to be overcome to harmonize bioequivalence approaches to ensure development of optimally performing and affordable drug products for use by health practitioners and patients in the global community.

Due to significant recognition of the BA/bioequivalence concept all over the world, tremendous advancements have been made by the FDA as well as various national, international, and supra national regulatory authorities. In parallel, pharmaceutical industry and academia are also contributing in the area of assessment of bioequivalence. Currently available approaches to determine bioequivalence of generic products are largely standardized due to discussion and consensus reached among various stakeholders at numerous national and international meetings, conferences, and workshops (e.g., American Association of Pharmaceutical Scientists, Federation Internationale Pharmaceutique). Thus the currently available excellent scientific and regulatory guidance documents are due to the combined efforts of industry, academia, and regulatory scientists.

GLOBAL DIVERSITY

The adaptation of the bioequivalence concept worldwide for years has enabled the production and approval of quality generic products through profound scientific, technical, and regulatory advances (especially through replicate designs, application of BCS, scaled average BE) by various approaches to assess BE for various complex and special groups of drugs. This continuing success story of bioequivalence is based on the contribution to efficacy, safety, and quality by international regulatory authorities, pharma industry researchers, academic researchers, and indeed the efforts from ICH, WHO, and various international conferences. However, a lot remains to be done, especially to promote global harmonization of bioequivalence approaches, which should focus on uniformity, standardization of nomenclature, agreement on general concepts, alternative approaches for locally acting drug products, choice of test procedures, outlier challenge, consideration of bioequivalence criteria and objectives, all of which reflect regulatory decision-making standards, as well as ensuring product quality over time for both innovator and generic drugs. To achieve these objectives efforts should continue from international health organizations, pharmaceutical industries, researchers, and regulatory authorities to understand and to develop more efficient and scientifically valid approaches to assess BE and develop generic drugs in a cost-effective manner.

The magnitude of regulatory influence is often dictated by the availability of resources, expertise, and lack of regulation or its implementation. Thus there is a greater need to harmonize the regulatory environment globally for bioequivalence assessment as far as practicable so that the drug product marketed in different parts and regions of the world would have optimum drug product quality in terms of interchangeability. In recent years, some significant progress has been made towards harmonization; in addition some regulatory authorities are also in the process of cooperating with their counterparts from other countries to harmonize the regulatory requirements while streamlining their own regulatory requirements.

Tremendous work towards harmonization was initiated and completed by some organizations, especially the ICH and the World Health Organization (WHO). ICH is a consortium of regulatory authorities from Europe, Japan, and the United States which has focused primarily on developing guidelines

for standardizing and harmonizing the regulatory requirements, mainly for aspects of chemistry and manufacturing control, safety, and efficacy of new drug product quality. In addition, it has developed specific documents for the content and format of drug product dossiers. It has not yet focused on harmonizing the requirements for approval of generic equivalents. On the other hand, the WHO has made remarkable progress specifically in developing international consensus on the regulatory requirements for assessing bioequivalence for marketing authorization of multi-source pharmaceutical products for interchange-ability, selection of comparator product for bioequivalence assessment, and other related regulatory documents. Apart from the ICH and WHO other European and Asian organizations (national and international) are actively involved in harmonization efforts for assessing of bioequivalence and improving the quality of pharmaceutical products globally.

GLOBAL AGENCIES

Every country now has its own individual regulatory authority as well as regulatory guidance for bioequivalence studies, and the regulatory environment of the respective country of marketing influences the magnitude of assessment of bioequivalence of drug product. The regulatory authorities of various countries and international organizations are listed and briefly described in Table 16.1.

GENERAL ASSESSMENT OF BIOEQUIVALENCE

The global paradigm for the assessment of bioequivalence of different drug products remains based on the fundamental assumption that two products are equivalent when the rate and extent of absorption of the test/generic drug does not show a significant difference from the rate and extent of absorption of the reference/brand drug under similar experimental conditions as defined. Global agencies classify bioequivalence studies in the descending order of preference as:

1. Pharmacokinetic endpoint studies
2. Pharmacodynamic endpoint studies
3. Clinical endpoint studies
4. In vitro endpoint studies

Pharmacokinetic Endpoint Studies

These studies are most widely preferred to assess bioequivalence for drug products, where drug level can be determined in an easily accessible biological fluid (such as plasma, blood, urine) and drug level is correlated with the clinical effect. The statutory definition of BA and bioequivalence, expressed in rate and extent of absorption of the active moiety or ingredient to the site of action, emphasizes the use of pharmacokinetic measures to indicate release of the drug substance from the drug product with absorption into the systemic circulation. Regulatory guidance recommends that measures of systemic exposure be used to reflect clinically important differences between test and reference products in BA and bioequivalence studies. These measures include (i) total exposure AUC_{0-t} or $AUC_{0-\infty}$ for single-dose studies and $AUC_{0-\tau}$ for steady-state studies, (ii) peak exposure (C_{max}), and (iii) early exposure (partial AUC to peak time of the reference product of an immediate-release drug product). Reliance on systemic exposure measures will reflect comparable rate and extent of absorption, which, in turn, will achieve the underlying goal of assuring comparable therapeutic effects. Single-dose studies to document bioequivalence were preferred because they are generally more sensitive in assessing in vivo release of the drug substance from the drug product when compared to multiple-dose studies. Table 16.4 describes the general pharmacokinetic parameters (primary and secondary) for single-dose, multiple-dose, and urinary data.

The following are the circumstances that demand multiple-dose study/steady-state pharmacokinetics:

- Dose- or time-dependent pharmacokinetics
- For modified-release products for which the fluctuation in plasma concentration over a dosage interval at steady state needs to be assessed
- If problems of sensitivity preclude sufficiently precise plasma concentration measurements after single-dose administration
- If the intra-individual variability in the plasma concentration or disposition precludes the possibility of demonstrating bioequivalence in a reasonably sized single-dose study and this variability is reduced at steady state
- When a single-dose study cannot be conducted in healthy volunteers due to tolerability reasons, and a single-dose study is not feasible in patients
- If the medicine has a long terminal half-life, and blood concentrations after a single dose cannot be followed for a sufficient time
- For those medicines that induce their own metabolism or show large intra-individual variability
- For combination products for which the ratio of plasma concentration of the individual substances is important
- If the medicine is likely to accumulate in the body
- For enteric-coated preparations in which the coating is innovative

Under normal circumstances, blood should be the biological fluid sampled to measure drug concentrations. Most drugs may be measured in serum or plasma; however, in some drugs, whole blood (e.g., tacrolimus) may be more appropriate for analysis. If the blood concentrations are too minute to be detected and a substantial amount (40%) of the drug is eliminated unchanged in the urine, the urine may serve as the biological fluid to be sampled (e.g., alendronic acid).

Table 16.2 shows lists the primary pharmacokinetic parameters used in bioavailability and bioequivalence studies.

TABLE 16.1
Global Regulatory Agencies and Organizations

Country	Agency	Web Address
Armenia	Scientific Center of Drug and Medical Technologies Expertise (SCDMTE)	www.pharm.am/
ASEAN	Association of Southeast Asian Nations Consultative Committee for Standards and Quality	www.aseansec.org/
Australia	Therapeutic Goods Administration (TGA)	www.tga.gov.au/
Belgium	Pharmaceutical Inspectorate	http://afigp.fgov.be/
Brazil	National Health Surveillance Agency (ANVISA)	www.anvisa.gov.br/
Bulgaria	Drug Agency	www.bda.bg/
Canada	Health Canada	www.hc-sc.gc.ca/
China, People's Republic of	National Institute for the Control of Pharmaceutical and Biological Products	www.nicpbp.org.cn/cmsweb/
Colombia	Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA)	http://web.invima.gov.co/
Czech Republic	State Institute for Drug Control	www.sukl.cz/
Europe	European Medicines Agency (EMA)	www.ema.europa.eu/
European Union	European Commission and EMEA	www.ema.europa.eu/
Fiji	Ministry of Health	www.health.gov.fj/
Finland	National Agency for Medicines	www.nam.fi/
France	Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS)	www.afssaps.fr/
Germany	Federal Institute for Drugs and Medical Devices	www.bfarm.de/
Japan	Global GMP Harmonization	www.nihs.go.jp/drug/section3/hiyama070518-3.pdf
Global Harmonization Task Force	GHTF	www.ghtf.org/
Greece	National Organization for Medicines	www.eof.gr/
Hong Kong	Department of Health	www.dh.gov.hk/
Iceland	Icelandic Medicines Agency (IMA)	www.imca.is/
India	Central Drugs Standard Control Organization (CDSCO)	http://cdsco.nic.in/
Indonesia	Ministry of Health	www.depkes.go.id/
International Conference on Harmonization	ICH	www.ich.org/
Ireland	Health Products Regulatory Authority (HPRA)	www.hpra.ie
Israel	Ministry of Health	www.health.gov.il/
Italy	National Institute of Health	www.iss.it/
Japan	Pharmaceuticals and Medical Devices Agency (PMDA)	www.pmda.go.jp/
Kenya	Ministry of Health	www.publichealth.go.ke/
Korea	Korea Food and Drug Administration (KFDA)	www.kfda.go.kr/
Malaysia	National Pharmaceutical Control Bureau	http://portal.bpfk.gov.my/
Mexico	Ministry of Health	www.salud.gob.mx/
Namibia	Ministry of Health and Social Services	www.healthforall.net/grnmhss/
Netherlands	Medicines Evaluation Board	www.cbg-meb.nl/
New Zealand	Medicines and Medical Devices Safety Authority (MEDSAFE)	www.medsafe.govt.nz/
Norway	Norwegian Medicines Agency	www.legemiddelverket.no/
Poland	Drug Institute	www.il.waw.pl/
Saudi Arabia	Ministry of Health	www.moh.gov.sa/
Singapore	Health Sciences Authority (HSA)	www.hsa.gov.sg
South Africa	Medicines Control Council (MCC)	www.mccza.com/
Spain	Spanish Drug Agency	www.msc.es/
Sri Lanka	Ministry of Health	www.health.gov.lk/
Sweden	Medical Products Agency	www.lakemedelsverket.se/
Switzerland	Swiss Agency for Therapeutic Products	www.swissmedic.ch/
Taiwan	Department of Health (DOH)	www.doh.gov.tw/
Tanzania	Ministry of Health	www.tanzania.go.tz/

(*Continued*)

TABLE 16.1 (CONTINUED)
Global Regulatory Agencies and Organizations

Country	Agency	Web Address
United Arab Emirates	Federal Department of Pharmacies	www.uae.gov.ae/
United Kingdom	Medicines and Healthcare products Regulatory Agency (MHRA)	www.mhra.gov.uk/
United States	U.S. Food and Drug Administration (FDA)	www.fda.gov/
World Health Organization	WHO	www.who.int/
Zimbabwe	Ministry of Health and Child Welfare	www.gta.gov.zw/health.html

TABLE 16.2
Primary Pharmacokinetic Parameters Used in Bioavailability and Bioequivalence Testing

Study Type	Primary Parameters	Secondary Parameters
Single-dose	C_{max}, AUC_{0-t}, $AUC_{0-\infty}$	T_{max}, AUC%extrapolation, MRT, Kel, $t_{1/2}$
Steady-State	$C_{max}(ss)$, $C_{min}(ss)$, $AUC_{0-\tau}$	$T_{min}(ss)$, $T_{max}(ss)$, % swing, % fluctuation
Urinary-based	Ae(0–t), Ae(0–∞), R_{max}	T_{lag}

Pharmacodynamic Endpoint Studies

Pharmacokinetic studies measure systemic exposure but are generally inappropriate to document local delivery BA and bioequivalence. In such cases, BA may be measured, and bioequivalence may be established, based on a pharmacodynamic study, providing an appropriate pharmacodynamic endpoint is available. Pharmacodynamic evaluation is measurement of the effect on a pathophysiological process, such as a function of time, after administration of two different products to serve as a basis for bioequivalence assessment. Regulatory authorities request justification from the applicant for the use of pharmacodynamic effects/parameters for the establishment of bioequivalence criteria. These studies generally become necessary under two conditions: (1) if the drug and/or metabolite(s) in plasma or urine cannot be analyzed quantitatively with sufficient accuracy and sensitivity; (2) if drug concentration measurement cannot be used as surrogate endpoints for the demonstration of efficacy and safety of the particular pharmaceutical product. The other important specifications for pharmacodynamic studies include (i) a dose–response relationship should be demonstrated; (ii) sufficient measurements should be taken to provide an appropriate pharmacodynamic response profile; (iii) the complete dose–effect curve should remain below the maximum physiological response; (iv) all pharmacodynamic measurements/methods should be validated for specificity, accuracy, and reproducibility. Examples of these pharmacodynamic studies include locally acting drug products and oral inhalation drug products, such as metered dose inhalers and dry powder inhalers, and topically applied dermatologic drug products, such as creams and ointments. Bronchodilator drug products, such as albuterol metered dose inhalers, produce relaxation of smooth muscle of the airways. For these drug products, a pharmacodynamic endpoint, based either on increase in forced expiratory volume in one second (FEV) or on measurement of PD_{20} or PC_{20} (the dose or concentration, respectively, of a challenge agent), is clinically relevant and may be used for BA and bioequivalence studies.

Clinical Endpoint Studies or Comparative Clinical Trials

In the absence of pharmacokinetic and pharmacodynamic approaches, adequate and well-controlled clinical trials may be used to establish bioequivalence. Several international regulatory authorities provide general information about the conduct of clinical studies to establish bioequivalence.

In Vitro Endpoint Studies

More recently, a Biopharmaceutics Classification System (BCS) has categorized drug substances as having either high or low solubility and permeability and drug products as exhibiting rapid dissolution. According to this approach, drug substances may be classified into four primary groups:

1. Highly soluble and highly permeable
2. Highly permeable and poorly soluble
3. Highly soluble and poorly permeable
4. Poorly soluble and poorly permeable

Using this BCS approach, a highly permeable, highly soluble drug substance formulated into a rapidly dissolving drug product may need only in vitro dissolution studies to establish bioequivalence. In addition, in vitro approaches to document bioequivalence for drugs with no known bioavailability problems and approved before 1962 remain acceptable as per FDA regulations. Dissolution tests can also be used to reduce the number of in vivo studies in other circumstances and to

(i) assess batch-to-batch quality and support batch release; (ii) provide process control and quality assurance; and (iii) assess the need for further bioequivalence studies relative to minor post-approval changes, where they function as a signal of bioinequivalence.

DESIGN AND ANALYSIS

The general considerations for the advancement of conducting bioequivalence studies are:

- Study design and protocol
- Bioanalysis
- Selection of appropriate analyte(s)
- Bioequivalence metrics and data treatment
- Statistical approaches and analysis
- Acceptance criteria for bioequivalence

Study Design

Successfully determining the bioequivalence of generic drugs to their respective reference drugs depends mostly on design and managing the conduct of the study such that the highest quality samples are obtained. Some regulatory authorities provide specific information on reference-listed drugs to be used to demonstrate bioequivalence (see Table 16.3).

Attention should also be paid to sizing the study properly (to achieve sufficient statistical power to demonstrate bioequivalence); enrolling subjects as per relevant inclusion and exclusion criteria; ensuring that the appropriate overall design (simple two-period crossover, replicate design to gain direct information on within-subject variability for both test and reference product or parallel design) can adequately address the question at hand; standardization of the environmental conditions (such as, fasting, fed, ambulatory, supine); and ensuring that good clinical practices are strictly adhered to and documented. All of these should be planned a priori and embodied in the overall protocol and study plan for the smooth execution of bioequivalence studies.

Generally the study design and number of studies (single-dose and/or multiple-dose and/or fasting and/or fed) depend on the RLD or reference listed drug product, physicochemical properties of the drug, its pharmacokinetic properties, and proportionality in composition with justification along with respective regulatory guidance and specifications. Table 16.4 describes various study designs generally used for bioequivalence studies.

Genetic variations among ethnic and/or racial backgrounds can alter the drug disposition (e.g., white persons who predominantly express less P-glycoprotein in intestinal epithelial cells than black persons) and thus lead to potential sources of variability in pharmacokinetic parameters apart from geographical, food habits, and metabolic variations. For bioequivalence studies, these problems will be minimized using crossover designs, and hence US and Europe regulatory agencies (but not Japan, Korea, and Mexico, for example) are accepting bioequivalence studies from other countries also, as these factors mostly do not have much effect on test and reference products. Bioequivalence studies should be generally performed on a healthy population unless safety warrants (patient population should be preferred if the risk associated with the drug is higher in healthy populations, e.g., anticancer drugs) as they facilitate the provision of adequate information to detect formulation differences and allow extrapolation of this information to populations for which the brand drug is approved.

The regulatory specifications on strength to be investigated, demographics, sample size, number of studies required, fasting and/or fed requirements, standardization of experimental conditions (fluid intake, posture, and physical activity), add-on design, and sampling and washout criteria are briefly described in Tables 16.5 to 16.12.

As a result of random variation or a larger than expected relative difference, there is no guarantee that the sample size as calculated will pass the standards. If the study is run with the appropriate size and the standards are not met, the sponsor may add more subjects, and this approach is generally referred to as an "add-on" study (see Table 16.11).

Bioanalysis

In a general prospective of BA/bioequivalence studies, bioanalysis should be the subsequent step following clinical operations of the study, and it should be executed with strict adherence to good laboratory practices, standard operating procedures, and specific regulatory requirements. Bioanalysis is a term generally used to describe the quantitative measurement of a compound (drug) or its metabolite in biological fluids, primarily blood, plasma, serum, urine, or tissue extracts. Bioanalysis typically consists of two important components: (1) sample preparation and (2) detection of

TABLE 16.3
Agencies Providing Specific Information on Drugs to Conduct Bioequivalence Studies

Country	URL
USA	www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075214.htm
Canada	http://webprod.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp
Europe	www.medicines.org.uk/EMC/browsedocuments.aspx
Australia	www.ebs.tga.gov.au/

TABLE 16.4
Brief Description of Bioavailability and Bioequivalence Testing Designs

Design	Significance	Advantages	Disadvantages
Crossover	• When intra-subject CV (approx. 15%) is usually substantially smaller than that inter-subject CV (approx. 30%) • Generally recommended by all regulatory authorities	• Since the treatments are compared on the same subject, the inter-subject variability does not contribute to the error variability • Subject randomization causes unbiased determination of treatment effects • Large information based on minimum sample size • Straightforward statistical analysis	• Carryover effects and period effects are possible due to inappropriate wash-out period • Long duration • Possibility of more drop outs leads to insufficient power • Not suitable for long half-life drugs • Not optimal for studies in patients and highly variable drugs
Parallel	• If the drug has a very long terminal elimination half-life • Duration of the washout time for the two-period crossover study is so long (if >1 month) • If the intra-subject CV is higher with crossover design	• Design is simple and robust • Drop outs will be comparatively less • Duration of the study is less than crossover study • Study with patients is possible • Straightforward statistical analysis	• Subjects cannot serve as their own controls for intra-subject comparisons • Large sample size is required • Lower statistical power than crossover • Phenotyping mandatory for drugs showing polymorphism
Replicate	• Useful for highly variable drugs (intra-subject CV ≥ 30%)	• Allows comparisons of within-subject variances for the test and reference products • Indicates whether a test product exhibits higher or • lower within-subject variability in the bioavailability measures when compared to the reference product • Provides more information about the intrinsic factors • underlying formulation performance • Reduces the number of subjects needed in the bioequivalence study • The number of subjects required to demonstrate bioequivalence can be reduced by up to about 50% • Design increases the power of the study when the variability in the systemic exposure of the test drug and formulation is high	• Involves larger volume of blood withdrawn from each subject • Longer duration of the entire study • Increased possibility of subject drop outs • Expensive
Variance balanced design	• For more than two formulations • Desirable to estimate the pairwise effects with the same degree of precision	• Allows the choice between two additional candidate test formulations • Comparison of test formulation with several reference formulations • Standard design for the establishment of dose proportionality	• Statistical analysis is more complicated (especially when drop-out rate is high) • May need measures against multiplicity (increasing the sample size)

the desired compound using a validated method. Excellent scientific and regulatory guidance documents are available that outline the requirements for a fully validated method. The application of validated methodology presupposes that the most appropriate analyte is monitored to attest to the question of bioequivalence.

SELECTION OF APPROPRIATE ANALYTE(S)

Each regulatory authority has its own specifications for selection of an appropriate analyte to be measured as well as consideration for bioequivalence. Most commonly, the investigator should consult the relevant regulatory agency for guidance on a particular therapeutic agent. The general considerations are discussed in the following sections.

Parent Drug vs. Metabolite(s)

Bioequivalence based on test/reference comparisons of pharmacokinetic measures serves two purposes: (1) to act as a surrogate for therapeutic equivalence, (2) to provide in vivo evidence of pharmaceutical quality. The overall objective of

TABLE 16.5
Brief Description of the Criteria on Strength to Be Investigated in Bioequivalence Studies

Country	Linear Pharmacokinetics	Nonlinear Pharmacokinetics
Europe and Australia	General: The bioequivalence study should in general be conducted at the highest strength Highly soluble drug and any safety concern: Lower strength acceptable Problems of sensitivity of the analytical method: Highest strength acceptable	For drugs with nonlinear pharmacokinetics characterized by a more than proportional increase in AUC with increasing dose over the therapeutic dose range, the bioequivalence study should in general be conducted at the highest strength. As for drugs with linear pharmacokinetics a lower strength may be justified if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons. Likewise a higher dose may be used in case of sensitivity problems of the analytical method in line with the recommendations given for products with linear pharmacokinetics above. For drugs with a less than proportional increase in AUC with increasing dose over the therapeutic dose range, bioequivalence should in most cases be established both at the highest strength and at the lowest strength (or strength in the linear range), i.e., in this situation two bioequivalence studies are needed. If the nonlinearity is not caused by limited solubility but is due to, e.g., saturation of uptake transporters and provided that (a) the same manufacturing process is used; (b) qualitative composition of the different strengths is the same; (c) compositions of the strengths are quantitatively proportional; (d) appropriate in vitro dissolution data should confirm the adequacy of waiving additional in vivo bioequivalence testing and the test and reference products do not contain any excipients that may affect gastrointestinal motility or transport protein, it is sufficient to demonstrate bioequivalence of proteins at the lowest strength (or strength in the linear range).
United States	Reference listed drug in the Orange Book; usually the highest strength if formulations are proportionally similar. For an ANDA, conducting an in vivo study on a strength that is not the highest may be appropriate for reasons of safety, subject to approval by the Division of Bioequivalence, Office of Generic Drugs and provided that the following conditions are met: (a) linear elimination kinetics has been shown over the therapeutic dose range; (b) the higher strengths of the test and reference products are proportionally similar to their corresponding lower strength; (c) comparative dissolution testing on the higher strength of the test and reference products is submitted and found to be appropriate.	Not specified
Saudi Arabia	For conventional solid oral drug products, in vivo bioequivalence studies are conducted on the highest strength. This requirement for the lower strengths can be waived provided: (a) in vivo bioequivalence is demonstrated on the highest strengths; (b) in vitro dissolution testing is acceptable; and (c) the formulations for the lower strengths are proportionally similar to the strength which has undergone in vivo bioequivalence testing (i.e., the ratio of active ingredients and excipients between the strengths is essentially the same).	Not specified
Canada	Generally use strength with largest sensitivity to identify differences in formulation. Reference product is: (1) a drug product that has been issued a notice of compliance pursuant to Section C.08.004 of the Food and Drug Regulations and is currently marketed in Canada by the innovator, or (2) a drug product acceptable to the Director.	
Asia	Test products in an application for a generic product are normally compared with the corresponding dosage form of an innovator medicinal product (reference product). The choice of reference product should be justified by the applicant and agreed upon by the regulatory authority. If the innovator product is not available, an alternative comparator product approved by the drug regulatory authority of the country can be used.	
New Zealand	When the drug product is the first market entry of that type of dosage form, the reference product should normally be the innovator's prompt-release formulation. The comparison should be between a single dose of the drug formulation and doses of the prompt-release formulation which it is intended to replace.	
Korea	Reference drug product is an approved drug product (or an approved imported drug product) the safety and efficacy of which have been established or recognized by the Commissioner of the KFDA.	

TABLE 16.6
Regulatory Criteria on Subject Demographics for Bioequivalence Studies

Country	Sex	Age (Years)	Body Mass Index (BMI) (kg/m^2)
India	Male or female	Healthy adult volunteers	Not specified
Asia	Either sex	18–55	18–30; Asians: 18–25
United States	Both sexes	>18	Not specified
Europe	Either sex	>18	18.5–30
Canada	Both sexes	18–55	Height/weight ratio for healthy volunteer subjects should be within 15% of the normal range
Australia	Either sex	18–55	Accepted normal BMI
South Africa	Either sex	18–55	Accepted normal BMI or within 15% of the ideal body mass or any other recognized reference
Russia	Both sexes	19–45	Weight of body does not fall outside the limits ±15% on Ketle total-height index
Korea	Healthy adult	19–55	Not specified
Japan	Healthy adult	Not specified	Not specified
People's Republic of China	Both sexes	18–40	Standard weight range
Mexico	Avoiding pharmacokinetic differences between sexes is well documented; volunteers of just one sex must be included	18–55	Weight 10% from the ideal weight
Saudi Arabia	If females are included in the study, the effects of gender differences and menstrual cycle (if applicable) are examined statistically	18–50	Within 15% of ideal body weight, height, and body build
New Zealand	Both sexes	Age range prior to the onset of age-related physiological changes (usually 18–60)	Average weight (e.g., within ±15% of their ideal weight as given in the current Metropolitan Life Insurance Company Height and Mass Tables)

bioequivalence is to ensure that generic products have efficacy and safety characteristics similar to those of the corresponding reference product. For the most part, traditional bioequivalence studies have been carried out on the basis of measurement of only the parent drug in body fluids such as plasma or serum. In some cases, however, monitoring a metabolite, or the parent and metabolite(s), may be more appropriate. A number of reasons for use of metabolite data have been put forward, such as (i) the parent is an inactive prodrug, (ii) plasma concentrations of the parent drug are too low to monitor because of inadequate assay sensitivity, (iii) the parent drug is metabolized rapidly to an active metabolite, and (iv) the parent drug and a metabolite both have therapeutic activities but the metabolite is present in higher concentrations when the parent drug is rapidly and extensively metabolized such that only metabolite(s) data are available.

Enantiomers vs. Racemates

For BA/bioequivalence studies, measurement of both enantiomers may be important. For bioequivalence studies, measurement of the racemate using an achiral assay has been recommended, without measurement of individual enantiomers except when (i) the enantiomers exhibit different pharmacodynamic characteristics; (ii) the enantiomers exhibit different pharmacokinetics; (iii) the primary activity resides with the minor enantiomers; and (iv) nonlinear absorption is present (as expressed by a change in the enantiomers concentration ratio with change in the input rate of the drug) for at least one of the enantiomers.

Drug Products with Complex Mixtures

Certain drug products may contain complex drug substances, i.e., active moiety or active ingredient(s), which are mixtures of multiple synthetic and/or natural source components. Some or all of the components of these complex drug substances may not be characterized by chemical structure and/or biological activity. In this circumstance, BA and bioequivalence studies may be based on selected markers of peak and total exposure.

TABLE 16.7
Regulatory Criteria on Sample Size for Bioequivalence Studies

Country	Minimum	Sample Size Specifications
India	Should not be <16 unless justified for ethical reasons	The number of subjects required for a study should be statistically significant and should be sufficient to allow for possible withdrawals or removals (drop outs) from the study
Asia	Should not be <12	The number of subjects required is determined by (a) the error variance associated with the primary characteristic to be studied as estimated from a pilot experiment, from previous studies or from published data; (b) the significance level desired; (c) the expected deviation from the reference product compatible with bioequivalence (delta, i.e., percentage difference from 100%); and (d) the required power
United States	12	A sufficient number of subjects should complete the study to achieve adequate power for a statistical assessment
Europe	Should not be <12	The number of subjects to be included in the study should be based on an appropriate sample size calculation
Canada	12	(a) Obtain an estimate of the intra-subject Cv from the literature or from a pilot study; (b) choose one of Figures 3.1 through 3.3 (mentioned in bioequivalence guidance document) by determining which one has the closest rounded-up Cv to that estimated in (a), above; (c) choose an expected true ratio of test over reference means (usually 100%) and move up the graph to the 0.90 probability of acceptance; (d) a linear extrapolation between given sample sizes is adequate. This sample size calculation must be provided in the study protocol. More subjects than the sample size calculation required should be recruited into the study. This strategy allows for possible drop outs and withdrawals
Australia	Should not be <16 unless justified	Same as that of Asian guidelines
South Africa	Should not be <12 (general); 20 subjects (for modified release oral dosage forms)	The number of subjects should be justified on the basis of providing at least 80% power of meeting the acceptance criteria; alternatively, the sample size can be calculated using appropriate power equations, which should be presented in the protocol
Russia	18	In quantity sufficient for ensuring statistical significance of study. Thus capacity of the statistical test for bioequivalence study must be supported at a level of not less than 80% for revealing 20% distinctions between comparison parameter
Korea	12	The number of subjects should meet the requirements for statistical validity. The number of subjects can be determined based on the characteristics of the active component of the pertinent drug product
Japan	20	A sufficient number of subjects for assessing bioequivalence should be included. If bioequivalence cannot be demonstrated because of an insufficient number, an add-on subject study can be performed using not less than half the number of subjects in the initial study. A sample size of 20 (n = 10/group) for the initial study and pooled size of 30 for initial plus add-on subject study may suffice if test and reference products are equivalent in dissolution and similar in average AUC and C_{max}
Saudi Arabia	A number of subjects of less than 24 may be accepted (with a minimum of 12 subjects) when statistically justifiable	Generally recommends a number of 24 normal healthy subjects. Should enroll a number of subjects sufficient to ensure adequate statistical results, which is based on the power function of the parametric statistical test procedure applied. The number of subjects should be determined using appropriate methods taking into account the error variance associated with the primary parameters to be studied (as estimated for a pilot experiment, from previous studies or from published data), the significance level desired ($\alpha = 0.05$), and the deviation from the reference product compatible with bioequivalence (±20%) and compatible with safety and efficacy
New Zealand	12	The number of subjects should provide the study with a sufficient statistical power (usually ≥80%) to detect the allowed difference (usually 20%) between the test and reference medicines for AUC and C_{max} This number (n) may, in many cases, be estimated in advance from published or pilot study data using formulae If the calculated number of subjects appears to be higher than is ethically justifiable, it may be necessary to accept a statistical power which is less than desirable. Normally it is not practical to use more than about 40 subjects in a bioavailability study
Mexico	Sample size must not be <24 subjects considering both sequences, or it must meet the requirement related to a difference to be detected of ±20% for the reference product's mean, associated with a type-i error (*) of 0.05 and a minimal potency of (1-*) of 0.8 for this kind of design. A sample size of <24 subjects must be scientifically justified	
Brazil	The number of healthy volunteers shall at all times assure an adequate statistical power to guarantee reliability of bioequivalence study results	

TABLE 16.8
Regulatory Criteria on Number of Studies Required for Conducting Bioequivalence Studies

Country	Immediate-Release Formulations	Modified-Release Formulations
India	Generally a single-dose, nonreplicate, fasting study Food-effect studies are required (1) when it is recommended that the study drug should be taken with food (as would be in routine clinical practice); (2) when fasting-state studies make assessment of C_{max} and T_{max} difficult. If multiple-study design is important, appropriate dosage administered and sampling be carried out to document attainment of steady state	Should conduct fasting as well as food-effect studies. If multiple-study design is important, appropriate dosage administered and sampling carried out to document attainment of steady state
United States	Generally two studies: • A single-dose, nonreplicate fasting study • A food-effect, nonreplicate study Food effect study can be excepted in the following cases: (1) When both test product and RLD are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability (BCS Class I); or (2) when the dosage and administration section of the RLD label states that the product should be taken only on an empty stomach; or (3) when the RLD label does not make any statements about the effect of food on absorption or administration. If food effect is mentioned in the RLD label and if multiple-study design is important, appropriate dosage administered and sampling be carried out to document attainment of steady state	Should conduct fasting as well as food-effect studies. If multiple-study design is important, appropriate dosage administered and sampling be carried out to document attainment of steady state
Europe and Australia	Generally a single-dose, nonreplicate, fasting study Food-effect studies are required if the Summary of Product Characteristics of the reference product contains specific recommendations in relation to food interaction	Should conduct fasting, food-effect as well as steady-state studies
Canada	Generally comparative BA studies conducted in the fasting state Fed study is acceptable if there is a documented serious safety risk to subjects from single-dose administration of the drug or drug product in the absence of food; then an appropriately designed study conducted in the presence of only a quantity of food sufficient to prevent the toxicity may be acceptable for purposes of bioequivalence assessment. For complicated IR formulations (narrow therapeutic range drugs, highly toxic drugs, and nonlinear drugs): both fasted and fed studies	Usual requirement is for both fasted and fed studies. If multiple-study design is important, appropriate dosage administered and sampling be carried out to document attainment of steady state
South Africa	Should be done under fasting conditions unless food effects affect bioavailability of drug or reference product dosage recommended	Both fed and fasted studies are required. If multiple-study design is important, it should be carried out as per regulatory specifications
Korea	Generally a single-dose, nonreplicate, fasting study	Should conduct fasting, food-effect as well as steady-state studies
Japan	Both fasting as well as food-effect studies	Should conduct fasting, food-effect as well as steady-state studies
Saudi Arabia	Generally a single-dose, nonreplicate, fasting study is required. Food-effect studies are required (1) if there is documented evidence of effect of food on drug absorption, (2) the drug is recommended to be administered with food, (3) the drug may produce gastric irritation under fasting conditions, thus may be taken with food	Should conduct fasting as well as food-effect studies
New Zealand	Generally a single-dose fasting study is required Fed study is required when it is recommended that the drug be given with food, or fasted studies make assessment of C_{max} and T_{max} difficult	Should conduct fasting as well as food-effect studies. Steady-state studies are generally required if the drugs are likely to accumulate along with single-dose studies

BIOEQUIVALENCE METRICS AND DATA TREATMENT

The most frequent data treatment involves analysis of variance using a suitable program such as SAS® (Statistical Analysis System, SAS Institute, Cary, NC) or WinNonlin® (Pharsight Corporation, St. Louis, MO) so that contributions from subject, period, product/formulation, and interactions between these can be examined. Geometric mean ratios and log-transformed data are examined to test the hypothesis that the 90% confidence interval of extent (AUC_{0-t}) and $AUC_{0-\infty}$) and the maximum concentration (C_{max}) fall within the acceptance limits of 80% to 125%. More recently, other data treatments have been popular, which include partial area measurements and exposure metrics including C_{max}/AUC, especially with highly variable drugs (HVDs) and with drugs having a long terminal $t_{1/2}$, specialized dosage forms, and/or whose time to C_{max} is considered important (e.g., certain analgesics). In all of these

TABLE 16.9
Regulatory Criteria for Conducting Fasting and Fed Bioequivalence Studies

Country	Fasting Requirements	Fed-Study Requirement
India	Overnight fast (at least 10 h), with a subsequent fast of 4 h following dosing. For multiple-dose fasting studies, when an evening dose must be given, 2 h before and after the dosing	950–1000 kcal of high-fat breakfast approximately 15 min before dosing (at least 50% of calories must come from fat, 15–20% from proteins and rest from carbohydrates) The vast ethnic and cultural restrictions of the Indian subcontinent preclude the recommendation of a single standard high fat; in this case protocol should specify the appropriate and suitable diet
United States	Following an overnight fast of at least 10 h, with a subsequent fast of 4 h post dose	A high-fat (approximately 50% of total caloric content of the meal), high- calorie (approximately 800–1000 calories) meal is recommended. This test meal should derive approximately 150, 250, and 500–600 calories from protein, carbohydrate, and fat, respectively. The caloric breakdown of the test meal should be provided in the study report. If the caloric breakdown of the meal is significantly different from the one described above, a scientific rationale is required for this difference Following an overnight fast of at least 10 h, subjects should start the recommended meal 30 min prior to dosing. Study subjects should eat this meal in 30 min or less; however, the drug product should be administered 30 min after start of the meal
Europe and Australia	Should fast for at least 8 h prior to dosing, unless otherwise justified, and no food is allowed for at least 4 h post dose	The composition of the meal is recommended to be according to the SPC of the originator product. If no specific recommendation is given in the originator SPC, the meal should be a high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800 to 1000 kcal) meal. This test meal should derive approximately 150, 250, and 500–600 kcal from protein, carbohydrate, and fat, respectively. The composition of the meal should be described in terms of protein, carbohydrate, and fat content (specified in grams, calories, and relative caloric content (%))
Canada	Following an overnight fast of at least 10 h, with a subsequent fast of 4 h post dose	Should be a representative meal in which sufficient food is given to allow potential perturbation of systemic BA of the drug from the drug product. The sponsor should justify the choice of meal and relate the specific components and timing of food administration Example: Two eggs fried in butter, two strips of bacon, two slices of toast with butter, 120 g of hash browns, and 240 mL of whole milk
South Africa	Fasting prior to dosing and after dosing should be standardized	Use of high-calorie and high-fat meals is recommended
Korea	Should be fasted for at least 10 h before and up to 4 h after the drug administration	High-fat diet should be taken within 20 min in at least a 10-h fasting state. The drug products should be administered 30 min after the meal starts
Saudi Arabia	Following an overnight fast of at least 10 h, with a subsequent fast of 4 h post dose	A high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 1000 calories) breakfast. Alternative meals with equivalent nutritional content can be used
New Zealand	After an overnight fast of at least 10 h, with a subsequent fast of 2–4 h following dose administration	The meal should contain approximately 30–40 g of fat

cases, the objective has been to err on the side of protecting the consumer while at times increasing risk to the manufacturer. Hence, over the last 15 years, considerable debate has occurred globally about the fundamental scientific rationale used to establish bioequivalence for some of these "special" cases, in an effort to solve these issues associated with harmonization of drug equivalence approaches.

STATISTICAL APPROACHES

Considerable debate has ensued over the past 20 years on statistical testing and bioequivalence studies. After protracted, wide-ranging, and in-depth discussion among various experts from different locations, specific statistical regulatory guidance is available to investigators conducting bioequivalence studies. The various pharmacokinetic parameters derived from the plasma concentration–time curve are subjected to ANOVA in which the variance is partitioned into components according to subjects, periods, and treatments. The classical null hypothesis test is the hypothesis of equal means, H_0: $\mu_T = \mu_R$ (i.e., products are bioequivalent), where μ_T and μ_R represent the expected mean bioavailabilities of the test and reference products, respectively. The alternate hypothesis therefore is H_1: $\mu_T \neq \mu_R$ (i.e., products are bioinequivalent).

The detection of the difference becomes simply a function of sample size, and since the probable magnitude of the difference is the critical factor, this gives rise to two anomalies: (i) a large difference between two formulations which is nevertheless not statistically significant if error variability is high and/or sample size not large enough, (ii) a small difference,

TABLE 16.10
Regulatory Criteria on Fluid Intake, Posture, and Physical Activity for Bioequivalence Studies

Country	Fluid Intake	Posture and Physical Activity
India	Standardization of fluid intake and physical activity is required, and it should be stated in protocol	
United States	Subjects should be administered the drug product with 240 mL (8 fluid ounces) of water; water is allowed as desired except for 1 h before and 1 h after the drug administration	Standardized
Asia, Europe, and Australia	The drug products should be administered with a standardized volume of fluid (at least 150 mL). Prior to and during each study phase, subjects should be allowed water as desired except for 1hour before and after drug administration	As the bioavailability of an active moiety from a dosage form could be dependent upon gastrointestinal transit times, and regional blood flows, posture and physical activity may need to be standardized
Canada	On the morning of the study, up to 250 mL of water may be permitted up to 2 h before drug administration. The dose should be taken with water of a standard volume (e.g., 150 mL) and at a standard temperature. Two hours after drug administration, 250 mL of xanthine-free fluids is permitted	For most drugs, subjects should not be allowed to recline until at least 2 h after drug ingestion. Physical activity and posture should be standardized as much as possible to limit effects on gastrointestinal blood flow and motility. The same pattern of posture and activity should be maintained for each study day
South Africa	The volume of fluid administered at the time of dosing should be constant (e.g., 200 mL); fluids taken after dosing should also be standardized	Should be standardized
Korea	Drug products should be administered with 240 mL of water; drinking water 1 h before and after the administration of drug products is not allowed	Subjects should not be in a supine position at least 2 h after the administration of drug products and should maintain a posture and do only activities that would minimize the effects on their gastrointestinal blood flow rate and motility
Saudi Arabia	The test or reference products should be administered with about 8 fluid ounces (240 mL) of water; water allowed as desired except for 1 h before and after drug administration	Appropriate restrictions on fluid intake and physical activities should be made
New Zealand	The quantity, type, and timing of food and fluid taken concurrently with the medicine should be stated and should be controlled	Standardization of posture and physical activity is important. Subjects should not be allowed to recline until at least 2 h after oral administration of the medicine

TABLE 16.11
Regulatory "Add-On Criteria" for Conducting Bioequivalence Studies

Country	Add-On Criteria
Europe and Australia	It is acceptable to use a two-stage approach when attempting to demonstrate bioequivalence. An initial group of subjects can be treated and their data analyzed. If bioequivalence has not been demonstrated an additional group can be recruited and the results from both groups combined in a final analysis. If this approach is adopted appropriate steps must be taken to preserve the overall type I error of the experiment and the stopping criteria should be clearly defined prior to the study. The analysis of the first-stage data should be treated as an interim analysis and both analyses conducted at adjusted significance levels
South Africa	If the bioequivalence study was performed with the appropriate size but bioequivalence cannot be demonstrated because of a result of a larger than expected random variation or a relative difference, an add-on subject study can be performed using not less than half the number of subjects in the initial study. Combining is acceptable only if the same protocol was used and preparations from the same batches were used. Add-on designs must be carried out strictly according to the study protocol and standard operating procedures and must be given appropriate statistical treatment, including consideration of consumer risk
Canada	As a result of random variation or a larger than expected relative difference, there is no guarantee that the sample size as calculated will pass the standards. If the study is run with the appropriate size and the standards are not met, the sponsor may add more subjects (a minimum of 12). The same protocol should be used (i.e., same formulations, same lots, same blood sampling times, a minimum number of 12 subjects). The choice to use this strategy, as with all designs, should be declared and justified a priori. The level of confidence should be adjusted using the Bonferroni procedure. The t-value should be that for $P = 0.025$ instead of 0.05
Japan	Also for add-on study an additional ten subjects are recommended along with initial subjects

TABLE 16.12
Regulatory Criteria on Sampling and Washout Period for Conducting Bioequivalence Studies

Country	Sampling Criteria	Washout Criteria
India	*Blood sampling* Should be extended to at least three elimination half-lives; at least three sampling points during absorption phase, three–four at the projected T_{max}, and four points during elimination phase; sampling should be continued for a sufficient period to ensure that AUC_{0-t} to $AUC_{0-\infty}$ is only a small percentage (normally <20%) of the total AUC. Truncated AUC is undesirable except in the presence of enterohepatic recycling	Adequate and ideally it should be ≥five half-lives of the moieties to be measured
United States	*Urinary sampling* Collect urine samples for seven or more half-lives. Blood samples should be drawn at appropriate times to describe the absorption, distribution, and elimination phases of the drug; 12–18 samples, including a pre-dose sample, should be collected per subject per dose; should continue for at least three or more terminal half-lives of the drug	An adequate washout period (e.g., more than five half-lives of the moieties to be measured)
Europe	*Single-dose blood sampling* Sufficient sampling is required; frequent sampling around predicted T_{max}; avoid C_{max} for the first point; accommodate reliable estimate (AUC_{0-t}) covers at least 80% of $AUC_{0-\infty}$; at least three–four points during the terminal log-linear phase; AUC truncated at 72 h (AUC_{0-72h}) may be used as an alternative to AUC_{0-t} or comparison of extent of exposure *Multiple-dose blood sampling* Pre-dose sample should be taken immediately before (within 5 min) dosing, and the last sample is recommended to be taken within 10 min of the nominal time for the dosage interval to ensure an accurate determination of $AUC_{0-\tau}$ *Urinary sampling* Urine should normally be collected over no less than three times the terminal elimination half-life	Sufficient washout period (usually at least five terminal half-lives)
Australia	*Single-dose blood sampling* Should provide adequate estimation of C_{max}; cover plasma concentration time curve long enough to provide a reliable estimation of the extent of absorption; three–four samples during the terminal log-linear phase. AUC truncated at 72 h is permitted for long half-life drugs *Multiple-dose blood sampling* When differences between morning and evening or nightly dosing are known, sampling should be carried out over a full 24-h cycle	Adequate washout period
Canada	*Blood sampling* Sampling should be sufficient to account for at least 80% of the known $AUC_{0-\infty}$, C_{max}, and terminal disposition; three times the terminal half-life of the drug; 12–18 samples should be collected per each subject per dose; four or more points be determined during the terminal log-linear phase *Urine sampling* Urine should be collected over no less than three times the terminal elimination half-life. For a 24-h study, sampling times of 0–2, 2–4, 4–8, 8–12, and 12–24 h are usually appropriate.	Normally should be not less than ten times the mean terminal half-life of the drug. Normally, the interval between study days should not exceed 3–4 weeks
South Africa	*Blood sampling* Sampling should be sufficient to account for at least 80% of the known $AUC_{0-\infty}$, C_{max}; collecting at least three–four samples above the LOQ during the terminal log-linear phase; sampling period is approximately three terminal half-lives of the drug; AUC truncated at 72 h is permitted for long half-life drugs; 12–18 samples should be collected per each subject per dose; at least three–four samples above LOQ should be obtained during the terminal log-linear phase *Urine sampling* Sufficient urine should be collected over an extended period and generally no less than seven times the terminal elimination half-life; for a 24-h study, sampling times of 0–2, 2–4, 4–8, 8–12, and 12–24 h post dose are usually appropriate	Adequate washout period
Korea	*Blood sampling* Sampling should be sufficient to estimate all the required parameters for BA; cover three or more times the terminal half-life; at least two points before T_{max}; sufficient to account for at least 80% of the known $AUC_{0-\infty}$; number of blood samples should be >12; AUC truncated at 72 h is permitted for long half-life drugs *Urine sampling* Adequate number of urine samples should be covered to estimate the amount and excretory rate	Adequate and should be >five times the half-life of the active ingredients

(*Continued*)

TABLE 16.12 (CONTINUED)
Regulatory Criteria on Sampling and Washout Period for Conducting Bioequivalence Studies

Country	Sampling Criteria	Washout Criteria
Saudi Arabia	Sufficient samples are collected to estimate all the required parameters during absorption and elimination for bioequivalence assessment. A sampling period extending to at least four–five terminal elimination half-lives of the drug or four–five the longest half-life of the pertinent analyte (if more than one analyte) is usually sufficient	An adequate washout period (e.g., more than five half-lives of the moieties to be measured)
New Zealand	*Single-dose blood sampling* Sampling should be sufficient to account for at least 80% of the known $AUC_{0-\infty}$; should extend to at least three elimination half-lives of the drug; truncated AUC is undesirable except in unavoidable circumstances like the presence of enterohepatic recycling *Multiple-dose blood sampling* Sampling should be carried out over a full 24-h cycle so that any effects of circadian rhythms may be detected, unless these rhythms can be argued not to have practical significance *Urine sampling* Adequate number of urine samples should be covered to estimate the amount and excretory rate. For a 24-h study, sampling times of 0–2, 2–4, 4–8, 8–12, and 12–24 h are usually appropriate. Where urinary excretion is measured in a single-dose study it is necessary to collect urine for seven or more half-lives	An adequate washout period (at least three times the dominating half-life)

probably of no therapeutic importance whatsoever, which is shown to be statistically significant if error variability is minimal and/or sample size adequately large.

The first case suggests a lack of sensitivity in the analysis and the second an excess of it. Consequently, any practice that increases the variability of the study (sloppy design, assay variability, and within-formulation variability) would reduce the chances of finding a significant difference and hence improve the chances of concluding bioequivalence. The FDA therefore recognized that a finding of no statistical significance in the first case was not necessarily evidence of bioequivalence and consequently asked for a retrospective examination of the power of the test of null hypothesis.

Adequate statistical approaches should be considered to establish the bioequivalence of generic product to that of reference product. Much worldwide discussion and interaction has focused on facilitating the appropriate statistical approaches to establish interchangeability between generic drug and reference drug. The pertinent statistical approaches include (i) study power; (ii) 75/75 rule; and (iii) 90% confidence interval.

Study Power

The conduct of a bioequivalence study should require some prior knowledge of the performance of the products (generic and brand drugs) in the human body so that an appropriate number of test subjects can be enrolled and provide adequate power to test the hypothesis with a reasonable likelihood (i.e., at least 80%) that the two products are indeed bioequivalent. In fact, the alternative hypothesis that two products (generic and brand drugs) are statistically different leads to the conclusion that they are not bioequivalent. The two criteria considered most important to understand are the inherent variability of the drug and the geometric mean ratio between the test and reference product. Both of these parameters can be determined through the conduct of a pilot study (n = 6–12) to determine the proper sample size required for the pivotal study to establish bioequivalence as well as to minimize the possibility of undersizing the study.

75/75 Rule

This approach was the first application wherein individual BE (IBE) was being tested. The biomedical community felt that unless the change in the biological system was greater than 20% to 25%, it would really not pose a significant clinical risk of invalidating the use of one therapeutic strategy vs. another. This formed the basis for the 75/75 rule, which states that two products are equivalent if, and only if, at least 75% of the individuals being tested had ratios (of the various pharmacokinetic parameters obtained from the individual results) between the 75% and 125% limits and the study conducted has the statistical power to detect a 20% difference between the two products. This approach was sound until the arrival of the 90% confidence interval. Later the 75/75 rule lost most of its appeal when it was noted that both the test and reference products each have their own variability, and, therefore, a 90% confidence interval approach was more appropriate for giving some consideration to the differential variability between the test and reference products.

90% Confidence Interval

Westlake was the first to suggest the use of confidence intervals as a BE test to evaluate whether the mean amount of drug absorbed using the test formulation was close to the mean amount absorbed of the reference product. Subsequently, in July 1992, the guidance on *Statistical Procedures for Bioequivalence Studies Using a Standard Two-treatment Crossover Design* was released by the FDA. It was revised

in 2001 and is available as *Statistical Approaches to Establishing Bioequivalence* (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ ucm070244.pdf). This is based primarily on average BE (ABE), wherein the average values for the pharmacokinetic parameters were determined for the test and reference products and compared using a 90% confidence interval for the ratio of the averages using a two one-sided *t*-tests procedure. The ABE approach for BE, however, has limitations for addressing drug switchability, since it focuses only on the comparison of population averages between the test and reference formulations. This concept was really based on the fact that if the ratios of the two pharmacokinetic parameters of clinical interest (such as AUC, C_{max}) are to be compared, each with their own variability which may or may not be randomly distributed, then such a comparison can truly be done only through a confidence interval approach. This concept is well accepted by almost all regulatory authorities to establish the BE.

ACCEPTANCE CRITERIA FOR BIOEQUIVALENCE

An equivalence approach is generally recommended, which usually relies on (i) a criterion to allow the comparison; (ii) a confidence interval for the criterion; and (iii) a bioequivalence limit, to show that two products are equivalent if, and only if, at least 75% Log transformation of exposure measures (C and AUC) of the individuals being tested had ratios (of the various pharmacokinetic parameters obtained from the individual results) between the 75% and 125% limits, and the study conducted has the statistical power to detect a 20% difference between the two products. This approach was sound until the arrival of the 90% confidence interval. Later the 75/75 rule lost most of its appeal when it was noted that both the test and reference products each have their own variability, and, therefore, a 90% confidence interval approach was more appropriate for giving some consideration to the differential and is generally recommended by various regulatory authorities. To compare measures in these studies, data are generally analyzed by using an average bioequivalence criterion with some considerations allowed for special category drugs.

General

To establish bioequivalence, the calculated 90% confidence interval should fall within a bioequivalence limit of 80% to 125% using logarithm-transformed data (adopted since the concentration parameters C_{max} and AUC may or may not be normally distributed). Currently, the bioequivalence limits of 80% to 125% have been applied to almost all drug products by regulatory authorities. More detailed information on acceptance criteria for bioequivalence is given in Table 16.13.

For Highly Variable Drugs

In the context of bioequivalence, HVDs are considered to be drugs and drug products exhibiting intra-subject variability greater than 30% coefficient of variation in the pharmacokinetic measures, AUC, and/or C_{max}. Due to this high variability a large sample size may be needed in BE

TABLE 16.13
Regulatory Acceptance Criteria for Bioequivalence

	90% Confidence Interval on Log-Transformed Data					
	Single-Dose Study			Steady-State Study		
Country	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$	C_{max}	C_{min}	AUC_{τ}
India	80–125	80–125	80–125	80–125	80–125	80–125
Asia	80–125	80–125	80–125	80–125	80–125	80–125
United States	80–125	80–125	80–125	80–125	80–125	80–125
Europe	80–125	80–125	Not applicable	80–125		80–125
Canada	Ratio must be 80–125. Need to pass also on potency corrected data. Add-on studies may be allowed if intra-CV greater than expected	80–125	Not applicable	80–125	80–125	80–125
Australia	80–125	80–125	Not applicable	80–125	80–125	80–125
South Africa	75–133	80–125	Not applicable	75–133	75–133	80–125 (including % swing and % fluctuation)
Russia	75–133	80–125	80–125	75–133	75–133	80–125
Korea	80–125	80–125	80–125	80–125	80–125	80–125
Mexico	80–125	80–125	Not applicable	80–125	80–125	80–125
Saudi Arabia	80–125	80–125	80–125	80–125	80–125	80–125 (including % swing and % fluctuation)
New Zealand	80–125	80–125	80–125	80–125	80–125	80–125

studies to give adequate statistical power to meet FDA BE limits, and thus designing BE studies for HVDs is challenging. Consequently development of generic products for HVDs is a major concern for the generic drugs industry. Major regulatory agencies also considered different approaches for evaluating bioequivalence of highly variable drugs. From 2004 onward the FDA started looking for alternative approaches to resolve this issue and eventually found that replicate crossover design and scaled average BE provides a good approach for evaluating the bioequivalence of highly variable drugs and drug products as it would effectively decrease sample size, without increasing patient risk. Recently the FDA has issued *Method for Statistical Analysis Using the Reference-Scaled Average Bioequivalence Approach for Progesterone Capsules*, which clearly states how to perform statistical analysis for HVDs, such as progesterone, using the replicate crossover design and reference-scaled ABE approach (more information is available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf). The various regulatory agency acceptance criteria for HVDs are given in Table 16.14.

For Narrow Therapeutic Index Drugs (NTIDs)

NTIDs can be defined as drugs that require therapeutic drug concentration or pharmacodynamic monitoring and/or drugs for which drug product labeling indicates a narrow therapeutic range designation. Perhaps tighter restrictions on these drugs would aid in the establishment of truly bioequivalent drug products within this class. Thus, additional testing and controls may be needed to ensure the quality of these drug products. The regulatory acceptance criterion for NTIDs is given in Table 16.14. A list of these drugs is provided in Table 16.15.

THE WORLD HEALTH ORGANIZATION GUIDELINES

The WHO Interchangeability Requirement includes providing a bioequivalence study report that comprises, in the case of multi-source (generic) preparations, a bioequivalence study based on the WHO guidelines. Bioequivalence data are required from all oral preparations except aqueous solutions at the time of administration. Orally or parenterally administered aqueous solutions will be assessed by chemical-pharmaceutical characteristics only. Also, a bioequivalence study is required from preparations indicated for serious conditions requiring assured therapeutic response. All compounds in the present list correspond to this characteristic. Instead of a bioequivalence trial, a comparative clinical trial using clinical or pharmacodynamic endpoints can be presented. These endpoints should be justified and validated for the compound, and the trial should be designed to show equivalence. A trial showing the absence of significant difference cannot be accepted.

The bioequivalence study report should contain at least the following items:

- Description of study design. The most appropriate study type is a two-period randomized crossover study. If other study types were used (e.g., parallel group design), these should be justified by the applicant. In general, a single-dose study with a sufficiently long period for blood samples collection is acceptable.

TABLE 16.14
Regulatory Bioequivalence Acceptance Criteria for Special Class Drugs

	Highly Variable Drugs 90% Confidence Interval Log-Transformed Data		Narrow Therapeutic Index Drugs 90% Confidence Interval Log-Transformed Data	
Country	**C_{max}**	**AUC**	**C_{max}**	**AUC_{0-t}**
Asia	The interval must be prospectively defined, e.g., 0.75–1.33 and justified for addressing in particular any safety or efficacy concerns for patients switched between formulations	In rare cases a wider acceptance range may be acceptable if it is based on sound clinical justification	Acceptance interval may need to be tightened	Acceptance interval may need to be tightened
United States	GMR (80–125) 95% upper bound for $(\mu_T - \mu_R)/\delta^2$ WR # 0.7976 (using scaled average approach)	GMR (80–125) 95% upper bound or $(\mu_T - \mu_R)/\delta^2$ WR # 0.7976 (using scaled average approach)	80–125	80–125
Europe	–	–	90.00–111.11	90.00–111.11
Canada	GMR (80–125)	GMR (80–125) 90% CI (80–125)	–	–
Saudi Arabia	75–133	Wider acceptance range may be acceptable, and this should be justified clinically	90–111	–
Japan	–	–	90.00–111.11	90.00–111.11

TABLE 16.15
Narrow Therapeutic Index Drugs (FDA)

Aminophylline Tablets, ER Tablets	Carbamazepine Tablets, Oral Suspension
Clindamycin Hydrochloride Capsules	Clonidine Hydrochloride Tablets
Clonidine Transdermal Patches	Dyphylline Tablets
Disopyramide Phosphate Capsules, ER Capsules	Ethinyl Estradiol/Progestin Oral Contraceptive Tablets
Guanethidine Sulfate Tablets	Isoetharine Mesylate Inhalation Aerosol
Isoproterenol Sulfate Tablets	Lithium Carbonate Capsules, Tablets, ER Tablets
Metaproterenol Sulfate Tablets	Minoxidil Tablets
Oxtriphylline Tablets, DR Tablets, ER Tablets	Phenytoin, Sodium Capsules (Prompt or Extended), Oral Suspension
Prazosin Hydrochloride Capsules	Primidone Tablets, Oral Suspension
Procainamide Hydrochloride, Capsules, Tablets, ER Tablets	Quinidine Sulfate Capsules, Tablets, ER Tablets
Quinidine Gluconate Tablets, ER Tablets	Theophylline Capsules, ER Capsules, Tablets, ER Tablets
Valproic Acid Capsules, Syrup	Divalproex, Sodium DR Capsules, DR Tablets
Warfarin, Sodium Tablets	

- Information about investigators, study site, study dates.
- Data about preparations used: Manufacturer, place of manufacture, batch number.
- The reference preparation in a bioequivalence study should be a well-known preparation used in most countries of the world. The best acceptable reference is the innovator preparation or product from the WHO list of international comparator products if listed.
- Characterization of study subjects. A bioequivalence study should be normally performed in healthy volunteers. If patients were used, the applicant should justify this. The number of subjects should not be smaller than 12. The study report should contain inclusion and exclusion criteria and listing of demographic data of all subjects.
- Description of study procedures. Administration of test products, meals, times of blood sampling, or urine collection periods should be described in the clinical report.
- Description and validation of drug determination methods in investigated material.
- Analytical method should be validated over the measured drug concentration range. Validation should contain methodology and results of sensitivity, specificity, accuracy, precision, and repeatability determination.
- All measured drug concentrations should be presented.
- Calculation methodology of pharmacokinetic parameters. Non-compartmental analysis is preferred. If modeled parameters were used, these models should be validated for the compound. All measured and calculated pharmacokinetic parameters should be presented in the report.
- Description of statistical methodology and results of statistical calculations. Statistical calculations should be based on the equivalence evaluation. The statistical method of choice is the two one-sided test procedure and the calculation of 90% confidence intervals of the test/reference.
- The main parameters to assess the bioequivalence are area under the plasma concentration–time curve (AUC) and maximum concentrations (C_{max}) ratios.
- The 90% confidence interval for the AUC ratio should lie within a bioequivalence range of 80–125%. In some specific cases of drugs with a narrow therapeutic range the acceptance range may need to be tightened.
- The 90% confidence interval for the C_{max} ratio should lie within a bioequivalence range of 80–125%. In some specific cases of drugs with a narrow therapeutic range the acceptance range may need to be tightened. In certain cases for drugs with an inherently high intra-subject variability, a wider acceptance range (e.g., 75–133%) may be acceptable. The range used must be defined prospectively and should be justified, taking into account safety and efficacy considerations.
- Summary of pharmacology, toxicology, and efficacy of the product. In case of products containing new active ingredients and new combinations of active ingredients, provide full information on safety and efficacy as defined in guidelines by the European Union, the U.S. Food and Drug Administration, or the Japanese Ministry of Health and Welfare.

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17 Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs—General Considerations

I. INTRODUCTION

This FDA guidance provides recommendations to sponsors and/or applicants planning to include bioavailability (BA) and bioequivalence (BE) information for drug products in investigational new drug applications (INDs), new drug applications (NDAs), and NDA supplements (referred to as the NDA BA and BE Draft FDA guidance).[1] This FDA guidance contains advice on how to meet the BA and BE requirements set forth in 21 CFR Part 320 as they apply to dosage forms intended for oral administration.[2] The FDA guidance may also be applicable to non-orally administered drug products when reliance on systemic exposure measures is suitable to document BA and BE (e.g., transdermal delivery systems and certain rectal and nasal drug products).[3] The FDA guidance should be helpful for applicants conducting BA and BE studies during the IND period for an NDA and also for applicants conducting BE studies during the post-approval period for certain changes to drug products that are the subject of an NDA.[4] This FDA guidance document is not intended to provide recommendations on studies conducted in support of demonstrating comparability or biosimilarity for biological products licensed under Section 351 of the Public Health Service Act.[5]

When finalized, this FDA guidance will revise and replace the parts of FDA's March 2003 FDA guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (the March 2003 BA and BE FDA guidance) relating to BA and BE studies for INDs, NDAs, and NDA supplements.[6] Since the March 2003 BA and BE FDA guidance was issued, FDA has determined that providing information on BA and BE studies in separate FDA guidance according to application type will be beneficial to sponsors and applicants. Thus, FDA is issuing this NDA BA and BE Draft FDA guidance and, as previously noted, has issued the ANDA BE Draft FDA guidance for ANDA and ANDA supplements.[7]

We recognize that this FDA guidance cannot address every issue pertaining to the assessment of BA or BE studies for INDs and NDAs, so we suggest sponsors and applicants contact the appropriate review division for FDA guidance on specific questions not addressed by this FDA guidance.

FDA's FDA guidance documents, including this FDA guidance, do not establish legally enforceable responsibilities. Instead, FDA guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency FDA guidance documents means that something is suggested or recommended but not required.

II. BACKGROUND

BA assessment of formulations is a component of new drug development. The approaches of evaluating BA and BE discussed in this FDA guidance are designed to aid FDA evaluation of the safety and effectiveness of a product that is the subject of an IND, NDA, or NDA supplement. In this endeavor, we use the totality of information available in the submission, which includes, among other things, information gathered using the principles of BE, exposure–response evaluations, and clinical trial results. The evaluation of BE in the generic drug context, by contrast, is used to support a determination that a generic product may be substituted for its reference listed drug and involves consideration of different types of data permitted in an ANDA. Accordingly, the approaches discussed in this FDA guidance may differ from similar discussions of BE in the ANDA BE Draft FDA guidance. For example, this NDA BA and BE Draft FDA guidance recommends assessment of the effect of food on BA using the approaches set forth in FDA's 2002 FDA guidance for industry on *Food-Effect Bioavailability and Fed Bioequivalence Studies* (the 2002 Food-Effect FDA guidance). Fasting BE studies generally are sufficient, given the totality of information we consider in evaluating INDs, NDAs, or NDA supplements. In contrast, we recommend in the ANDA BE Draft FDA guidance fed and fasting BE studies that will provide specific information to support a demonstration of BE under Section 505(j) of the FD&C Act and, in turn, to support substitutability. Even though the ANDA BE Draft FDA guidance revises and replaces the parts of the 2002 Food-Effect FDA guidance pertaining to ANDAs and ANDA supplements, this NDA BA and BE Draft FDA guidance does not replace the 2002 Food-Effect FDA guidance relating to studies for INDs, NDAs, and NDA supplements.[8]

A. General

Studies to measure BA and/or establish BE of a product are important elements in support of INDs, NDAs, and NDA supplements. *Bioavailability* means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action [21 CFR

320.1(a)]. BA data provide an estimate of the fraction of the drug absorbed, as well as providing information related to the pharmacokinetics of the drug.

Bioequivalence means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study [21 CFR 320.1(e)]. Studies to establish BE between two products are important for certain formulation or manufacturing changes occurring during the drug development and post-approval stages. In BE studies, the exposure profile of a test drug product is compared to that of a reference drug product.

B. Bioavailability

BA for a given formulation provides an estimate of the relative fraction of the orally administered dose that is absorbed into the systemic circulation. BA for orally administered drug products can be documented by comparing a systemic exposure profile to that of a suitable reference product. A profile can be generated by measuring the concentration of active ingredients and/or active moieties over time and, when appropriate, active metabolites over time in samples collected from the systemic circulation. Systemic exposure profiles reflect both release of the drug substance from the drug product and a series of possible pre-systemic/systemic actions on the drug substance after its release from the drug product.

FDA's regulations at 21 CFR 320.25 set forth guidelines for in vivo BA studies. As provided in this regulation, the reference product for BA studies should be a solution, suspension, or intravenous (IV) dosage form [21 CFR 320.25(d)(2) and (3)]. The purpose of conducting a BA study with an oral solution as a reference is to assess the impact of formulation on BA. Conducting a BA study with an IV reference enables assessment of the impact of route of administration on BA and defines the absolute BA of the drug released from the drug product.

C. Bioequivalence

As noted previously, both BA and BE focus on the release of a drug substance from a drug product and subsequent absorption into systemic circulation. As a result, we recommend that approaches to determining BE generally follow approaches similar to those used for BA. Demonstrating BE involves a more formal comparative test that uses specific references with specified criteria for comparisons and predetermined BE limits for such criteria.

1. Preapproval Changes

BE documentation can be useful during the IND period to compare (1) early and late clinical trial formulations; (2) formulations used in clinical trials and stability studies, if different; (3) clinical trial formulations and to-be-marketed drug products, if different; and (4) product strength equivalence, as appropriate. In each comparison, the new formulation, formulation produced by the new method of manufacture, or new strength is the candidate or test product, and the prior formulation, prior method of manufacture, or prior strength is the reference product. The decision to document BE during drug development is generally left to the judgment of the sponsor, using the principles of relevant FDA guidance (in this FDA guidance, see Sections II.C.2, Post-Approval Changes, and III.D, In Vitro Studies) to determine when changes in components, composition, and/or method of manufacture suggest that further in vitro and/or in vivo studies be performed.

2. Post-Approval Changes

In the presence of certain major changes in components, composition, manufacturing site, and/or method of manufacture after approval, FDA recommends that in vivo BE be demonstrated for the drug product after the change in comparison to the drug product before the change. Under Section 506A(c)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 U.S.C. 356a(c)(2)], certain post-approval changes that require completion of studies must be submitted in a supplement and approved by FDA before distributing a drug product made with the change.

Information on the types of recommended in vitro dissolution and in vivo BE studies for immediate-release and modified-release drug products approved as NDAs for specified post-approval changes is provided in the following FDA guidance*:*

- *SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Control; In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*
- *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*

3. BE Considerations

BE studies are usually conducted using a crossover design. For such studies, intrasubject variability should be considered when determining the study sample size. In cases when a parallel design is necessary to evaluate BE, consideration should be given to total variability, including inter-subject variability instead of just intrasubject variability.

A test product might fail to demonstrate bioequivalence because it has measures of rate and/or extent of absorption compared to the reference product outside acceptable higher or lower limits. For example, when the test product results in a systemic exposure that is significantly higher than that of the reference product, the concern is the typically limited experience from a safety standpoint for higher systemic concentrations. When the test product has a systemic exposure that is significantly lower than that of the reference product, the concern is potentially a lack of therapeutic efficacy of the test product.

When the variability of the test product is greater than the reference product, the concern relates to both safety and efficacy, because it may suggest that the performance of the test product is not comparable to the reference product, and the test product may be too variable to be clinically useful.

When BE is not demonstrated, the sponsor should demonstrate that the differences in rate and extent of absorption do not significantly affect the safety and efficacy based on available dose–response or concentration–response data. In the absence of this evidence, failure to demonstrate BE may suggest that the test product should be reformulated, or the method of manufacture for the test product should be changed, or additional safety or efficacy data may be needed for the test product. In some cases, conclusions of BE based on the peak drug concentration (C_{max}) and area under the plasma concentration–time curve (AUC) between the test product and the reference product may be insufficient to demonstrate that there is no difference in safety or efficacy if the systemic concentration–time profiles of the test product and the reference product are different [e.g., time to reach peak drug concentration (T_{max}) is different]. For example, differences in the shape of the systemic concentration profile between the test and reference products could imply that the test product may not produce the same clinical response as the reference product. In such cases, additional data analysis (e.g., partial AUCs), exposure–response evaluation, or clinical studies may be recommended to evaluate the BE of the two products.

III. METHODS TO DOCUMENT BA AND BE

Under FDA's regulations, applicants must use the most accurate, sensitive, and reproducible method available to demonstrate BA or BE of a product [21 CFR 320.24(a)]. As noted in 21 CFR 320.24, several in vivo and in vitro methods can be used to measure BA and to establish BE. These include, in general order of preference, pharmacokinetic (PK) studies, in vitro tests predictive of human in vivo BA (in vitro–in vivo correlation), pharmacodynamic (PD) studies, studies with clinical benefit endpoints, and other in vitro studies. In addition, where in vivo data are appropriate to demonstrate BA, our regulations provide guidelines on specific types of in vivo BA studies (see 21 CFR 320.25 through 320.29). This FDA guidance predominantly focuses on the use of PK studies to document BA or BE.

A. Pharmacokinetic Studies

1. General Considerations

FDA's regulations generally define BA and BE in terms of rate and extent of absorption of the active ingredient or moiety to the site of action.[9] For in vivo studies, the regulations also provide for use of PK measures in an accessible biological matrix such as blood, plasma, and/or serum to indicate release of the drug substance from the drug product into the systemic circulation.[10] BA and BE frequently rely on PK measures such as AUC to assess extent of systemic exposure and C_{max} and T_{max} to assess rate of systemic absorption. PK-based comparisons to describe relative BA or make BE determinations are predicated on an understanding that measuring the active moiety or ingredient at the site of action is generally not possible and on an assumption that some relationship exists between the efficacy/safety and concentration of the active moiety and/or its important metabolite(s) in the systemic circulation. A typical study is conducted as a crossover study. The crossover design reduces variability caused by patient-specific factors, thereby increasing the ability to discern differences because of formulation.

2. Pilot Study

If the sponsor chooses, a pilot study in a small number of subjects can be carried out before proceeding with a full-scale BA or BE study. The pilot study can be used to validate analytical methodology, assess PK variability, determine sample size to achieve adequate power, optimize sample collection time intervals, and determine the length of the washout period needed between treatments. For example, for conventional immediate-release products, careful timing of initial samples may avoid a subsequent finding in a full-scale study that the first sample collection occurs after the C_{max}. For modified-release products, a pilot study can help determine the sampling schedule needed to assess lag time and dose dumping. The results of a pilot study can be used as the sole basis to document BA or BE provided the study's design and execution are suitable and a sufficient number of subjects have completed the study.

3. Full-Scale Study

General recommendations for a standard BA or BE study based on PK measurements are provided in Appendix A. Non-replicate crossover study designs are recommended for BA and BE studies of immediate-release and modified-release dosage forms. However, sponsors and/or applicants have the option of using replicate designs for BE studies.

Replicate crossover designs are used to allow estimation of (1) within-subject variance for the reference product or for both the test and reference products, and (2) the subject by formulation interaction variance component. This design accounts for the inter- occasion variability that may confound the interpretation of a BE study as compared to a non-replicate crossover approach. The recommended method of analysis for non-replicate or replicate studies to evaluate BE is average BE, as discussed in Section IV. Recommendations for conducting and evaluating replicate study designs can be found in the FDA guidance for industry *Statistical Approaches to Establishing Bioequivalence.*

4. Study Population

Subjects recruited for BA or BE studies should be 18 years of age or older and capable of giving informed consent. In general, BA and BE studies should be conducted in healthy volunteers if the product can be safely administered to this population. A study in healthy volunteers is likely to produce less PK variability compared with that in patients with potentially confounding factors such as underlying and/

or concomitant disease and concomitant medications. Male and female subjects should be enrolled in BA and BE studies unless there is a specific reason to exclude one sex. Such exclusions could be related to the drug product being indicated in only one sex or a greater potential for adverse reactions in one sex compared to the other. For example, oral contraceptives are evaluated in female subjects because the indication is specific to females. If a drug has the potential to be a teratogen, the drug product should be evaluated in male subjects.

Female subjects enrolled in the study should not be pregnant at the beginning of the study and should not become pregnant during the study. In some instances (e.g., when safety considerations preclude use of healthy subjects), it may be necessary to evaluate BA and BE in patients for whom the drug product is intended. In this situation, sponsors and/or applicants should attempt to enroll patients whose disease process is expected to be stable for the duration of the study.

5. Single-Dose and Multiple-Dose (Steady-State) Testing

This FDA guidance generally recommends single-dose PK studies to assess BA and BE because they are generally more sensitive than steady-state studies in assessing rate and extent of release of the drug substance from the drug product into the systemic circulation.

FDA's regulations at 21 CFR 320.27 provide guidelines on the design of a multiple-dose in vivo BA study. This regulation also identifies instances in which multiple-dose BA studies may be required:

i. There is a difference in the rate of absorption but not in the extent of absorption.
ii. There is excessive variability in bioavailability from subject to subject.
iii. The concentration of the active drug ingredient or therapeutic moiety, or its metabolite(s), in the blood resulting from a single dose is too low for accurate determination by the analytical method.
iv. The drug product is an extended-release dosage form.[11]

We recommend that if a multiple-dose study design is performed, appropriate dosage administration and sampling be carried out to document attainment of steady state.

6. Bioanalytical Methodology

We recommend that sponsors ensure that bioanalytical methods for BA and BE studies be accurate, precise, specific, sensitive, and reproducible. A separate FDA guidance, *Bioanalytical Method Validation*, is available to assist sponsors in validating bioanalytical methods.[12]

7. Administration Under Fasted/Fed Conditions

The BA or BE study should be conducted under fasting conditions (after an overnight fast of at least 10 hours) except when tolerability issues are anticipated with fasting. In these cases, we recommend that applicants conduct only a fed study. A separate FDA guidance, *Food-Effect Bioavailability and Fed Bioequivalence Studies*, is available to assist sponsors.

8. Moieties to Be Measured

The active ingredient that is released from the dosage form or its active moiety and, when appropriate, its active metabolites[13] should be measured in biological fluids collected in BA studies.

Measurement of the active ingredient or the active moiety, rather than metabolites, is generally recommended for BE studies because the concentration–time profile of the active ingredient or the active moiety is more sensitive to changes in formulation performance than that of the metabolite, which is more reflective of metabolite formation, distribution, and elimination. The following are instances when an active metabolite(s) should be measured.

- Measurement of a metabolite(s) is necessary when the active ingredient or the active moiety concentrations are too low to allow reliable analytical measurement in blood, plasma, or serum. In this case, the metabolite should be measured in lieu of the active ingredient or active moiety. We recommend that the confidence interval approach be applied to the metabolite data obtained from these studies.
- Measurement of a metabolite(s) is necessary in addition to the active ingredient or active moiety if the metabolite is formed by pre-systemic metabolism and contributes meaningfully to efficacy and/or safety. The confidence interval approach should be used for all moieties measured. However, the BE criteria are only generally applied to the active ingredient or active moiety. Sponsors should contact the appropriate review division to determine which moieties should be measured.

9. Pharmacokinetic Measures of Systemic Exposure

This FDA guidance recommends that systemic exposure measures be used to evaluate BA and BE. Exposure measures are defined relative to peak, partial, and total portions of the plasma, serum, or blood concentration–time profile, as described here:

- Peak Exposure

We recommend that peak exposure be assessed by measuring the C_{max} obtained directly from the systemic drug concentration data without interpolation. The T_{max} can provide important information about the rate of absorption. The first point of a concentration– time curve based on blood and/or plasma measurements is sometimes the highest concentration, which raises a question about the measurement of true C_{max} because of insufficient early sampling times. A carefully conducted pilot study may help to avoid this problem. Collection of an early time point between 5 and 15 minutes after dosing followed by additional sample collections (e.g., two to five) in the first hour after dosing may be sufficient to assess early peak

concentrations. If this sampling approach is followed, we consider the data to be adequate, even when the highest observed concentration occurs at the first time point.

- Total Exposure (Extent of Absorption)

For single-dose studies, we recommend that the measurement of total exposure be:

- Area under the plasma, serum, or blood concentration time curve from time zero to time t (AUC_{0-t}), where t is the last time point with a measurable concentration.
- Area under the plasma, serum, or blood concentration time curve from time zero to time infinity ($AUC_{0-\infty}$), where $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$. C_t is the last measurable drug concentration, and λ_z is the terminal or elimination rate constant calculated according to an appropriate method.
- For drugs with a long half-life, truncated AUC can be used (see Section VII.D, Long-Half-Life Drugs).

For steady-state studies, we recommend that the measurement of total exposure be the area under the plasma, serum, or blood concentration–time curve from time zero to time tau over a dosing interval at steady state ($AUC_{0-\tau}$), where tau is the length of the dosing interval.

- Partial Exposure

For orally administered drug products, BA and BE can generally be demonstrated by measurements of peak and total exposure. For certain classes of drugs and under certain circumstances (e.g., to assess onset of an analgesic effect), an evaluation of the partial exposure could be used to support the performance of different formulations by providing further evidence of therapeutic effect. This FDA guidance recommends the use of partial AUC as a partial exposure measure. The time to truncate the partial area should be related to a clinically relevant PD measure. We also recommend that sufficient quantifiable samples be collected to allow adequate estimation of the partial area. For questions on the suitability of the PD measure or use of partial exposure in general, we recommend that sponsors and/or applicants consult the appropriate review division.

10. Comparison of PK Measures in BE Studies

An equivalence approach is recommended for BE comparisons. The recommended approach relies on (1) a criterion to allow the comparison, (2) a confidence interval for the criterion, and (3) a BE limit. Log-transformation of exposure measures before statistical analysis is recommended. This FDA guidance recommends use of an average BE criterion to compare systemic exposure measures for replicate and non-replicate BE studies of both immediate- and modified-release products. For additional information on data analysis, refer to Appendix A and to the FDA guidance for industry on *Statistical Approaches to Establishing Bioequivalence.*

B. Other Approaches to Support BA/BE

In certain circumstances, other approaches are recommended to support a demonstration of BA/BE. Below are some general considerations regarding these other approaches. Sponsors should consult FDA's guidance for industry for additional information on these methods as well.[14]

1. In Vitro Tests Predictive of Human In Vivo BA

In vitro–in vivo correlation (IVIVC) is an approach to describe the relationship between an in vitro attribute of a dosage form (e.g., the rate or extent of drug release) and a relevant in vivo response (e.g., plasma drug concentration or amount of drug absorbed). This model relationship facilitates the rational development and evaluation of extended-release dosage forms. Once an IVIVC is validated, the in vitro test serves as a surrogate for BA and/or BE testing, as well as a tool for formulation screening and setting of the dissolution/drug-release acceptance criteria.

Specifically, in vitro dissolution/drug-release characterization is encouraged for all extended-release product formulations investigated (including prototype formulations), particularly if in vivo absorption characteristics are being defined for the different product formulations. Such efforts may enable the establishment of an IVIVC. When an IVIVC or association is established [21 CFR 320.24(b)(1)(ii)], the in vitro test can serve not only as a quality control specification for the manufacturing process but also as an indicator of how the product will perform in vivo.

Additional information on the development and validation of an IVIVC can be found in the FDA guidance for industry *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations*.

2. Pharmacodynamic Studies

PD studies are not recommended for orally administered drug products when the drug is absorbed into systemic circulation and a PK approach can be used to assess systemic exposure and evaluate BA or BE. PK endpoints are preferred because they are generally the most accurate, sensitive, and reproducible approach. However, in instances where a PK endpoint is not possible, a well- justified PD endpoint can be used to demonstrate BA or BE.

3. Comparative Clinical Studies

Clinical endpoints can be used in limited circumstances, for example, for orally administered drug products when the measurement of the active ingredients or active moieties in an accessible biological fluid (PK approach) or PD approach is not possible. Because these circumstances do not occur very often, use of this approach is expected to be rare.

4. In Vitro Studies

Under certain circumstances, BA and BE can be evaluated using in vitro approaches (e.g., dissolution/drug-release testing) during the preapproval and post-approval phases [see 21 CFR 320.24(b)(5) and (6)]. For example, for orally

administered drugs that are highly soluble and highly permeable, and for which the drug product is rapidly dissolving, documentation of BE using an in vitro approach (dissolution/drug-release studies) may be appropriate based on the Biopharmaceutics Classification System.[15]

The following FDA guidance documents provide recommendations on the development of dissolution methodology, setting specifications, and the regulatory applications of dissolution testing:

- *Dissolution Testing of Immediate-Release Solid Oral Dosage Forms*
- *Extended-Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations*

In addition, we recommend that sponsors consult other FDA guidance for additional information on when in vitro data may be appropriate to demonstrate BA or BE of a product.

IV. DOCUMENTING BA AND BE FOR VARIOUS DOSAGE FORMS

This section summarizes the recommendations for documenting BA and BE studies based on the specific dosage forms and whether these evaluations occur preapproval or post-approval.

A. Solutions and Other Solubilized Dosage Forms

For oral solutions, elixirs, syrups, tinctures, or other solubilized forms, in vivo BA and/or BE are generally self-evident, and a requirement of in vivo data for a product may be waived [21 CFR 320.22(b)(3)]. In such instances, the applicant would be deemed to have complied with and fulfilled any requirement for in vivo data.[16] Although a comparative study is not necessary, characterization of the pharmacokinetics of the drug is required [21 CFR 314.50(d)(3)]. In addition, in vivo BE studies that compare different solution formulations are waived based on the assumptions that release of drug substance from the drug product is self-evident and that the solutions do not contain any excipients that significantly affect drug absorption. However, there are certain excipients that may alter the BA (e.g., sorbitol may reduce the BA of drugs, and vitamin E may enhance the BA) in amounts sometimes used in oral liquid dosage forms. In this case, evaluation of in vivo BA and/or BE may be required.

B. Immediate-Release Products

Included in this discussion are capsules, tablets (including conventional, buccal, chewable, orally disintegrating, and sublingual dosage forms), and suspensions.

1. Preapproval Changes

For BA and BE studies, we recommend a single-dose, fasting study be performed. Under certain circumstances, multiple-dose BA studies (see Section III.A.5) and/or food-effect studies may be necessary (see the FDA guidance for industry *Food-Effect Bioavailability and Fed Bioequivalence).* Unconventional dosage forms (buccal, chewable, orally disintegrating, and sublingual dosage forms) should be administered according to intended label use/instructions. In addition, a BA study may be needed with the unconventional dosage form swallowed intact to assess the impact of accidental swallowing of the intact product. Sampling should adequately capture the T_{max} and C_{max} in addition to total exposure.

We recommend that in vitro dissolution be evaluated for all orally administered products. In vitro dissolution test conditions could be the same or different for unconventional compared to conventional dosage forms. If differences in dissolution data exist, they should be discussed with the appropriate review division.

2. Post-Approval Changes

Information on the types of in vitro dissolution and in vivo BE studies needed for approved immediate-release drug products when post-approval changes are made is provided in an FDA guidance for industry entitled *SUPAC-IR: Immediate Release Solid Oral Dosage Forms Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*. We recommend that for post-approval changes, the in vitro or in vivo comparison be made between the post-change and pre-change products.

C. Modified-Release Products

Modified-release (MR) products include extended-release (controlled-release, sustained- release)[17] and delayed-release products.

Extended-release (ER) products are dosage forms that are designed to extend or prolong the release of active ingredient or active moiety from the drug product and may allow a reduction in dosing frequency as compared to when the drug is administered in an immediate-release (IR) dosage form. These drug products can be developed to reduce fluctuations in plasma concentrations when compared to an IR product. ER products can be capsules, tablets, granules, pellets, or suspensions.

Delayed-release (DR) drug products are dosage forms that release active ingredient or active moiety at a time later than immediately after administration (i.e., these drug products exhibit a lag time in quantifiable plasma concentrations). Typically, coatings (e.g., enteric coatings) are used to delay the release of the drug substance until the dosage form has passed through the acidic medium of the stomach. Generally, DR products are treated as IR products. However, if the DR product has complex release characteristics, the relevant review division should be contacted for additional FDA guidance.

If the drug product is an ER product, the following recommendations apply.

1. Preapproval: BA and BE Studies

FDA's regulations at 21 CFR 320.25(f) address the purpose of a BA study for an extended-release product, which is to determine if certain delineated conditions are met.[18] This regulation

also provides that "the reference material(s) for such a bioavailability study shall be chosen to permit an appropriate scientific evaluation of the extended release claims made for the drug product."[19] Appropriate reference products may include

> (1) a solution or suspension of the active drug ingredient or therapeutic moiety, (2) a currently marketed non-controlled-release drug product containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling of the non-controlled release drug product, and (3) a currently marketed ER drug product subject to an approved full NDA containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling of currently marketed ER product.[20]

In general, the PK profile of the ER product may not match that of the approved IR product (e.g., T_{max} is different) or, in some cases, to another ER product. In such a case, establishing similar PK profiles using C_{max} and AUC may not be sufficient to show that the ER product is bioequivalent to the IR product. Thus, additional safety or efficacy studies or PK/PD assessments may be recommended. This FDA guidance recommends that the following BA studies and food-effect BA studies be conducted for an ER drug product submitted as an NDA for the scenarios described below:

New ER formulation comparison to an already approved IR product

- For drugs with linear pharmacokinetics over the therapeutic dose range: A fasting study should be conducted comparing the ER product administered as a single dose at the highest strength to the IR reference administered over the least common time interval to achieve equivalent total dose as for the ER product.[21] If for safety reasons the highest strength cannot be used, a lower strength may be acceptable.
- For drugs with nonlinear pharmacokinetics over the therapeutic dose range: At a minimum, a single dose of the highest and lowest strengths of the ER product should be compared to their corresponding IR references administered over the ER dosing interval. If the relative BA of intermediate ER strengths cannot be inferred based on the above studies, a single-dose fasting study for the intermediate strength(s) of the ER product should be compared to the corresponding IR reference administered over the ER dosing interval.
- When the ER strengths are not proportionally similar in composition, a single-dose fasting dosage strength equivalence assessment study[22] or a dosage strength proportionality study[23] for the ER product should be conducted.
- A single-dose food-effect study should be conducted on the highest ER strength (see the 2002 Food-Effect FDA guidance).
- A steady-state study should be conducted on the highest strength of the ER product compared to an approved IR reference dosed to achieve equivalent total dose as for the ER product.

New ER product (ER_{new}) comparison to an approved ER product (ER_{old}) with a different dosing interval (i.e., where ER_{new} and ER_{old} have unequal dosing intervals)

- The recommendations are the same as outlined in the previous section (development of a new ER formulation given an already approved IR product) except for the choice of the reference product. In this case, the reference product could be either the approved ER_{old} or IR product.

New ER product (ER_{new}) comparison to an approved ER product (ER_{old}) with the same dosing interval

- A single-dose fasting BE study on the highest strength of the ER_{new} product compared to the ER_{old} product. If ER_{new} and ER_{old} are of different strength, then comparison of ER_{new} vs. ER_{old} should be made based on dose using the highest strengths.
- A single-dose, food-effect study should be conducted on the highest ER_{new} strength.
- When the ER_{new} strengths are not proportionally similar in composition, a single-dose fasting dosage strength equivalence assessment study or a dosage strength proportionality study[24] for the ER_{new} product should be conducted.
- In some cases, BE between the new and old ER products may not be sufficient to ensure that there is no difference in safety or efficacy if the PK profiles of the two ER products do not match (e.g., T_{max} is different). Additional data analysis or clinical studies may be needed to ensure that the two products are clinically equivalent.

2. Post-Approval Changes

Information on the types of in vitro dissolution and in vivo BE studies for ER drug products approved in the presence of specific post-approval changes are provided in an FDA guidance for industry *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*. We recommend that for post-approval changes, the in vitro or in vivo comparison be made between the post-change and pre-change products.

D. Batch Size

For pivotal BE studies, the test batch should be representative of the production batches. Therefore, the size of the test batch should be at least 10% of the planned production batch size or a minimum of 100,000 units, whichever is larger.

V. ADDITIONAL INFORMATION ON IN VITRO APPROACHES

A. In Vitro Studies Conducted in Support of a Waiver of an In Vivo BA or BE Data Requirement

As discussed above, FDA's regulations contemplate that if in vivo BA or BE data are required for a product, a sponsor may seek a waiver of that requirement under certain circumstances.[25]

For example, in some instances, in vivo BA or BE is self-evident based on certain characteristics of the drug product [21 CFR 320.22(b)], and therefore, any in vivo data requirement has been deemed to have been met. In other delineated circumstances, an in vivo BA or BE data requirement may be waived, and in vitro data may be accepted in lieu of in vivo data [21 CFR 320.22(d)]. For example, an in vivo data requirement may be waived for different strengths of an immediate-release drug product under 21 CFR 320.22(d)(2) when (1) the drug product is in the same dosage form, but in a different strength; (2) this different strength is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval; and (3) the new strength meets an appropriate in vitro test as outlined in the regulation.[26] In addition, for waiving higher strengths, linearity of the pharmacokinetics over the therapeutic dose range should be demonstrated.

This FDA guidance defines *proportionally similar* in the following ways:

- All active and inactive ingredients are in exactly the same proportion between different strengths (e.g., a tablet of 50-mg strength has all the inactive ingredients, at exactly half the quantities of a tablet of 100-mg strength and twice those of a tablet of 25-mg strength).
- For high-potency drug substances (where the amount of active drug substance in the dosage form is relatively low), (1) the total weight of the dosage form remains nearly the same for all strengths (within ±10 % of the total weight of the strength on which a BE was performed), (2) the same inactive ingredients are used for all strengths, and (3) the change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients.
- Bilayer tablets are considered to be one formulation even though they consist of two separate layers with different compositions. In assessing the proportional similarity of the different strengths, all components of both layers should be proportionally similar. The fact that only one layer is proportionally similar and the other is not clearly indicates that the products (whole tablet) are not proportionally similar. This is relevant because there can be interactions between the different tablet layers, which can differ across different strengths because of the different size of the layers and the varying amounts of excipients present in each layer.

Exceptions to the above definitions may be possible if adequate justification is provided and discussed with the appropriate review division.

B. In Vitro Studies Conducted in Support of Demonstrating BA or BE

FDA may determine that in vitro data are the most accurate, sensitive, and reproducible method to demonstrate BA or BE in other contexts [21 CFR 320.24(b)(5) and (6)].[27] Below we provide additional FDA guidance on the conduct of such studies.

1. Immediate-Release Formulations (Capsules, Tablets, and Suspensions)

In vitro data can be used to compare formulations of drug products under certain circumstances. If an applicant seeks to demonstrate the BA or BE of immediate-release formulations for capsules, tablets, and suspensions using in vitro data, FDA recommends that sponsors generate dissolution profiles for all strengths using an appropriate dissolution method. If the dissolution results indicate that the dissolution characteristics of the product are not dependent on the pH and product strength, dissolution profiles in one medium are usually sufficient to support demonstrating BE. Otherwise, dissolution data in at least three media (e.g., pH 1.2, 4.5, and 6.8) are recommended. The f_2 test should be used to compare profiles from the different strengths of the product (see FDA guidance for industry, *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*). An f_2 value $\geq$50 indicates a sufficiently similar dissolution profile to support a biowaiver. For an f_2 value <50, discussion with the appropriate review division is recommended to determine whether an in vivo study is needed. The f_2 approach is not suitable for rapidly dissolving drug products (e.g., $\geq$85% dissolved in 15 minutes or less).

- *Over-Encapsulation of Clinical Trial Formulations*

During the course of drug development, sponsors sometimes have to blind the formulations that they use in the clinical trials. In certain situations, the only difference between the to-be-marketed and clinical trial formulations is that the dosage form is put into a capsule. This over-encapsulation is done mainly for blinding purposes. It may be possible to support bioequivalence of the to-be-marketed and clinical trial formulations using in vitro data only, provided that no other excipients are added to the capsule and the dissolution profiles are comparable in three media: pH 1.2, pH 4.5, and pH 6.8.

- *Scale-up and Post-Approval Changes*

Certain formulation changes in components and composition, scale-up, manufacturing site, manufacturing process, or equipment can be made post-approval. Depending on the possible impact of the manufacturing change on the release of the active ingredient from the formulation and its BA, certain manufacturing changes for IR products can be approved based solely on similarity of the dissolution profiles between

the post-change and pre-change formulations. Information on recommendations for using in vitro dissolution and in vivo BE studies for immediate-release drug products in such circumstances is provided in FDA's FDA guidance for industry on *SUPAC IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*. The same principles described in the FDA guidance can be applied to preapproval changes in which the to-be-marketed formulation differs from the clinical trial formulation.

2. Modified-Release Formulations

The use of in vitro data may be acceptable for modified-release drug products for which specific post-approval changes are sought. This use of data are delineated in the FDA guidance for industry *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*. The same principles described in the FDA guidance may also apply to preapproval changes. Additional considerations for use of in vitro data are described below.

- *Beaded Capsules: Lower/Higher Strength*

For ER beaded capsules where the strength differs only in the number of beads containing the active moiety, a single-dose, fasting BA or BE study, as appropriate, should be carried out on the highest strength. In vivo BA or BE of one or more lower strengths can be demonstrated based on dissolution profile comparisons, with an in vivo BA or BE study only on the highest strength (unless safety reasons preclude the administration of the highest strength to healthy volunteers). The dissolution profiles for each strength should be generated using the recommended dissolution method. If the dissolution method has not been finalized, dissolution profiles should be generated in at least three media (e.g., pH 1.2, 4.5, and 6.8). In vivo BE studies for higher strengths may not be necessary based on (1) clinical safety and/or efficacy data on the proposed dose and the need for the higher strength, (2) linearity of pharmacokinetics over the therapeutic dose range, and (3) the same dissolution procedures being used for all strengths with similar dissolution results. The f_2 test can be used to demonstrate similar profiles among the different strengths of the product.

- *MR Dosage Forms: Lower Strength*

For MR dosage forms, when the drug product is in the same dosage form but in a different strength and when (1) the drug exhibits linear pharmacokinetics, (2) the various strengths are proportionally similar in their active and inactive ingredients,[28] and (3) the drug-release mechanism is the same, an in vivo BA or BE determination of one or more lower strengths can be demonstrated based on dissolution profile comparisons, with an in vivo BA or BE study only on the highest strength. The dissolution profiles for each strength should be generated using the recommended dissolution method. If the dissolution method has not been finalized, dissolution profiles should be generated in at least three media (e.g., pH 1.2, pH 4.5, and pH 6.8). The dissolution profile should be generated on the test and reference products of all strengths using the same dissolution test conditions.

VI. SPECIAL TOPICS

A. Alcoholic Beverage Effects on MR Drug Products

The consumption of alcoholic beverages may affect the release of a drug substance from an MR formulation. The formulation may lose its MR characteristics, leading to more rapid drug release and altered systemic exposure. This more rapid drug release may have deleterious effects on the drug's safety and/or efficacy.

In vitro assessments of the drug release from the drug product using media with various alcohol concentrations should be conducted. Based on the results of the in vitro assessments, an in vivo BA study of the drug product when administered with alcohol may be needed.

B. Enantiomers vs. Racemates

During development of a racemic drug product, the racemate should be measured in BA studies. It may also be important to measure the individual enantiomers of the racemate to characterize the pharmacokinetics of the enantiomers. For the development of a specific enantiomer, chiral inversion should be assessed.

Measurement of the racemate using an achiral assay is recommended for BE studies. Measurement of individual enantiomers in BE studies is recommended only when all of the following conditions are met: (1) the enantiomers exhibit different PD characteristics, (2) the enantiomers exhibit different PK characteristics, (3) primary efficacy and safety activity resides with the minor enantiomer, and (4) nonlinear absorption is present (as expressed by a change in the enantiomer concentration ratio with change in the input rate of the drug) for at least one of the enantiomers. In such cases, we recommend that BE criteria be applied to the enantiomers separately.

C. Drug Products with Complex Mixtures as the Active Ingredients

Certain drug products may contain complex drug substances (i.e., active moieties or active ingredients that are mixtures of multiple synthetic and/or natural source components). Some or all of the components of these complex drug substances may not be fully characterized with regard to chemical structure and/or biological activity. Quantification of all active or potentially active components in BA and BE studies may not be possible. In such cases, we recommend that BA and BE studies be based on a select number of components.

Criteria for component selection typically include the amount of the moiety in the dosage form, plasma or blood levels of the moiety, and biological activity of the moiety. When PK approaches are infeasible to assess rate and extent of absorption of a drug substance from a drug product, PD, clinical, or in vitro approaches may be appropriate.

D. Long-Half-Life Drugs

In a BA or PK study involving an IR oral product with a long half-life (≥24 hours), adequate characterization of the half-life should include blood sampling over a long period of time. For BA or BE determination of a drug product containing a drug with a long half-life, a non-replicate, single-dose, crossover study can be conducted, provided an adequate washout period is used. If the crossover study is problematic, a study with a parallel design can be used. For either a crossover or parallel study, we recommend that the sample collection time be adequate to ensure completion of gastrointestinal transit (approximately 2 to 3 days) of the drug product and absorption of the drug substance. C_{max} and a suitably truncated AUC can be used to characterize peak and total drug exposure, respectively. For drugs that demonstrate low intrasubject variability in distribution and clearance, a truncated AUC (e.g., $AUC_{0-72\,hr}$) can be used in place of AUC_{0-t} or $AUC_{0-\infty}$. For drugs that demonstrate high intrasubject variability in distribution and clearance, AUC truncation should not be used. In such cases, we recommend that sponsors and/or applicants consult the appropriate review division.

E. Orally Administered Drugs Intended for Local Action

Documentation of BA and BE when the drug substance produces its effects by local action in the gastrointestinal tract can be achieved either by using pharmacokinetics, an acceptable PD end point, clinical efficacy and safety studies, and/or suitably designed and validated in vitro studies, as appropriate. For such cases, we recommend that sponsors and/or applicants consult the appropriate review division. Additional safety studies may also be recommended to characterize the local safety of the product. The in vitro studies should reflect important clinical effects or should be more sensitive to changes in product performance compared to a clinical study. To ensure comparable safety, additional studies with and without food may help in understanding the degree of systemic exposure that occurs following administration of a drug product intended for local action in the gastrointestinal tract.

F. Combination/Co-administered Drug Products

Two or more active ingredients can be formulated as a single drug product, which is referred to as a combination drug product. Generally, the purpose of an in vivo BA study involving a combination drug product is to compare the rate and extent of absorption of each active drug ingredient or therapeutic moiety in the combination drug product to the rate and extent of absorption of each active drug ingredient or therapeutic moiety administered concurrently in separate single-ingredient preparations [21 CFR 320.25(g)].

For the purpose of defining BA or determining BE when required, this FDA guidance recommends that the following studies be conducted for a combination drug product:

- A two-treatment, single-dose, fasting study of the combination drug product versus single-ingredient drug products administered concurrently as a single treatment or an approved combination product containing the same active ingredients. This study should use the highest strength of the combination product with matching doses of individual drug products.
- Certain alternative study designs may also be acceptable depending on the specific situation. For instance, in the case of a combination product consisting of two components, a three-treatment study design comparing the combination drug product vs. single-ingredient drug products administered separately may be appropriate.
- A single-dose, food-effect study on the combination drug product.

BE studies for the combination product should include the measurement of systemic concentrations of each active ingredient. The confidence interval approach should be applied to each measured entity of the combination drug product and its reference product.

In specific cases, drug products are given in combination (not co-formulated) with the objective of increasing the exposure of one of the drugs (subject drug). The second drug is not intended to have a therapeutic effect and is given only to increase the systemic exposure of the subject drug. When both the subject and second drug are new molecular entities, the BA of each should be assessed separately. If a BE study is needed for the subject drug for any reason, the subject drug should be administered with the second drug for both test and reference products. The corresponding PK results, including confidence intervals for BE criteria, should be applied to the subject drug. It is not necessary to measure the concentrations of the second drug. BE studies that are needed for the second drug should be conducted only with the second drug; the subject drug is not dosed with the second drug. When the combination includes a new molecular entity and an approved product, only the BA of the new molecular entity should be assessed. It is assumed that the BA of the approved product has been previously evaluated.

G. Endogenous Substances

Drug products can be developed that contain compounds that are endogenous to humans (e.g., testosterone). When the endogenous compounds are identical to the drug that is being administered, determining the amount of drug released from the dosage form and absorbed by each subject is difficult. In most cases, it is important to measure and approximate

the baseline endogenous levels of the compound in blood (plasma) and subtract these levels from the total concentrations measured from each subject after the drug product is administered. In this way, an estimate of actual drug availability from the drug product can be achieved, and therefore BA and BE can be assessed. Endogenous substances may have homeostatic processes that affect their production and therefore impact their systemic concentrations. To reduce the complication of these homeostatic processes and to potentially avoid the need for baseline correction, an alternative approach might be to enroll patients in BA and BE studies with low or no production of the endogenous substances instead of healthy volunteers.

Baseline concentrations of the endogenous substance produced by the body are measured in the time period prior to study drug administration. Depending on the proposed indication, subtraction of the time-averaged baseline or time-matched baseline from the post-dose concentration for each subject may be recommended. When the endogenous levels are influenced by diet, strict control of the dietary intake of the compound prior to and during the study may also be appropriate. To achieve a stable baseline, subjects should be housed at the clinic for a sufficient time prior to the study and served standardized meals with similar content of the compound to that of the meals served on the PK sampling day.

In either case, baseline concentrations should be determined for each dosing period, and baseline corrections should be period-specific. If a negative plasma concentration value results after baseline correction, this should be set to 0 prior to calculating the baseline-corrected AUC. Pharmacokinetics and statistical analysis should be performed on both uncorrected and corrected data as appropriate. Because of the complexities associated with endogenous compounds, we recommend that sponsors and/or applicants contact the appropriate review division for additional FDA guidance.

H. Drug Products with High Intrasubject Variability

In addition to the traditional approach and the use of average BE using replicate designs, the use of a reference-scaled BE approach using a replicate design can be considered. This approach should be reserved for drugs that demonstrate a high intrasubject variability (≥30%). The reference-scaled average BE approach adjusts the BE limits of highly variable drugs by scaling to the within-subject variability of the reference product in the study and imposes a limit of 0.8 to 1.25 on the geometric mean ratio.[29] The appropriate review division should be consulted when planning the use of the reference-scaled BE approach.

APPENDIX A: GENERAL STUDY DESIGN AND DATA HANDLING

The following general approaches are recommended, recognizing that the elements can be adjusted for certain drug substances and drug products.

Study Conduct

- The BA or BE study should be conducted under fasting conditions (after an overnight fast of at least 10 hours). If the BA or BE study needs to be conducted with food, a separate FDA guidance *Food-Effect Bioavailability and Fed Bioequivalence Studies* is available to assist sponsors.
- The test and reference products should be administered with about 8 ounces (240 milliliters) of water to an appropriate number of subjects.
- Generally, the highest marketed strength should be administered as a single unit. If warranted, to achieve sufficient bioanalytical sensitivity multiple units of the highest strength can be administered, provided the total single dose remains within the labeled dose range and the total dose is safe for administration to the study subjects.
- An adequate washout period (e.g., >half-lives of the moieties to be measured) should separate each treatment.
- The lot numbers of both test and reference listed products and the expiration date for the reference product should be stated. We recommend that the assayed drug content of the test product batch not differ from the reference product by more than ±5%. The sponsor should include a statement of the composition of the test product and, if possible, a side-by-side comparison of the compositions of test and reference listed products. In accordance with 21 CFR 320.38, and 21 CFR 320.63, samples of the test and reference listed product must be retained for at least 5 years. For additional information, please refer to the FDA guidance for industry on *Handling and Retention of Bioavailability and Bioequivalence Testing Samples.*
- Before and during each study phase, we recommend that subjects (1) be allowed water as desired except for 1 hour before and after drug administration, (2) be provided standard meals no less than 4 hours after drug administration, and (3) abstain from alcohol for 24 hours before each study period and until after the last sample from each period is collected.

Sample Collection and Sampling Times

- We recommend that under normal circumstances, blood, rather than urine or tissue, be used.

In most cases, drug or metabolites are measured in serum or plasma. However, in certain cases, such as when an assay of sufficient sensitivity cannot be developed for plasma, whole blood may be more appropriate for analysis. We recommend that blood samples be drawn at appropriate times to describe the absorption, distribution, and elimination phases of the drug. For most drugs we recommend that 12 to 18 samples, including a pre-dose sample, be collected per subject per dose.

This sampling should continue for at least three or more terminal elimination half-lives of the drug to capture 90% of the relevant AUC. For multiple-dose studies, sampling should occur across the dose interval and include the beginning and the end of the interval. The exact timing for sample collection depends on the nature of the drug and the rate of input from the administered dosage form. The sample collection should be spaced in such a way that the maximum concentration (C_{max}) of the drug in the blood and terminal elimination rate constant (λz) can be estimated accurately.

Three or more samples should be obtained during the terminal log-linear phase to obtain an accurate estimate of λ_z from linear regression. We recommend recording the actual clock time when samples are drawn, as well as the elapsed time related to drug administration.

Subjects with Pre-Dose Plasma Concentrations

- If the pre-dose concentration is ≤5% of C_{max} value in that subject, the subject's data without any adjustments can be included in all PK measurements and calculations. We recommend that if the pre-dose value is >5% of C_{max}, the subject should be dropped from all PK evaluations. The subject data should be reported, and the subject should be included in safety evaluations.

Data Deletion because of Vomiting

- We recommend that data from subjects who experience emesis during the course of a study for immediate-release products be deleted from statistical analysis if vomiting occurs at or before two times median T_{max}. For modified-release products, subjects who experience emesis at any time during the labeled dosing interval should not be included in PK analysis.

Data Submission and Analysis

The following PK information is recommended for submission:

- Plasma concentrations and time points.
- Subject, period, sequence, treatment.
- Inter-subject, intrasubject, and/or total variability, if available.
- For single-dose studies: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, λ_z, and $t_{1/2}$.
- For steady-state studies: $AUC_{0-\tau,}$ $C_{maxss,}$ $T_{max,}$ C_{minss} (lowest concentration in a dosing interval), C_{trough} (concentration at the end of the dosing interval), C_{avss} (average concentration during a dosing interval), degree of fluctuation $[(C_{max} - C_{min})/C_{avss}]$, swing $[(C_{maxss} - C_{minss})/C_{minss}]$. C_{trough} should be measured for several dosing intervals to assess whether steady-state was achieved.
- In addition to the above information, clearance and volume of distribution should be reported for BA studies.

In addition, we recommend that the following statistical information be provided for $AUC_{0-t,}$ $AUC_{0-\infty}$, and Cmax:

- Geometric means
- Arithmetic means
- Geometric mean ratios
- 90% confidence intervals (CI)

We also recommend that logarithmic transformation be provided for measures used for BE demonstration. An FDA guidance for industry, *Statistical Approaches to Establishing Bioequivalence*, is available.

Rounding off of Confidence Interval Values

We recommend that applicants *not round off* CI values; therefore, to pass a CI limit of 80% to 125%, the value should be at least 80.00% and not more than 125.00%.

NOTES

1. This FDA guidance was developed by the Office of Clinical Pharmacology, Office of Translational Sciences, and the Office of New Drugs Quality Assessment, Office of Pharmaceutical Science, in the Center for Drug Evaluation and Research (CDER) at the U.S. Food and Drug Administration (FDA).
2. BA and BE information for drug products in abbreviated new drug applications (ANDAs) and ANDA supplements are not the subject of this FDA guidance. FDA has issued a separate draft FDA guidance on this topic entitled *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (December 2013) (ANDA BE Draft FDA guidance). The ANDA BE Draft FDA guidance, when finalized, will represent FDA's current thinking on this topic. Many FDA guidance are referenced throughout this document. The FDA guidance referred to in this footnote, as well as others referenced throughout the remainder of the document, can be found on the FDA Drugs FDA guidance Web page at www.fda.gov/Drugs/FDAguidanceComplianceRegulatoryInformation/FDA guidance/default.htm. We update FDA guidance periodically. To make sure you have the most recent version of an FDA guidance, check the FDA Drugs FDA guidance Web page.
3. These dosage forms include tablets, capsules, solutions, suspensions, conventional/immediate-release drug products, and modified (extended, delayed)-release drug products.
4. *Bioequivalence* is a statutory term reflected in the Federal Food, Drug, and Cosmetic Act (FD&C Act) in Section 505(j) [21 U.S.C. 355(j)], which requires ANDA applicants to demonstrate, among other things, that the proposed generic product is bioequivalent to its reference listed drug. Section 505(j)(2)(A)(iv) of the FD&C Act; see also Section 505(j)(8) of the FD&C Act. There is no similar statutory requirement for an NDA applicant either under Section 505(b)(1) or (b)(2) of the FD&C Act to demonstrate bioequivalence of its proposed product to another product. As a scientific matter, however,

the same or a similar showing of the bioavailability of two products in the NDA context may be needed for the purposes of evaluating the safety or effectiveness of a product. For ease of the reader, we refer to such evaluations of the relative bioavailability for two or more products as an evaluation of bioequivalence in this FDA guidance.

5. For information on these types of studies, see FDA's Drugs FDA guidance Web page. See footnote #2 for information on accessing this Web page.
6. Revisions to the March 2003 BA and BE FDA guidance include (1) expansion of the section on modified-release products, (2) addition of a section on concomitant administration of drug products and combination drug products, (3) addition of a section on alcoholic beverage effects on modified-release dosage forms, (4) addition of an endogenous substance section, (5) addition of a section on drug products with high intrasubject variability, and (6) removal of references to BE studies conducted for ANDAs. The FDA guidance also makes other revisions for clarification.
7. See footnote #2
8. Accordingly, the FDA is revising the 2002 Food-Effect FDA guidance.
9. 21 CFR 320.1(a) and (e).
10. See, e.g., 21 CFR 320.24(b)(1)(i). If serial measurements of the drug or its metabolites in plasma, serum, or blood cannot be accomplished, then measurement of urinary excretion can be used.
11. 21 CFR 320.27(a)(3).
12. See also 21 CFR 320.29.
13. See 21 CFR 320.24(b)(1)(i).
14. See footnote #2.
15. See the FDA guidance for industry on *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*. This document provides complementary information on the Biopharmaceutics Classification System (BCS).
16. See 21 CFR 320.22(b)(3).
17. For the purpose of this FDA guidance, the terms *extended*, *controlled*, and *sustained* are used interchangeably.
18. 21 CFR 320.25(f)(1).
19. 21 CFR 320.25(f)(2).
20. 21 CFR 320.25(f)(2)(i), (ii), and (iv). We recommend that a sponsor seeking to use as a reference product "a currently marketed extended release drug product subject to an approved full new drug application containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling proposed for the extended release drug product," under 21 CFR 320.25(f)(2)(iii), consult with the Agency before commencing such a study.
21. For example, when a 150-milligram (mg) ER product administered once daily (QD) is being developed that gives an approved 50-mg IR reference product administered three times a day (TID) or a 75-mg product administered two times a day (BID), a comparison of the 150-mg ER product administered as a single dose could be compared to either the 50-mg IR reference product administered TID or 75-mg IR reference product administered BID. In this case, the least common time interval is 24 hours.
22. If three strengths, 10 mg, 25 mg, and 50 mg, are being developed for a new ER dosage form, the dosage strength equivalence study should be conducted using 5×10 mg, 2×25 mg, and 1×50 mg to achieve constancy of dose.
23. If three strengths, 10 mg, 25 mg, and 50 mg, are being developed for a new ER dosage form, the dosage strength proportionality study should be conducted using 1×10 mg, 1×25 mg, and 1×50 mg to achieve constancy of dose, and the dosage strength proportionality study should be conducted using 1×10 mg, 1×25 mg, and 1×50 mg.
24. 21 CFR 320.21(b) (giving applicants the option of submitting information that "would permit FDA to waive the submission of evidence demonstrating in vivo bioequivalence") and 320.21(f) (requiring that the information submitted in support of a waiver request "shall meet the criteria set forth in § 320.22").
25. 21 CFR 320.21(b) (giving applicants the option of submitting information that "would permit FDA to waive the submission of evidence demonstrating in vivo bioequivalence") and 320.21(f) (requiring that the information submitted in support of a waiver request "shall meet the criteria set forth in § 320.22").
26. See also 21 CFR 322.22(d)(3) and (4) for additional bases for waiver. Also, FDA, for good cause, may waive a requirement for the submission of evidence of in vivo bioavailability or bioequivalence if waiver is compatible with the protection of the public health. For full NDAs, FDA may defer a requirement for the submission of evidence of in vivo bioavailability if deferral is compatible with the protection of the public health [21 CFR 320.22(e)].
27. In such instances, no waiver under 21 CFR 320.21 and 320.22 is necessary.
28. If the formulations of all the strengths are not compositionally proportional, in vitro data can be submitted for the middle strength(s) if the following data are acceptable: (1) BA or BE data, as appropriate, for both the highest and the lowest strengths, and (2) in vitro multimedia dissolution comparison profiles using f_2 evaluation.
29. For general principles of the reference-scaled approach, refer to Davit B, Conner D. Reference-Scaled Average Bioequivalence Approach. In: Kanfer I, Shargel L, Eds. *Generic Drug Product Development*.

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18 FDA 483 Observations

FDA's Office of Regulatory Affairs (ORA) is the lead office for all field activities, including inspections and enforcement. During an inspection, ORA investigators may observe conditions they deem to be objectionable. These observations are listed on an FDA Form 483 when, in an investigator's judgment, the observed conditions or practices indicate that an FDA-regulated product may be in violation of FDA's requirements.

The Product and Program Areas where the FDA inspects include the following categories; the numbers indicate the 483s issued for each category in the fiscal year 2017:

- Biologics: 115
- Drugs: 694
- Devices: 1030
- Human Tissue for Transplantation: 61
- Radiological Health: 31
- Parts 1240 and 1250: 75
- Foods (includes Dietary Supplements): 2662
- Veterinary Medicine: 244

The formulations provided in this book should meet all current cGMP requirements, along with the lists of approved excipients and the level of excipients used in the FDA-approved products. However, assuring that the products are manufactured in a cGMP environment is pivotal to marketing success. In providing a summary of the 483s issued by the FDA, it becomes very clear that most of these violations are avoidable, as they pertain to maintaining a documentation system appropriate for the purpose.

Table 18.1 lists the type of citations issued by the FDA for the inspection of drug manufacturing facilities. The description only includes a general category observation; the actual 483 will provide details of how the FDA reached the conclusion.

Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals

Subpart A—General Provisions

§ 211.1—Scope
§ 211.3—Definitions

Subpart B—Organization and Personnel

§ 211.22—Responsibilities of quality control unit
§ 211.25—Personnel qualifications
§ 211.28—Personnel responsibilities
§ 211.34—Consultants

Subpart C—Buildings and Facilities

§ 211.42—Design and construction features
§ 211.44—Lighting
§ 211.46—Ventilation, air filtration, air heating and cooling
§ 211.48—Plumbing
§ 211.50—Sewage and refuse
§ 211.52—Washing and toilet facilities
§ 211.56—Sanitation
§ 211.58—Maintenance

Subpart D—Equipment

§ 211.63—Equipment design, size, and location
§ 211.65—Equipment construction
§ 211.67—Equipment cleaning and maintenance
§ 211.68—Automatic, mechanical, and electronic equipment
§ 211.72—Filters

Subpart E—Control of Components and Drug Product Containers and Closures

§ 211.80—General requirements
§ 211.82—Receipt and storage of untested components, drug product containers, and closures
§ 211.84—Testing and approval or rejection of components, drug product containers, and closures
§ 211.86—Use of approved components, drug product containers, and closures
§ 211.87—Retesting of approved components, drug product containers, and closures
§ 211.89—Rejected components, drug product containers, and closures
§ 211.94—Drug product containers and closures

Subpart F—Production and Process Controls

§ 211.100—Written procedures; deviations
§ 211.101—Charge-in of components
§ 211.103—Calculation of yield
§ 211.105—Equipment identification
§ 211.110—Sampling and testing of in-process materials and drug products
§ 211.111—Time limitations on production
§ 211.113—Control of microbiological contamination
§ 211.115—Reprocessing

Subpart G—Packaging and Labeling Control

§ 211.122—Materials examination and usage criteria
§ 211.125—Labeling issuance
§ 211.130—Packaging and labeling operations
§ 211.132—Tamper-evident packaging requirements for over-the-counter (OTC) human drug products
§ 211.134—Drug product inspection
§ 211.137—Expiration dating

Subpart H—Holding and Distribution

§ 211.142—Warehousing procedures
§ 211.150—Distribution procedures

Subpart I—Laboratory Controls

§ 211.160—General requirements
§ 211.165—Testing and release for distribution
§ 211.166—Stability testing
§ 211.167—Special testing requirements
§ 211.170—Reserve samples
§ 211.173—Laboratory animals
§ 211.176—Penicillin contamination

Subpart J—Records and Reports

§ 211.180—General requirements
§ 211.182—Equipment cleaning and use log
§ 211.184—Component, drug product container, closure, and labeling records
§ 211.186—Master production and control records
§ 211.188—Batch production and control records
§ 211.192—Production record review
§ 211.194—Laboratory records
§ 211.196—Distribution records
§ 211.198—Complaint files

Subpart K—Returned and Salvaged Drug Products

§ 211.204—Returned drug products
§ 211.208—Drug product salvaging

TABLE 18.1
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.22(d)	Procedures not in writing, fully followed	The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed].	185
21 CFR 211.160(b)	Scientifically sound laboratory controls	Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality, and purity.	124
21 CFR 211.192	Investigations of discrepancies, failures	There is a failure to thoroughly review [any unexplained discrepancy] [the failure of a batch or any of its components to meet any of its specifications] whether or not the batch has been already distributed.	100
21 CFR 211.100(a)	Absence of written procedures	There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.	91
21 CFR 211.67(b)	Written procedures not established/followed	Written procedures are not [established] [followed] for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product.	68
21 CFR 211.165(a)	Testing and release for distribution	Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the [final specifications] [identity and strength of each active ingredient] prior to release.	64
21 CFR 211.68(b)	Computer control of master formula records	Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.	62

(*Continued*)

TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.113(b)	Procedures for sterile drug products	Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not [established] [written] [followed].	62
21 CFR 211.68(a)	Calibration/inspection/checking not done	Routine [calibration] [inspection] [checking] of [automatic] [mechanical] [electronic] equipment is not performed according to a written program designed to assure proper performance.	61
21 CFR 211.166(a)	Lack of written stability program	There is no written testing program designed to assess the stability characteristics of drug products.	61
21 CFR 211.110(a)	Control procedures to monitor and validate performance	Control procedures are not established which [monitor the output] [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.	56
21 CFR 211.67(a)	Cleaning/sanitizing/maintenance	Equipment and utensils are not [cleaned] [maintained] [sanitized] at appropriate intervals to prevent [malfunctions] [contamination] that would alter the safety, identity, strength, quality, or purity of the drug product.	54
21 CFR 211.25(a)	Training—operations, GMPs, written procedures	Employees are not given training in [the particular operations they perform as part of their function] [current good manufacturing practices] [written procedures required by current good manufacturing practice regulations].	53
21 CFR 211.188	Prepared for each batch, include complete information	Batch production and control records [are not prepared for each batch of drug product produced] [do not include complete information relating to the production and control of each batch].	51
21 CFR 211.165(e)	Test methods	The [accuracy] [sensitivity] [specificity] [reproducibility] of test methods have not been [established] [documented].	50
21 CFR 211.42(c)(10)(iv)	Environmental monitoring system	Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.	47
21 CFR 211.63	Equipment design, size, and location	Equipment used in the manufacture, processing, packing, or holding of drug products is not [of appropriate design] [of adequate size] [suitably located] to facilitate operations for its [intended use] [cleaning and maintenance].	44
21 CFR 211.100(b)	SOPs not followed/documented	Written production and process control procedures are not [followed in the execution of production and process control functions] [documented at the time of performance].	43
21 CFR 211.180(e)(2)	Items to cover on annual reviews	Written procedures are not [established] [followed] for evaluations done at least annually and including provisions for a review of [complaints] [recalls] [returned or salvaged drug products] [investigations conducted for each drug product].	41
21 CFR 211.194(a)	Complete test data included in records	Laboratory records do not include complete data derived from all tests, examinations, and assay necessary to assure compliance with established specifications and standards. Specifically, ***	39
21 CFR 211.42(c)(10)(v)	Cleaning system	Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the [room] [equipment] to produce aseptic conditions.	38
21 CFR 211.22(a)	Lack of quality control unit	There is no quality control unit.	38
21 CFR 211.198(a)	Complaint handling procedure	Procedures describing the handling of written and oral complaints related to drug products are [not written or followed] [deficiently written or followed].	37

(*Continued*)

TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.113(a)	Procedures for non-sterile drug products	Procedures designed to prevent objectionable microorganisms in drug products not required to be sterile are not [established] [written] [followed].	33
21 CFR 211.25(a)	Training, education, experience overall	Employees engaged in the [manufacture] [processing] [packing] [holding] of a drug product lack the [education] [training] [experience] required to perform their assigned functions.	31
21 CFR 211.113(b)	Validation lacking for sterile drug products	Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include [adequate] validation of the sterilization process.	30
21 CFR 211.25(a)	GMP training frequency	GMP training is not conducted [on a continuing basis] [with sufficient frequency] to assure that employees remain familiar with cGMP requirements applicable to them.	29
21 CFR 211.192	Written record of investigation incomplete	Written records of investigations into [unexplained discrepancies] [the failure of a batch or any of its components to meet specifications] do not [always] include the conclusions and follow-up.	29
21 CFR 211.160(a)	Following/documenting laboratory controls	Established [specifications] [standards] [sampling plans] [test procedures] [laboratory control mechanisms] are not [followed] [documented at the time of performance].	28
21 CFR 211.165(b)	Microbiological testing	Each batch of drug product required to be free of objectionable microorganisms is not tested through appropriate laboratory testing.	27
21 CFR 211.188(b)	Batch production and batch control record requirements	The batch production and control records are deficient in that they do not include documentation of the accomplishment of each significant step in [manufacturing] [processing] [packing] [holding].	26
21 CFR 211.160(b)(4)	Calibration—at intervals, written program, remedial action	The calibration of [instruments] [apparatus] [gauges] [recording devices] is not done at suitable intervals [in accordance with an established written program] [with provisions for remedial action in the event accuracy and/or precision limits are not met].	26
21 CFR 211.192	Quality control unit review of records	Drug product production and control records are not [reviewed] [approved] by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed.	25
21 CFR 211.194(a)(4)	Complete test data	Laboratory records are deficient in that they do not include a complete record of all data obtained during testing.	25
21 CFR 211.142(b)	Storage under appropriate conditions	Drug products are not stored under appropriate conditions of [temperature] [humidity] [light] so that their identity, strength, quality, and purity are not affected.	25
21 CFR 211.198(a)	Procedures to be written and followed	Procedures describing the handling of all written and oral complaints regarding a drug product are not [established] [written] [followed].	25
21 CFR 211.111	Establishment of time limitations	Time limits are not established when appropriate for the completion of each production phase to assure the quality of the drug product.	24
21 CFR 211.58	Buildings not maintained in good state of repair	Buildings used in the [manufacturing] [processing] [packing] [holding] of a drug product are not maintained in a good state of repair.	24
21 CFR 211.160(a)	Deviations from laboratory control requirements	Deviations from written [specifications] [standards] [sampling plans] [test procedures] [laboratory mechanisms] are not [recorded] [justified].	23
21 CFR 211.84(d)(2)	Establish reliability of supplier's CoA	Establishment of the reliability of the component supplier's report of analyses is deficient in that the test results are not appropriately validated at appropriate intervals.	22

(*Continued*)

TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.180(e)	Records reviewed annually	Records are not maintained so that data therein can be reviewed at least annually to evaluate the quality standards of each drug product to determine the need for changes in specifications or manufacturing or control procedures.	22
21 CFR 211.100(b)	Procedure deviations recorded and justified	Deviations from written production and process control procedures are not [recorded] [justified].	22
21 CFR 211.84(d)(2)	Reports of analysis (components)	Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, without [performing at least one specific identity test on each component] [establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals].	22
21 CFR 211.160(a)	Lab controls established, including changes	The establishment of [specifications] [standards] [sampling plans] [test procedures] [laboratory control mechanisms], including any changes thereto, are not [drafted by the appropriate organizational unit] [reviewed and approved by the quality control unit].	21
21 CFR 211.182	Written records kept in individual logs	Written records of major equipment [cleaning] [maintenance] [use] are not included in individual equipment logs.	21
21 CFR 211.170(b)	Annual visual exams of drug products	Reserve samples from representative sample lots or batches of drug products selected by acceptable statistical procedures are not examined visually at least once a year for evidence of deterioration.	21
21 CFR 211.192	No written record of investigation	Written records are not [always] made of investigations into [unexplained discrepancies] [the failure of a batch or any of its components to meet specifications].	20
21 CFR 314.80(b)	Failure to develop written procedures	Written procedures have not been developed for the [surveillance] [receipt] [evaluation] [reporting to FDA] of post-marketing adverse drug experiences.	20
21 CFR 211.192	Extent of discrepancy, failure investigations	Investigations of [an unexplained discrepancy] [a failure of a batch or any of its components to meet any of its specifications] did not extend to [other batches of the same drug product] [other drug products that may have been associated with the specific failure or discrepancy].	19
21 CFR 211.100(a)	Changes to procedures not reviewed, approved	Changes to written procedures are not [drafted, reviewed, and approved by the appropriate organizational unit] [reviewed and approved by the quality control unit].	19
21 CFR 211.22(a)	Authority lacking to review records, investigate errors	The quality control unit lacks authority to [review production records to assure that no errors have occurred] [fully investigate errors that have occurred].	18
21 CFR 211.80(a)	Procedures to be in writing	Written procedures are lacking which describe in sufficient detail the [receipt] [identification] [storage] [handling] [sampling] [testing] [approval] [rejection] of [components] [drug product containers] [closures].	18
21 CFR 211.166(a)	Written program not followed	The written stability testing program is not followed.	18
21 CFR 211.122(a)	Written procedures describing in detail	There is a lack of written procedures describing in sufficient detail the [receipt] [identification] [storage] [handling] [sampling] [examination] [testing] of labeling and packaging materials.	17
21 CFR 211.125(a)	Strict control not exercised over labeling issued	Strict control is not exercised over labeling issued for use in drug product labeling operations.	17
21 CFR 211.56(b)	Written sanitation procedures lacking	There is a lack of written procedures [assigning responsibility] [providing cleaning schedules] [describing in sufficient detail the methods, equipment, and materials to be used] for sanitation.	17

(*Continued*)

TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.28(a)	Clothing appropriate for duties performed	Clothing of personnel engaged in the [manufacturing] [processing] [packing] [holding] of drug products is not appropriate for the duties they perform.	16
21 CFR 211.84(d)(1)	Component identity verification	Drug product component testing is deficient in that at least one specific test to verify the identity of each component is not performed.	16
21 CFR 211.130	Procedures are written and followed	Procedures designed to assure that correct [labels] [labeling] [packaging materials] are used for drug products are not [written] [followed].	15
21 CFR 211.180(e)(1)	Review of representative number of batches	Written procedures are not [established] [followed] for evaluations conducted at least annually to review records associated with a representative number of batches, whether approved or rejected.	15
21 CFR 211.46(b)	Equipment for environmental control	Equipment for adequate control over [air pressure] [micro-organisms] [dust] [humidity] [temperature] is not provided when appropriate for the manufacture, processing, packing, or holding of a drug product.	15
21 CFR 211.137(a)	Expiration date lacking	Drug products do not bear an expiration date determined by appropriate stability data to assure they meet applicable standards of identity, strength, quality, and purity at the time of use.	14
21 CFR 211.103	Actual vs. theoretical yields not determined	Actual yield and percentages of theoretical yield are not determined at the conclusion of each appropriate phase of [manufacturing] [processing] [packaging] [holding] of the drug product.	13
21 CFR 211.166(a)(3)	Valid stability test methods	The written stability program for drug products does not include [reliable] [meaningful] [specific] test methods.	13
21 CFR 211.56(a)	Sanitation—buildings not clean, free of infestation	Buildings used in the manufacture, processing, packing, or holding of drug products are not [maintained in a clean and sanitary condition] [free of infestation by rodents, birds, insects, and other vermin].	13
21 CFR 211.67(b)	Written procedures fail to include	Written procedures for cleaning and maintenance fail to include [assignment of responsibility] [maintenance and cleaning schedules] [description in sufficient detail of methods, equipment, and materials used] [description in sufficient detail of the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance] [instructions for removal or obliteration of previous batch identification] [instructions for protection of clean equipment from contamination prior to use] [parameters relevant to the operation].	13
21 CFR 211.80(a)	Written procedures not followed	Written procedures are not followed for the [receipt] [identification] [storage] [handling] [sampling] [testing] [approval] [rejection] of [components] [drug product containers] [closures].	13
21 CFR 211.142	Written warehousing procedures established/ followed	Procedures describing the warehousing of drug products are not [established] [followed].	13
21 CFR 314.80(c)(1)(i)	Late submission of 15-day report	Not all adverse drug experiences that are both serious and unexpected have been reported to FDA within 15 calendar days of initial receipt of the information.	13
21 CFR 211.22(a)	Approve or reject components, products	The quality control unit lacks the responsibility and authority to [approve] [reject] all [components] [drug product containers] [closures] [in process materials] [packaging material] [labeling] [drug products].	12

(*Continued*)

TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.80(b)	Handling and storage to prevent contamination	There was a failure to handle and store [components] [drug product containers] [closures] at all times in a manner to prevent contamination.	12
21 CFR 211.42(c)	Defined areas of adequate size for operations	The [separate or defined areas] [control systems] necessary to prevent contamination or mix-ups are deficient.	11
21 CFR 211.84(d)(1)	Identity testing of each component	The identity of each component of a drug product is not verified by conducting at least one test to verify the identity, using specific identity tests if they exist.	11
21 CFR 211.165(f)	Failing drug products not rejected	Drug products failing to meet established [standards] [specifications] [quality control criteria] are not rejected.	11
21 CFR 211.160(b)(4)	Establishment of calibration procedures	Procedures describing the calibration of instruments, apparatus, gauges, and recording devices are [not written or followed] [deficiently written or followed].	11
21 CFR 211.22(c)	Approve or reject procedures or specs	The quality control unit lacks responsibility to [approve] [reject] all procedures or specifications impacting on the [identity] [strength] [quality] [purity] of drug products.	10
21 CFR 211.67(c)	Cleaning/maintenance records not kept	Records are not kept for the [maintenance] [cleaning] [sanitizing] [inspection] of equipment.	10
21 CFR 211.42(c)(10)(iii)	Air supply	Aseptic processing areas are deficient regarding air supply that is filtered through high-efficiency particulate air filters under positive pressure.	10
21 CFR 211.188(a)	Accurate reproduction	The batch production and control records are deficient in that they are not [an accurate reproduction of the appropriate master production or control record] [checked for accuracy, dated, and signed].	10
21 CFR 211.186(b)(9)	Manufacturing instructions and specifications	The master production and control records are deficient in that they do not include complete [manufacturing] [control] [instructions] [sampling] [testing] [procedures] [specifications] [special notations] [precautions].	10
FDCA 503B(a)(10)	Drug product label, outsourcer facility	The labels of your outsourcing facility's drug products are deficient.	10
21 CFR 211.42(a)	Buildings of suitable size, construction, location	Buildings used in the manufacture, processing, packing, or holding of a drug product do not have the suitable [size] [construction] [location] to facilitate cleaning, maintenance, and proper operations.	9
21 CFR 211.42(c)(1)	Incoming material area	Separate or defined areas to prevent contamination or mix-ups are deficient regarding operations related to the receipt, identification, storage, and withholding from use of [components] [drug product containers] [closures] [labeling] pending sampling, testing, or examination by the quality control unit before release for manufacturing or packaging.	9
21 CFR 211.105(b)	Distinctive ID or code not recorded in batch record	The batch records do not record the distinctive [identification number] [code] [name of equipment] to identify major equipment to show the specific equipment used in the manufacture of a batch of a drug product.	9
21 CFR 211.150(b)	Distribution recall system	The distribution system is deficient in that each lot of drug product cannot be readily determined to facilitate its recall if necessary. Specifically, ***	9
21 CFR 211.165(c)	Sampling and testing plans not described	Sampling and testing plans for drug products are not described in written procedures which include the [method of sampling] [number of units per batch to be tested].	9
21 CFR 211.166(b)	Adequate number of batches on stability	An adequate number of batches of each drug product are not tested [nor are records of such data maintained] to determine an appropriate expiration date.	9

(*Continued*)

TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.167(a)	Sterility/pyrogen-free testing	Each batch of drug product purporting to be [sterile] [pyrogen-free] is not laboratory tested to determine conformance to such requirements.	9
21 CFR 211.186(a)	Signature and checking of records—two persons	The master production and control records for each batch size of drug product are not [prepared, dated, and signed by one person with a full handwritten signature] [independently checked, dated, and signed by a second person].	9
21 CFR 211.110(a)	Written in-process control procedures	Written procedures are not [established] [followed] that describe the [in-process controls] [tests] [examinations] to be conducted on appropriate samples of in-process materials of each batch.	9
21 CFR 211.160(b)(3)	Acceptance of drug products	Determinations of conformance to appropriate written specifications for acceptance are [not made] [deficient] for drug products.	9
21 CFR 211.22(a)	Contract drug products—lack of responsibility	The quality control unit lacks responsibility for approving or rejecting drug products [manufactured] [processed] [packed] [held] under contract by another company.	8
21 CFR 211.101(d)	Component addition checked by second person	Each component is not added to a batch by one person and verified by a second person.	8
21 CFR 211.87	Retest of approved components/containers/ closures	Approved [components] [drug product containers] [closures] are not retested or reexamined as appropriate for identity, strength, quality, and purity after [storage for long periods] [exposure to conditions that might have an adverse effect] with subsequent approval or rejection by the quality control unit.	8
21 CFR 211.84(a)	Components withheld from use pending release	Each lot of [components] [drug product containers] [closures] is not withheld from use until the lot has been sampled, tested, examined, and released by the quality control unit.	8
21 CFR 211.180(c)	Records not made readily available to FDA	Records associated with drug product [components] [containers] [closures] [labeling] [production] [control] [distribution] and within the retention period for such records were not made readily available for authorized inspection.	8
21 CFR 211.186(a)	Written procedures followed	Procedures for the preparation of master production and control records are not [described in a written procedure] [followed].	8
21 CFR 211.198(b)(2)	Complaint investigation/follow-up findings	Complaint records are deficient in that they do not include the findings of the [investigation] [follow-up].	8
21 CFR 211.84(d)(2)	Component identification test	Specific identification tests are not conducted on components that have been accepted based on the supplier's report of analysis.	8
21 CFR 211.89	Quarantine of rejected components et al.	Rejected [components] [drug product containers] [closures] are not controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.	8
21 CFR 211.68(b)	Backup data not assured as exact and complete	Backup data are not assured as [exact] [complete] [secure from alteration, erasure, or loss] through keeping hard copy or alternate systems.	8
21 CFR 211.166(a)	Results not used for expiration dates, storage cond.	Results of stability testing are not used in determining [appropriate storage conditions] [expiration dates].	8
21 CFR 211.198(b)(2)	Written record of complaint to include findings, follow-up	Written records of investigation of a drug complaint do not include [the findings of the investigation] [the follow-up].	8

(*Continued*)

TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.186(b)(9)	Complete instructions, procedures, specifications et al.	Master production and control records lack [complete manufacturing and control instructions] [sampling and testing procedures] [specifications] [special notations] [precautions to be followed].	8
21 CFR 314.81(b)(1)(ii)	Failure to meet specifications	An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning a failure of one or more distributed batches of a drug to meet the specifications established for it in the application.	8
21 CFR 211.68(b)	Backup file not maintained	Failure to maintain a backup file of data entered into the computer or related system.	7
21 CFR 211.68(a)	Written calibration/inspection records not kept	Records of the [calibration checks] [inspections] of automatic, mechanical, or electronic equipment, including computers or related systems, are not maintained.	7
21 CFR 211.125(f)	Procedures written and followed	Procedures describing in sufficient detail the controls employed for the issuance of labeling are not [written] [followed].	7
21 CFR 211.84(e)	Rejecting when specifications not met	Failure to reject any lot of [components] [drug product containers] [closures] that did not meet the appropriate written specifications for identity, strength, quality, and purity.	7
21 CFR 211.167(a)	Sterility/pyrogens—test methods written, followed	Test procedures relative to appropriate laboratory testing for [sterility] [pyrogens] are not [written] [followed].	7
21 CFR 211.194(d)	Laboratory equipment calibration records	Laboratory records do not include complete records of the periodic calibration of laboratory [instruments] [apparatus] [gauges] [recording devices].	7
21 CFR 211.194(a)(8)	Identification of person performing review of lab records	Laboratory records are deficient in that they do not include the [initials] [signature] of the second person reviewing the record for accuracy.	7
21 CFR 211.198(a)	Reporting of adverse drug experience to FDA	Written procedures describing the handling of all written and oral complaints do not include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the Food and Drug Administration.	7
21 CFR 211.194(a)(8)	Second person sign off	Laboratory records do not include the initials or signature of a second person showing that the original records have been reviewed for [accuracy] [completeness] [compliance with established standards].	7
21 CFR 314.81(b)(2)	Timely submission	An annual report was not submitted [each year] [within 60 days of the anniversary date of U.S. approval of the application] to the FDA division responsible for reviewing the application.	7
21 CFR 211.25(b)	Supervisor training/education/experience	Individuals responsible for supervising the [manufacture] [processing] [packing] [holding] of a drug product lack the [education] [training] [experience] to perform their assigned functions in such a manner as to assure the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess.	6
21 CFR 211.68(b)	Input/output verification	Input to and output from [the computer] [related systems of formulas] [records or data] are not checked for accuracy.	6
21 CFR 211.42(c)(5)	Mfg/processing operations area	Separate or defined areas to prevent contamination or mix-ups are deficient regarding the manufacturing and processing operations.	6

(*Continued*)

TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.42(c)(10)(vi)	Equipment to control conditions	Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.	6
21 CFR 211.84(d)(2)	Component written specification	Component testing is deficient in that each component is not tested for conformity with all appropriate written specifications for purity, strength, and quality. Specifically, ***	6
21 CFR 211.52	Washing and toilet facilities are deficient	Washing and toilet facilities lack [hot and cold water] [soap or detergent] [air driers or single-service towels] [cleanliness].	6
21 CFR 211.100(a)	Approval and review of procedures	Written procedures are not [drafted, reviewed, and approved by the appropriate organizational units] [reviewed and approved by the quality control unit].	6
21 CFR 211.160(b)(3)	Drug product sample	Drug product samples are not [representative of the entire batch] [properly identified].	6
21 CFR 211.160(b)(4)	Written calibration procedures	Written calibration procedures for instruments, apparatus, gauges, and recording devices are deficient in that they do not include specific [directions] [schedules] [limits for accuracy and precision] [provisions for remedial action if limits are not met].	6
21 CFR 211.165(d)	Acceptance criteria for sampling and testing	Acceptance criteria for the sampling and testing conducted by the quality control unit are not adequate to assure that batches of drug products meet [each appropriate specification] [appropriate statistical quality control criteria] as a condition for their approval and release.	6
21 CFR 211.170(b)	Reserve samples identified, representative, stored	Reserve drug product samples are not [appropriately identified] [representative of each lot or batch of drug product] [retained and stored under conditions consistent with product labeling].	6
21 CFR 211.194(a)(2)	Suitability of testing methods verified	The suitability of all testing methods is not verified under actual conditions of use.	6
21 CFR 211.194(a)(5)	Calculations performed are in the records	Laboratory records do not include a record of all calculations performed in connection with the test.	6
21 CFR 211.42(b)	Adequate space lacking to prevent mix-ups and contamination	The building lacks adequate space for the orderly placement of equipment and materials to prevent mix-ups between [different components] [drug product containers] [closures] [labeling] [in-process materials] [drug products] and to prevent contamination.	6
21 CFR 211.22(b)	Adequate lab facilities not available	Adequate lab facilities for testing and approval or rejection of [components] [drug product containers] [closures] [packaging materials] [in-process materials] [drug products] are not available to the quality control unit.	5
21 CFR 211.42(c)(7)	Quarantined drug products area	Separate or defined areas to prevent contamination or mix-ups are deficient regarding operations related to the quarantine storage of drug products prior to release.	5
21 CFR 211.194(c)	Testing and standardization of standards et al.	Laboratory records do not include complete records of any testing and standardization of laboratory [reference standards] [reagents] [standard solutions].	5
21 CFR 211.110(c)	In-process materials characteristics testing	In-process materials are not tested for [identity] [strength] [quality] [purity] and approved or rejected by the quality control unit [during the production process] [after storage for long periods].	5
21 CFR 211.150(b)	Recall facilitation	A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary has not been established.	5

(*Continued*)

TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.160(b)(4)	Instruments, apparatus, et al. not meeting specs	The use of [instruments] [apparatus] [gauges] [recording devices] not meeting established specifications was observed.	5
21 CFR 211.188(b)(12)	Investigations made into any unexplained discrepancy	Batch production and control records do not include the results of any investigation made into any unexplained discrepancy, whether or not the batch of drug product had already been distributed.	5
21 CFR 211.198(a)	Complaints reviewed by quality control unit	Written procedures describing the handling of complaints do not include provisions for [review by the quality control unit of any complaint involving the possible failure of a drug product to meet any of its specifications] [a determination as to the need for an investigation of any unexplained discrepancy] [explaining the reasons for the failure of the batch or any of its components to meet specifications].	5
21 CFR 211.194(a)(4)	Data secured in course of each test	Laboratory records do not include a complete record of all data secured in the course of each test, including all [graphs] [charts] [spectra] from laboratory instrumentation, properly identified to show the [specific component] [drug product container] [closure] [in-process material] [lot tested] [drug product tested].	5
21 CFR 314.80(c)(2)	Late submission of annual safety reports	Not all annual periodic adverse drug experience reports have been submitted within 60 days of the anniversary date of the approval of the application.	5
21 CFR 211.25(c)	Inadequate number of personnel	The number of qualified personnel is inadequate to [perform] [supervise] the [manufacture] [processing] [packing] [holding] of each drug product.	4
21 CFR 211.28(a)	Protective apparel not worn	Protective apparel is not worn as necessary to protect drug products from contamination.	4
21 CFR 211.42(c)(10)	Aseptic processing area	Separate or defined areas to prevent contamination or mix-ups are deficient regarding operations related to aseptic processing of drug products.	4
21 CFR 211.42(c)(10)(i)	Floors, walls, ceiling surfaces	Aseptic processing areas are deficient in that [floors] [walls] [ceilings] are not smooth and/or hard surfaces that are easily cleanable.	4
21 CFR 211.134(a)	Correct labels during finishing operations	Packaged and labeled products are not examined during finishing operations to provide assurance that containers and packages in the lot have the correct label.	4
21 CFR 211.134(c)	Examinations documented	The results of the examination of the packaged and labeled products were not documented in the batch production or control records.	4
21 CFR 211.142(a)	Quarantine—actual practice	Drug products are not quarantined before being released by the quality control unit.	4
21 CFR 211.82(b)	Quarantine storage of components	Incoming [components] [drug product containers] [closures] are not stored under quarantine until they have been tested or examined, as appropriate, and released.	4
21 CFR 211.84(b)	Representative samples	Representative samples are not taken of each shipment of each lot of [components] [drug product containers] [closures] for testing or examination.	4
21 CFR 211.84(d)(3)	Establish reliability of supplier's CofA	Establishment of the reliability of the [container] [closure] supplier's report of analyses is deficient in that the test results are not appropriately validated at appropriate intervals.	4
21 CFR 211.94(b)	Protection from external factors	Container closure systems do not provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.	4

(*Continued*)

TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.94(c)	Containers and closures clean, sterilized, pyrogen-free	Drug product [containers] [closures] were not [clean] [sterilized and processed to remove pyrogenic properties] to assure that they are suitable for their intended use.	4
21 CFR 211.166(a)(4)	Testing in same container—closure system	The written stability program does not assure testing of the drug product in the same container-closure system as that in which the drug product is marketed.	4
21 CFR 211.166(c)(1)	Homeopathic drugs, assessment of stability	There is no written assessment of stability of homeopathic drug products based at least on [testing or examination of the drug product for compatibility of the ingredients] [marketing experience with the drug product to indicate that there is no degradation of the product for the normal or expected period of use].	4
21 CFR 211.182	Specific information required in individual logs	Individual equipment logs do not show [time] [date] [product] [lot number of each batch processed].	4
21 CFR 211.184(c)	Individual inventory record	Records fail to include an individual inventory record of each [component] [reconciliation of the use of each component] [drug product container] [drug product closure] with sufficient information to allow determination of any associated batch or lot of drug product.	4
21 CFR 211.188(b)(8)	Labeling control records and label copies	The batch production and control records are deficient in that they do not include [complete labeling control records] [specimen] [copy] of labeling.	4
21 CFR 211.196	Distribution record requirements	Distribution records do not contain the [name and strength of the drug product] [description of dosage form] [name and address of consignee] [date and quantity shipped] [lot or control number of drug product].	4
21 CFR 211.194(a)(2)	Laboratory test method verification	Verification of the suitability of the testing methods is deficient in that they are not [performed under actual conditions of use] [documented on the laboratory records].	4
21 CFR 211.101(b)	Measured components for manufacturing	Components for drug product manufacturing are not [weighed] [measured] [subdivided as appropriate].	4
21 CFR 211.105(a)	Identification of containers, lines, equipment	All [compounding and storage containers] [processing lines] [major equipment] used during the production of a batch of drug product is not properly identified at all times to indicate [contents] [the phase of processing of the batch].	4
21 CFR 211.160(b)(2)	In-process sample representation/identification	In-process samples are not [representative] [properly identified].	4
21 CFR 211.84(d)(2)	Testing each component for conformity with specs	Each component is not tested for conformity with all appropriate written specifications for purity, strength, and quality.	4
21 CFR 211.150	Written distribution procedure	Written distribution procedures are not [established] [followed].	4
21 CFR 211.170(b)	Reserve drug product sample quantity—all tests	The reserve sample of drug product does not consist of at least twice the quantity necessary to perform all the required tests of drug product.	4
21 CFR 314.80(c)(2)	Interval	Periodic reports of non-alert adverse drug experiences have not been submitted [quarterly for an application which was approved less than three years ago] [yearly for an application which was approved three or more years ago].	4
21 CFR 314.80(c)(2)	Late submission of quarterly safety reports	Not all quarterly periodic adverse drug experience reports have been submitted within 30 days of the close of the quarter.	4
21 CFR 212.30(b)	Equipment not clean	You did not implement procedures to ensure that all your equipment is clean.	4

(*Continued*)

TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.67(b)(2)	Cleaning SOPs/schedules	Procedures for the cleaning and maintenance of equipment are deficient regarding maintenance and cleaning schedules, including, where appropriate, sanitizing schedules.	3
21 CFR 211.67(b)(3)	Cleaning SOPs/instructions	Procedures for the cleaning and maintenance of equipment are deficient regarding sufficient detail of the methods, equipment, and materials used in the cleaning and maintenance operation, and the methods of disassembly and reassembling equipment as necessary to assure proper cleaning and maintenance.	3
21 CFR 211.67(b)(5)	Cleaning SOPs/equipment protection	Procedures for the cleaning and maintenance of equipment are deficient regarding the protection of clean equipment from contamination prior to use.	3
21 CFR 211.42(c)(2)	Rejected material area	Separate or defined areas to prevent contamination or mix-ups are deficient regarding operations related to the holding of rejected [components] [drug product containers] [closures] [labeling] before disposition.	3
21 CFR 211.42(c)(9)	Control/lab operations area	Separate or defined areas to prevent contamination or mix-ups are deficient regarding laboratory controls and operations.	3
21 CFR 211.122(a)	Sampling/testing of labeling/packaging materials	Labeling and packaging materials are not [representatively sampled] [examined] [tested] upon receipt and before use in packaging and labeling of a drug product.	3
21 CFR 211.122(d)	Label storage access limited to authorized personnel	Access to the storage area for labels and labeling materials is not limited to authorized personnel.	3
21 CFR 211.122(e)	Destruction of obsolete labeling	Obsolete or outdated labels, labeling, and packaging materials are not destroyed.	3
21 CFR 211.130(c)	Lot or control number assigned	The drug product is not identified with a lot or control number that permits the determination of the history of the manufacture and control of the batch.	3
21 CFR 211.180(b)	Record maintenance 1 year (except exempt OTC)	All records of [production] [control] [distribution] [components] [drug product containers] [closures] [labeling] associated with a batch of drug product were not maintained at least one (1) year after the expiration date.	3
21 CFR 211.166(a)(1)	Sample size—test intervals	The written stability program for drug products does not include [sample size] [test intervals] based on statistical criteria for each attribute examined to assure valid estimates of stability.	3
21 CFR 211.166(b)	Accelerated stability studies	Accelerated stability studies, combined with basic stability information, used to support tentative expiration dates are not supported with ongoing full shelf-life studies.	3
21 CFR 211.188(b)(3)	Identification of components and in-process materials	The batch production and control records are deficient in that they do not include specific identification of each [batch of component] [in-process material] used.	3
21 CFR 211.198(a)	Adverse drug experience	Complaint procedures are deficient in that they do not include provisions that allow for the review to determine if the complaints represent [serious] [unexpected adverse drug experiences] which are required to be reported to FDA.	3
21 CFR 211.46(c)	Air filtration system lacking in production area	The production area air supply lacks an appropriate air filtration system.	3
21 CFR 211.46(c)	Exhaust systems inadequate to control air contamination	Adequate exhaust systems or other systems to control contaminants are lacking in areas where air contamination occurs during production.	3
21 CFR 211.48(a)	Plumbing system defects	The plumbing system contains defects that could contribute to the contamination of drug products.	3

(*Continued*)

TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.56(c)	Written procedures lacking for use of pesticides, etc.	Written procedures are lacking for the use of [rodenticides] [insecticides] [fungicides] [fumigating agents] [cleaning and sanitizing agents] designed to prevent the contamination of [equipment] [components] [drug product containers] [closures] [packaging, labeling materials] [drug products].	3
21 CFR 211.101(d)	Verification of component addition	Each component is not added to the batch by one person and verified by a second person.	3
21 CFR 211.204	Returned drug procedures in writing and followed	Procedures describing the [holding] [testing] [reprocessing] of returned drug products are not [in writing] [followed].	3
21 CFR 211.80(d)	Status of each lot identified	Each lot of [components] [drug product containers] [closures] was not appropriately identified as to its status in terms of being quarantined, approved, or rejected.	3
21 CFR 211.160(b)(3)	Drug products—samples representative, identified properly	Samples taken of drug products for determination of conformance to written specifications are not [representative] [properly identified].	3
21 CFR 211.188(a)	Accurate reproduction included	Batch production and control records for each batch of drug product produced do not include an accurate reproduction of the appropriate master production or control record which was checked for accuracy, dated, and signed.	3
21 CFR 211.188(b)(7)	Actual yield, % of theoretical yield	The batch production and control records do not include a statement of the [actual yield] [percentage of theoretical yield] at appropriate stages of processing for each batch of drug product produced.	3
21 CFR 211.186(b)(7)	Theoretical yield statement including percentages	Master production and control records lack a statement of theoretical yield [including the maximum and minimum percentages of theoretical yield beyond which investigation is required].	3
21 CFR 211.186(b)(8)	Description of containers, labels, et al.	Master production and control records lack [a description of the drug product containers, closures, and packaging materials] [a specimen or copy of each label and all other labeling] [the signatures and dates entered by the person or persons responsible for the approval of labeling].	3
21 CFR 211.194(a)(2)	Reference and method not stated	Laboratory records of methods of testing used do not [indicate the method] [provide the reference] when employing methods in [recognized standard references] [an approved new drug application and the referenced method is not modified].	3
21 CFR 212.30(a)	Prevention of contamination	Your facilities are not adequate to ensure the prevention of contamination of [equipment] [product] by [substances] [personnel] [environmental conditions] that could reasonably be expected to have an adverse effect on product quality.	3
21 CFR 212.20(d)	Determination need for investigation	When errors occurred or a production batch failed to meet specifications, you did not [determine the need for an investigation] [conduct an investigation] [take appropriate corrective actions] when necessary.	3
21 CFR 212.60(b)	Testing procedures—conformance to standards	Each laboratory did not have testing procedures which are designed to ensure that [components] [in-process materials] [PET drug products] conform to appropriate standards including established standards of identity, strength, quality, and purity.	3
FDCA 503B(a)(10)	Container label, outsourcer facility	The container labels of your outsourcing facility's drug products are deficient.	3

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TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.42(b)	Product flow through building is inadequate	The flow of [components] [drug product containers] [closures] [labeling] [in-process materials] [drug products] though the building is not designed to prevent contamination.	2
21 CFR 211.101(c)	Weighing/measuring/subdividing supervision	Component [weighing] [measuring] [subdividing] operations are not adequately supervised.	2
21 CFR 211.115(a)	Reprocessing procedures not written or followed	Procedures prescribing a system for reprocessing batches to ensure that the reprocessed batches will conform with all established standards, specifications, and characteristics are not [written] [followed].	2
21 CFR 211.125(d)	Destruction of excess labels with lot numbers	Excess labeling bearing lot or control numbers is not destroyed.	2
21 CFR 211.137(d)	Expiration date location on labeling	Drug product expiration dates do not appear on the labeling in the manner prescribed by regulations.	2
21 CFR 211.80(d)	Disposition recorded by lot identification	The distinctive code for each lot of [components] [drug product containers] [closures] is not used in recording the disposition of each lot.	2
21 CFR 211.80(d)	Identification of each lot in each shipment	Each lot in each shipment received was not identified with a distinctive code for each container or grouping of containers for [components] [drug product containers] [closures].	2
21 CFR 211.82(a)	Examination on receipt, before acceptance	Each container or grouping of containers of [components] [drug product containers] [closures] is not examined visually upon receipt and before acceptance for [appropriate labeling as to contents] [container damage] [broken seals] [contamination].	2
21 CFR 211.84(b)	Representative samples criteria	The [number of containers to be sampled] [amount of material taken from each container] is not based upon appropriate criteria.	2
21 CFR 211.84(c)(2)	Appropriate opening of component containers	The containers of components or drug product containers or closures which are sampled are not opened in a manner to prevent [contamination of their contents] [contamination of other components] [contamination of other drug product containers] [contamination of other closures].	2
21 CFR 211.94(a)	Reactive/additive/absorptive containers/ closures	Drug product containers or closures are [reactive] [additive] [absorptive] so as to alter the safety, identity, strength, quality, and purity of the drug beyond the official or established requirements.	2
21 CFR 211.166(a)(2)	Stability sample storage conditions described	The written stability program for drug products does not describe the storage conditions for samples retained for testing.	2
21 CFR 211.180(e)(2)	Review of problem drugs	The procedures for the annual quality standards record evaluation are deficient in that they do not address a review of [complaint] [recall] [returned drug product] [salvaged drug product] [investigation] records for each drug product.	2
21 CFR 211.182	Personnel dating/signing equipment log	The persons [performing] [double-checking] the cleaning and maintenance are not [dating] [signing or initialing] the equipment cleaning and use log.	2
21 CFR 211.194(e)	Stability testing records not included	Laboratory records do not include complete records of all stability testing performed.	2
21 CFR 211.44	Adequate lighting not provided	Adequate lighting is not provided in all areas.	2
21 CFR 211.56(a)	Trash and organic waste timely disposal	There is no provision to hold and dispose of [trash] [organic waste matter] in a timely and sanitary manner.	2

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TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.84(c)(4)	Composite sample top/middle/bottom	Sampling procedures are deficient regarding compositing for testing of samples collected from the top, middle, and bottom of the component container.	2
21 CFR 211.110(a)(3)	Mixing adequacy	The in-process control procedures were deficient in that they did not include an examination of the adequacy of mixing to assure uniformity and homogeneity.	2
21 CFR 211.110(b)	In-process materials specifications	In-process specifications are not [consistent with drug product final specifications] [derived from previous acceptable process average and process variability estimates where possible] [determined by the application of suitable statistical procedures where appropriate].	2
21 CFR 211.160(b)(1)	Specification description of sample/testing	The specifications for components, drug product containers or closures, and labeling are deficient in that they do not include a description of the [sampling plan] [testing procedures].	2
21 CFR 211.160(b)(4)	Test devices not meeting specifications	Test devices are deficient in that [instruments] [apparatus] [gauges] [recording devices] not meeting established specifications are used.	2
21 CFR 211.170(a)	Active ingredient retained sample kept	A sample which is representative of each lot in each shipment of each active ingredient is not [appropriately identified] [retained].	2
21 CFR 211.204	Record information inclusions	Records of returned drug products do not include the [name] [labeled potency] [lot, control, or batch number] [reason for return] [quantity] [date of disposition] [ultimate disposition].	2
21 CFR 211.84(d)(3)	Certificates of testing (containers, closures)	Certificates of testing of [containers] [closures] are accepted in lieu of testing without [a visual identification] [establishing the reliability of the supplier's test results through appropriate validation of the test results at appropriate intervals].	2
21 CFR 211.101(b)	Identification of new containers	For components removed from the original containers, the new container fails to be identified with [component name or item code] [receiving or control number] [weight or measure] [batch for which component was dispensed including product name, strength, and lot number].	2
21 CFR 211.160(b)(1)	Sampling and testing procedures described	Written specifications for laboratory controls do not include a description of the [sampling] [testing] procedures used.	2
21 CFR 211.160(b)(1)	Samples (various types) representative, identified properly	Samples taken to determine conformance to appropriate written specifications for the acceptance of each lot within each shipment of [components] [drug product containers] [closures] [labeling] are not [representative] [adequately identified].	2
21 CFR 211.160(b)(2)	In-process samples representative, identified properly	Samples taken of in-process materials for determination of conformance to specifications are not [representative] [properly identified].	2
21 CFR 211.165(d)	Acceptance/rejection levels	The statistical quality control criteria fail to include appropriate [acceptance levels] [rejection levels].	2
21 CFR 211.170(b)(1)	Retention time of reserve samples, in general	You did not retain reserve samples for drug products for one year after the expiration dates of the drug products.	2
21 CFR 211.188(b)(8)	Labeling control records including specimens or copies	Batch production and control records do not include complete labeling control records, including specimens or copies of all labeling used for each batch of drug product produced.	2
21 CFR 211.188(b)(5)	In-process and laboratory control results	Batch production and control records do not include [in-process] [laboratory control] results for each batch of drug product produced.	2

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TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.188(b)(3)	Identification of each component or in-process material	Batch production and control records do not include the specific identification of each batch of [component] [in-process material] used for each batch of drug product produced.	2
21 CFR 211.194(b)	Test method modification records do not include	Records maintained of any modification of an established method employed in testing do not include [the reason for the modification] [the data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method].	2
21 CFR 314.80(b)	Failure to review ADE information	Adverse drug experience information obtained or otherwise received from any source was not [promptly] reviewed, including information from [commercial marketing experience] [post-marketing clinical investigations] [post-marketing epidemiological/surveillance activities] [reports in the scientific literature] [unpublished scientific papers].	2
21 CFR 314.80(c)(2)	Failure to report non-alert ADEs	Individual ADEs which were not reported to FDA in a post-marketing 15-day alert have not been included in a periodic safety report.	2
21 CFR 314.80(c)(2)(ii)(A)	Incomplete periodic safety report	You failed to submit a periodic report containing [a narrative summary and analysis of the ADE information for the reporting interval in the report] [an analysis of the post marketing 15-day Alert Reports submitted during the reporting interval] [a history of actions taken since the last report because of adverse drug experiences] [an index with a line listing of your patient identification code and adverse reaction term(s) for all ICSRs you submitted for the reporting interval].	2
21 CFR 314.80(j)	Failure to maintain records	You failed to maintain for a period of 10 years records of all adverse drug experiences known to you, including raw data and any correspondence.	2
21 CFR 212.50	Adequate controls (general)	Your firm lacks adequate production and process controls to ensure the consistent production of a PET drug that meets the applicable standards of identity, strength, quality, and purity.	2
21 CFR 212.50(b)	Records to document all steps	You did not have master production and control records that document all steps in the PET drug production process.	2
21 CFR 212.60(f)	Lab written procedures	Laboratory written procedures are not [established] [followed] to ensure that the lab equipment is routinely [calibrated] [inspected] [checked] [maintained].	2
21 CFR 212.60(g)(3)	Record of all test data	Laboratory records did not contain a complete record of all data obtained in the course of each test.	2
21 CFR 361.1(c)(2)	Signatures of RDRC Chairman	The RDRC Chairman did not sign all [applications] [minutes] [reports] of the committee.	2
21 CFR 361.1(c)(2)	Numerical votes not in the minutes of any RDRC meetings	The minutes of an RDRC meeting did not include the numerical results of votes on protocols involving use in human subjects.	2
21 CFR 361.1(f)(1)	Packaging, labeling—Rx only	The label of a radioactive drug prepared, packaged, distributed, and primarily intended for use in the RDRC research project did not bear the statement "Rx only."	2
21 CFR 211.28(b)	Habits of good sanitation and health	Production personnel were not practicing good sanitation and health habits.	1
21 CFR 211.67(b)(6)	Cleaning SOP/inspection	Procedures for the cleaning and maintenance of equipment are deficient regarding inspection of the equipment for cleanliness immediately before use.	1

(*Continued*)

TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.42(d)	Penicillin processing area not kept separate	The operations relating to the [manufacture] [processing] [packing] of penicillin are not performed in facilities separate from those used for other drug products for human use. Specifically, ***	1
21 CFR 211.101(a)	Batches formulated to less than 100%	Written production and control procedures include batches formulated with the intent to provide less than 100% of the labeled or established amount of active ingredient.	1
21 CFR 211.42(c)(3)	Released material area	Separate or defined areas to prevent contamination or mix-ups are deficient regarding operations related to the storage of released [components] [drug product containers] [closures] [labeling].	1
21 CFR 211.42(c)(8)	Released drug products area	Separate or defined areas to prevent contamination or mix-ups are deficient regarding operations related to the storage of drug products after release.	1
21 CFR 211.115(b)	Reprocessing/quality control unit	Reprocessing was performed without the [review] [approval] of the quality control unit.	1
21 CFR 211.122(d)	Labels and labeling stored separately	Labels and other labeling materials are not stored separately with suitable identification for each different drug product, strength, dosage form, or quantity of contents.	1
21 CFR 211.125(b)	Examination of issued labels	Labeling materials issued for a batch were not carefully examined for identity and conformity to the labeling specified in the master or batch production records.	1
21 CFR 211.125(c)	Label reconciliation discrepancies evaluation/ investigation	Discrepancies found outside preset limits when reconciling the quantities of labeling issued, used, and returned were not [evaluated] [investigated].	1
21 CFR 211.130(a)	Prevention of cross-contamination, mix-ups	There is insufficient physical or spatial separation from operations and other drug products to prevent mix-ups and cross-contamination.	1
21 CFR 211.130(b)	Unlabeled filled containers controls	Filled drug product containers which are set aside and held in an unlabeled condition are not [identified] [handled] to preclude mislabeling of individual containers, lots, or portions of lots.	1
21 CFR 211.130(e)	Packaging line inspection before use	Inspection of the [packaging] [labeling] facilities immediately before use is not done to assure that all drug products have been removed from previous operations.	1
21 CFR 211.130(e)	Packaging line inspection after use	Inspection of the [packaging] [labeling] facilities is not done after use to assure that materials not suitable for subsequent operations have been removed.	1
21 CFR 211.86	Rotation of components/containers/closures	There is a lack of rotation so that the oldest approved stock of [components] [drug product containers] [closures] is used first.	1
21 CFR 211.150(a)	Distribution of oldest approved drugs	The oldest approved stock of drug products is not distributed first and there is no justification for this practice. Specifically, ***	1
21 CFR 211.80(c)	Storage off floor, spaced suitably	Bagged or boxed components of drug product [containers] [closures] are not [stored off the floor] [suitably spaced to allow cleaning and inspection].	1
21 CFR 211.84(c)(4)	Top/middle/bottom container sampling	Sampling procedures are deficient regarding sampling components from the top, middle, and bottom of container.	1
21 CFR 211.84(c)(6)	Identifying containers sampled	Markings of containers from which samples have been taken are deficient in that they do not show that samples have been removed from them. Specifically, ***	1

(*Continued*)

TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.84(d)(3)	Container/closure written test procedure	Drug product container and closure test procedures are deficient in that [containers] [closures] are not tested for conformance in accordance with appropriate written procedures. Specifically, ***	1
21 CFR 211.84(d)(6)	Objectionable microbiological contamination	Each lot of a [component] [drug product containers] [closures] liable to objectionable microbiological contamination is deficiently subjected to microbiological tests before use. Specifically, ***	1
21 CFR 211.165(f)	Reprocessed drug products not meeting acceptance criteria	Reprocessed drug material or product has not met appropriate [standards] [specifications] [relevant criteria] prior to acceptance and use.	1
21 CFR 211.167(c)	Controlled release test methods written, followed	Test procedures describing the testing of controlled release dosage form drug product are not [written] [followed].	1
21 CFR 211.180(e)(1)	Representative number of batches for annual review	The procedures for the annual quality standards record evaluation are deficient in that they do not address a review of a representative number of [approved] [rejected] batches.	1
21 CFR 211.180(f)	Responsible firm officials notified in writing	Procedures are not established which are designed to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of [investigations conducted] [recalls] [reports of inspectional observations issued by FDA] [any regulatory actions brought by FDA relating to good manufacturing practices].	1
21 CFR 211.182	Chronological order of equipment log entries	The entries in the equipment cleaning and use logs are not in chronological order.	1
21 CFR 211.184(b)	Component test records	The [component] [drug product container] [closure] [labeling] records do not include the [results of tests or examinations performed] [the conclusions derived from tests or examinations performed].	1
21 CFR 211.184(d)	Labeling: Documentation of exam and review	There is no documentation of the examination and review of labels and labeling for conformity with [established specifications] [the assigning of a lot or control number].	1
21 CFR 211.184(e)	Records of disposition of rejected material	Records do not include the disposition of rejected [components] [drug product containers] [closures] [labeling].	1
21 CFR 211.188(b)(5)	In-process and laboratory control results	The batch production and control records are deficient in that they do not include [in-process] [laboratory] control results.	1
21 CFR 211.188(b)(6)	Documentation of packaging and labeling area inspections	The batch production and control records are deficient in that they do not include documentation of the inspection of the [packaging] [labeling] area before and after use.	1
21 CFR 211.188(b)(11)	Identification of persons performing significant steps	The batch production and control records are deficient in that they do not include identification of persons [performing] [supervising] [checking] each significant step in the operation.	1
21 CFR 211.188(b)(12)	Documentation of batch investigations	The batch production and control records are deficient in that they do not include documentation of batch investigations performed.	1
21 CFR 211.208	No records maintained	No records are maintained for salvaged drug products.	1
21 CFR 211.194(a)(1)	Description and identification of samples	Laboratory records are deficient in that they do not include a [description and identification of the sample received] [quantity] [lot number] [date sample taken] [date sample received for testing].	1
21 CFR 211.194(a)(5)	Testing calculations	Laboratory records are deficient in that they do not include all calculations performed during testing.	1

(*Continued*)

TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.194(a)(7)	Identification of person performing the testing	Laboratory records are deficient in that they do not include the [initials] [signature] of the person performing the tests and the dates the tests were performed.	1
21 CFR 211.198(a)	Quality control review	Complaint procedures are deficient in that they do not include provisions that allow for the review and determination of an investigation by the quality control unit.	1
21 CFR 211.198(b)(1)	Complaint record required information	Complaint records are deficient in that they do not include the known [name and strength of the drug product] [lot number] [name of complainant] [nature of complaint] [reply to complainant].	1
21 CFR 211.198(b)(3)	Reason for not conducting complaint investigation	Complaint records are deficient in that they do not document the reason and the individual making the decision not to conduct a complaint investigation.	1
21 CFR 211.65(a)	Equipment construction—reactive surfaces	Equipment surfaces that contact [components] [in-process materials] [drug products] are 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.	1
21 CFR 211.46(a)	Adequate ventilation not provided	Adequate ventilation is not provided.	1
21 CFR 211.50	Sewage and refuse disposal in safe manner	Disposal of [sewage] [trash] [refuse] from the [building] [immediate premises] is not done in a safe and sanitary manner.	1
21 CFR 211.101(b)(4)	Subdivided component/container/finished drug	Containers holding subdivided components for drug product manufacturing are deficiently identified in that they lack the batch for which component was dispensed, including its name, strength, and lot number.	1
21 CFR 211.132(b)(1)	OTC products requiring tamper-evident packaging	OTC products packaged for retail sale which are not specifically excluded from the requirement for tamper-evident packaging are not sold in tamper-evident packages.	1
21 CFR 211.160(b)(1)	Determination of conformance	Determinations of conformance to appropriate written specifications for acceptance are deficient in that they are not made for each lot within each shipment of [components] [drug product containers] [closures] [labeling] used in the manufacture, processing, packing, or holding of drug products.	1
21 CFR 211.160(b)(2)	Acceptance of in-process materials	Determinations of conformance to appropriate written specifications for acceptance are [not made] [deficient] for in-process materials.	1
21 CFR 211.170(a)	Reserve sample quantity—active ingredients only	The reserve sample of active ingredient does not consist of at least twice the quantity necessary for all tests required to determine whether the active ingredient meets its established specifications.	1
21 CFR 211.56(b)	Written sanitation procedures not followed	Written procedures for sanitation are not followed.	1
21 CFR 211.68(b)	Written record not kept of program and validation data	A written record of the program along with appropriate validation data has not been maintained in situations where backup data is eliminated by computerization or other automated processes.	1
21 CFR 211.84(c)(4)	Compositing of sub-samples	Components which must be sampled from top, middle, and bottom of the container are not kept separate but instead are composited for testing.	1
21 CFR 211.84(d)(3)	Testing containers and closures conformity with specs	Containers and closures are not tested for conformance with all appropriate written procedures.	1

(*Continued*)

TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.101(d)	Component release checked by second person	Each container of component dispensed to manufacturing is not examined by a second person to assure that [the component was released by the quality control unit] [the weight or measure is correct as stated in the batch records] [the containers are properly identified].	1
21 CFR 211.115(a)	Reprocessing procedures lack steps to be taken	Reprocessing procedures lack the steps to be taken to ensure that reprocessed batches will conform with all established standards, specifications, and characteristics.	1
21 CFR 211.110(b)	In-process materials specifications testing	Examination and testing of samples are not done to assure that in-process materials conform to specifications.	1
21 CFR 211.110(a)	Control procedures fail to include the following	Control procedures fail to include [tablet or capsule weight variation] [disintegration time] [adequacy of mixing to assure uniformity and homogeneity] [dissolution time and rate] [clarity, completeness, or pH of solutions].	1
21 CFR 211.122(c)	Records fail to include	Records kept for each different labeling and packaging material shipment fail to include [the receipt] [results of examination or testing] [a statement of whether the shipment was accepted or rejected].	1
21 CFR 211.122(a)	Written procedures not followed	Written procedures for the [receipt] [identification] [storage] [handling] [sampling] [examination] [testing] of packaging and labeling materials are not followed.	1
21 CFR 211.130(e)	Packaging line inspection documentation	Results of inspection of packaging and labeling facilities are not documented in the batch production records.	1
21 CFR 211.142(a)	Quarantine—written procedures	Written procedures for the warehousing of drug products do not include quarantine of drug products before release by the quality control unit.	1
21 CFR 211.160(b)(3)	Drug products—sampling procedures/ specifications	Laboratory controls do not include a determination of conformance to [written descriptions of sampling procedures] [appropriate specifications] for drug products.	1
21 CFR 211.170(b)(3)	Retention time for exempt OTC drug products	You did not retain reserve samples for OTC drug products which were exempt from bearing an expiration date for 3 years after the lots or batches of drug products were distributed.	1
21 CFR 211.176	Failing to test for penicillin cross-contamination	Non-penicillin drug products were not tested for the presence of penicillin, when a reasonable possibility existed that a non-penicillin drug product has been exposed to a cross-contamination with penicillin.	1
21 CFR 211.188(b)(11)	Identification of persons involved, each significant step	Batch production and control records do not include the identification of the persons [performing] [directly supervising] [checking] each significant step in the operation, for each batch of drug product produced.	1
21 CFR 211.188(b)(6)	Inspection of packaging and labeling area	Batch production and control records do not include results of the inspection of the packaging and labeling area [before] [after] use for each batch of drug product produced.	1
21 CFR 211.198(b)(3)	Determination not to conduct investigation of complaint	The written record did not include the [reason an investigation was found not to be necessary] [name of the responsible person making the determination not to conduct an investigation] when an investigation into [unexplained discrepancies] [the failure of a batch or any of its components to meet specifications] was not conducted.	1
21 CFR 211.198(b)(1)	Written complaint record must include	Written complaint records do not include, where known, [the name and strength of the drug product] [lot number] [name of complainant] [nature of complaint] [reply to complainant].	1

(*Continued*)

TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 211.194(a)(1)	Sample identification and other information	Laboratory records do not include [a description of the sample received for testing] [the source or location from where the sample was obtained] [the quantity of the sample] [the lot number or other distinctive code of the sample] [the date the sample was taken] [the date the sample was received for testing].	1
21 CFR 211.204	Returned drug products with doubt cast as to safety et al.	Returned drug products held, stored, or shipped before or during their return under conditions which cast doubt on their safety, identity, strength, quality, or purity are not [destroyed] [subjected to examination, testing, or other investigation to prove the drug products do meet all the necessary parameters].	1
21 CFR 314.80(c)	[NDA prod] Fail to submit report in approved electronic format	You did not submit adverse drug experience information in electronic format.	1
21 CFR 314.80(c)(1)(iii)	Non-applicant reports to applicant	You, as a non-applicant, elected to submit to the applicant (rather than to FDA) all reports of adverse drug experiences that were both serious and unexpected. However, you did not submit each report to the applicant [within 5 calendar days of your receipt of the information].	1
21 CFR 314.81(b)(2) (iv)(b)	Mfg and control changes not requiring a supplemental app.	An annual report did not include a full description of the manufacturing and control changes not requiring a supplemental application, listed by date in the order in which they were implemented.	1
21 CFR 314.81(b)(2)	Form FDA 2252	A [completed] Form FDA 2252 (Transmittal of Periodic Reports for Drugs for Human Use) was not submitted with an annual report.	1
FDCA 760(b)(1)	No label copy submitted with AE report (non-Rx drug)	Copies of labels from on or within the retail package of a non-prescription drug did not accompany serious drug event report.	1
FDCA 760(c)(1)	Timing of AE report submission (non-RX drugs)	An adverse event report for a nonprescription drug was not submitted to the Secretary of HHS within 15 business days of receipt of the report.	1
FDCA 760(c)(2)	New medical information, timing of submission (non-Rx drugs)	An adverse event report for a nonprescription drug was not submitted to the Secretary of HHS within 15 business days of receipt of the report.	1
21 CFR 314.80(c)(1)(iii)	Non-applicant reports directly to FDA	You, as a non-applicant electing not to submit to the applicant all reports of serious and unexpected adverse drug experiences, failed to submit all reports directly to FDA within 15 calendar days of your receipt of the adverse drug experience information.	1
21 CFR 310.305(a)	Failure to develop written procedures	Written procedures have not been developed for the [surveillance] [receipt] [evaluation] [reporting to FDA] of post-marketing adverse drug experiences.	1
21 CFR 212.20(b)	Examine, approve, or reject	You did not approve or reject [components] [containers] [closures] [in-process materials] [packaging materials] [labeling] [finished dosage forms] in a manner that ensures compliance with procedures and specifications affecting the identity, strength, quality, or purity of a PET drug.	1
21 CFR 212.20(e)	Written QA procedures established, followed	You did not [establish] [follow] written quality assurance procedures.	1
21 CFR 212.40(c)	Designation of incoming lots	You did not designate each incoming lot of [components] [containers] [closures] as quarantined, accepted, or rejected.	1
21 CFR 212.40(c)	Use of reliable suppliers	You did not use a reliable supplier as a source of each lot of [component] [container] [closure].	1

(*Continued*)

TABLE 18.1 (CONTINUED)
Year 2017 FDA 483 Citations Issued for Inspection of Facilities Manufacturing Drugs

Reference Number	Short Description	Long Description	Frequency
21 CFR 212.60(c)	Analytical methods	Your laboratory analytical methods [are not suitable for their intended use] [are not sufficiently sensitive] [are not sufficiently specific] [are not accurate] [are not reproducible].	1
21 CFR 212.60(e)	Equipment	All equipment used to perform the testing is not [suitable for its intended purposes] [capable of producing valid results].	1
21 CFR 212.70(b)	Compendial test procedure	You did not first [verify] [document] that an established compendial test procedure works under the conditions of actual use.	1
21 CFR 212.71(b)	Documentation of non-conforming product investigation	You did not document [the results of the investigation] [what happened to the rejected PET drug product] for a PET drug product that did not meet specifications.	1
21 CFR 361.1(c)(2)	Representation of the required fields of expertise	The RDRC met without having the appropriate representation of the required fields of expertise.	1
21 CFR 361.1(c)(2)	RDRC has not kept minutes of its meetings	The RDRC did not keep minutes for each of its meetings.	1
21 CFR 361.1(c)(2)	RDRC did not meet at least once each quarter	The RDRC did not meet at least once each quarter in which research activity was authorized or conducted.	1
21 CFR 361.1(c)(3)	FDA research proposals not reported +30 subjects	The RDRC did not [immediately] report to FDA a research proposal that involves exposure of more than thirty (30) subjects.	1
21 CFR 361.1(f)(2)	Label—for research use	The label of a radioactive drug prepared, packaged, distributed, and primarily intended for use in the RDRC research project did not bear a statement that the drug is to be administered in compliance with radioactive drug research use.	1
21 CFR 361.1(f)(4)	Label—established name, quantity active ingredient	The label of a radioactive drug prepared, packaged, distributed, and primarily intended for use in the RDRC research project did not bear the established name and quantity of each active ingredient.	1
21 CFR 361.1(f)(5)	Label—radioactivity, amount	The label of a radioactive drug prepared, packaged, distributed, and primarily intended for use in the RDRC research project did not bear the [name and half-life of the radionuclide] [total quantity of radioactivity in the drug product's immediate container] [amount of radioactivity per unit volume or unit mass at a designated referenced time].	1
21 CFR 361.1(f)(9)	Label—name, address manufacturer	The label of a radioactive drug prepared, packaged, distributed, and primarily intended for use in the RDRC research project did not bear the [name] [address] of the manufacturer, packer, or distributor.	1
21 CFR 361.1(f)(11)	Label—parenteral drug, sterile	The label of a radioactive parenteral drug prepared, packaged, distributed, and primarily intended for use in the RDRC research project did not bear a statement as to whether the contents are sterile.	1
21 CFR 314.80(c)(2)(ii)(B)	Late submission of an ICSR	You failed to submit an ICSR for the reporting period [within 30 days of the close of the quarter] [within 60 days of the anniversary date of the approval of the application].	1
21 CFR 314.80(g)(1)	Failure to submit electronic format safety report	Not all safety report submissions were made in an electronic format.	1

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19 WHO Good Manufacturing Guidelines

QUALITY MANAGEMENT IN THE DRUG INDUSTRY: PHILOSOPHY AND ESSENTIAL ELEMENTS

The WHO provides GMP guidelines and also offers a program of GMP compliance certification. One of the most valuable documents is the WHO Technical Report 908, which is available at http://whqlibdoc.who.int/trs/WHO_TRS_908.pdf#page=46. In addition, the WHO offers many very useful GMP training programs (http://healthtech.who.int/pq/trainingresources/pq_pres/gmptraining/GMPBasicTraining.htm) that can be of great benefit to companies who may not have access to the inspections by the U.S. FDA or EMEA. It is important to know that the U.S. FDA inspection triggers only when there is an application pending for marketing authorization in the United States, whereas the European as well as the WHO GMP audits can be invited otherwise.

To assure that the interpretation of the WHO guidelines is properly understood, an appendix to this guideline includes the glossary of terms used.

Also included at the end of the chapter is a description of the various types of inspections that the WHO offers. It is important to know that WHO will offer inspections regardless of the status of marketing authorization applications; most manufacturers will request these inspections in anticipation of participation in the WHO Essential Drugs Program and register as certified suppliers, which will qualify the manufacturer to bid on various WHO-sponsored drug purchase programs.

In the drug industry at large, quality management is usually defined as the aspect of management function that determines and implements the "quality policy," that is, the overall intention and direction of an organization regarding quality, as formally expressed and authorized by top management. The basic elements of quality management are as follows:

- An appropriate infrastructure or "quality system," encompassing the organizational structure, procedures, processes, and resources.
- Systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality. The totality of these actions is termed "quality assurance."

Within an organization, quality assurance serves as a management tool. In contractual situations, quality assurance also serves to generate confidence in the supplier.

The concepts of quality assurance, GMP, and quality control are interrelated aspects of quality management. They are described here in order to emphasize their relationship and their fundamental importance to the production and control of pharmaceutical products.

1. Quality Assurance

1.1 Principle. "Quality assurance" is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including those outside the scope of this guide such as product design and development.

1.2 The system of quality assurance appropriate to the manufacture of pharmaceutical products should ensure that

(a) Pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such as those of good laboratory practice (GLP) and good clinical practice (GCP).

(b) Production and control operations are clearly specified in a written form and GMP requirements are adopted.

(c) Managerial responsibilities are clearly specified in job descriptions.

(d) Arrangements are made for the manufacture, supply, and use of the correct starting and packaging materials.

(e) All necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out.

(f) The finished product is correctly processed and checked, according to the defined procedures.

(g) Pharmaceutical products are not sold or supplied before the authorized persons (see also Sections 9.11 and 9.12) have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control, and release of pharmaceutical products.

(h) Satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored by the manufacturer, distributed, and subsequently handled so that quality is maintained throughout their shelf life.

(i) There is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system

(j) Deviations are reported, investigated, and recorded
(k) There is a system for approving changes that may have an impact on product quality.
(l) Regular evaluations of the quality of pharmaceutical products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement.

1.3 The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization, and do not place patients at risk due to inadequate safety, quality, or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment of staff in many different departments and at all levels within the company, the company's suppliers, and the distributors. To achieve the quality objective reliably, there must be a comprehensively designed and correctly implemented system of quality assurance incorporating GMP and quality control. It should be fully documented and its effectiveness monitored. All parts of the quality assurance system should be adequately staffed with competent personnel and should have suitable and sufficient premises, equipment, and facilities.

2. GMPs for Pharmaceutical Products

2.1 Good manufacturing practice is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. GMPs are aimed primarily at diminishing the risks inherent in any pharmaceutical production. Such risks are essentially of two types: Cross-contamination (in particular of unexpected contaminants) and mix-ups (confusion) caused by, for example, false labels being put on containers. Under GMP

(a) All manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications.
(b) Qualification and validation are performed.
(c) All necessary resources are provided, including
  (i) Appropriately qualified and trained personnel
  (ii) Adequate premises and space
  (iii) Suitable equipment and services
  (iv) Appropriate materials, containers, and labels
  (v) Approved procedures and instructions
  (vi) Suitable storage and transport and
  (vii) Adequate personnel, laboratories, and equipment for in-process controls
(d) Instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided.
(e) Operators are trained to carry out procedures correctly.
(f) Records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have, in fact, been taken and that the quantity and quality of the product are as expected; any significant deviations are fully recorded and investigated.
(g) Records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form.
(h) The proper storage and distribution of the products minimize any risk to their quality.
(i) A system is available to recall any batch of product from sale or supply.
(j) Complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products to prevent recurrence.

3. Sanitation and Hygiene

3.1 A high level of sanitation and hygiene should be practiced in every aspect of the manufacture of drug products. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product. Potential sources of contamination should be eliminated through an integrated comprehensive program of sanitation and hygiene. (For personal hygiene see Section 11, and for sanitation see Section 12, "Premises.")

4. Qualification and Validation

4.1 In accordance with GMP, each pharmaceutical company should identify what qualification and validation work is required to prove that the critical aspects of their particular operation are controlled.

4.2 The key elements of a qualification and validation program of a company should be clearly defined and documented in a validation master plan.

4.3 Qualification and validation should establish and provide documentary evidence that

(a) The premises, supporting utilities, equipment, and processes have been designed in

accordance with the requirements for GMP (design qualification or DQ).

(b) The premises, supporting utilities, and equipment have been built and installed in compliance with their design specifications (installation qualification or IQ).

(c) The premises, supporting utilities, and equipment operate in accordance with their design specifications (operational qualification or OQ).

(d) A specific process will consistently produce a product meeting its predetermined specifications and quality attributes (process validation, or PV, also called performance qualification, or PQ).

4.4 Any aspect of operation, including significant changes to the premises, facilities, equipment, or processes, which may affect the quality of the product, directly or indirectly, should be qualified and validated.

4.5 Qualification and validation should not be considered as one-off exercises. An ongoing program should follow their first implementation and should be based on an annual review.

4.6 The commitment to maintain continued validation status should be stated in the relevant company documentation, such as the quality manual or validation master plan.

4.7 The responsibility of performing validation should be clearly defined.

4.8 Validation studies are an essential part of GMP and should be conducted in accordance with predefined and approved protocols.

4.9 A written report summarizing the results recorded and the conclusions reached should be prepared and stored.

4.10 Processes and procedures should be established on the basis of the results of the validation performed.

4.11 It is of critical importance that particular attention is paid to the validation of analytical test methods, automated systems, and cleaning procedures.

5. Complaints

5.1 Principle. All complaints and other information concerning potentially defective products should be carefully reviewed according to written procedures and the corrective action should be taken.

5.2 A person responsible for handling the complaints and deciding the measures to be taken should be designated, together with sufficient supporting staff to assist him or her. If this person is different from the authorized person, the latter should be made aware of any complaint, investigation, or recall.

5.3 There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

5.4 Special attention should be given to establish whether a complaint was caused because of counterfeiting.

5.5 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for quality control should normally be involved in the review of such investigations.

5.6 If a product defect is discovered or suspected in a batch, consideration should be given to whether other batches should be checked in order to determine whether they are also affected. In particular, other batches that may contain reprocessed product from the defective batch should be investigated.

5.7 Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.

5.8 All decisions made and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

5.9 Complaints records should be regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.

5.10 The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, counterfeiting, or any other serious quality problems with a product.

6. Product Recalls

6.1 Principle. There should be a system to recall from the market, promptly and effectively, products known or suspected to be defective.

6.2 The authorized person should be responsible for the execution and coordination of recalls. He or she should have sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency.

6.3 There should be established written procedures, which are regularly reviewed and updated, for the organization of any recall activity. Recall operations should be capable of being initiated promptly down to the required level in the distribution chain.

6.4 An instruction should be included in the written procedures to store recalled products in a secure segregated area while their fate is decided.

6.5 All competent authorities of all countries to which a given product has been distributed should be promptly informed of any intention to recall the product because it is, or is suspected of being, defective.

6.6 The distribution records should be readily available to the authorized person, and they should contain sufficient information on wholesalers and directly supplied customers (including, for exported

products, those who have received samples for clinical tests and medical samples) to permit an effective recall.

6.7 The progress of the recall process should be monitored and recorded. Records should include the disposition of the product. A final report should be issued, including a reconciliation between the delivered and recovered quantities of the products.

6.8 The effectiveness of the arrangements for recalls should be tested and evaluated from time to time.

7. Contract Production and Analysis

7.1 Principle. Contract production and analysis must be correctly defined, agreed, and controlled in order to avoid misunderstandings that could result in a product or work or analysis of unsatisfactory quality.

General

7.2 All arrangements for contract manufacture and analysis, including any proposed changes in technical or other arrangements, should be in accordance with the marketing authorization for the product concerned.

7.3 The contract should permit the contract giver to audit the facilities of the contract accepter.

7.4 In the case of contract analysis, the final approval for release must be given by the authorized person.

The Contract Giver

7.5 The contract giver is responsible for assessing the competence of the contract accepter in successfully carrying out the work or tests required, for approval for contract activities, and for ensuring by means of the contract that the principles of GMP described in this guide are followed.

7.6 The contract giver should provide the contract accepter with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The contract giver should ensure that the contract accepter is fully aware of any problems associated with the product, work, or tests that might pose a hazard to premises, equipment, personnel, other materials, or other products.

7.7 The contract giver should ensure that all processed products and materials delivered by the contract accepter comply with their specifications or that the product has been released by the authorized person.

The Contract Accepter

7.8 The contract accepter must have adequate premises, equipment, knowledge, and experience and competent personnel to carry out satisfactorily the work ordered by the contract giver. Contract manufacture may be undertaken only by a manufacturer who holds a manufacturing authorization.

7.9 The contract accepter should not pass to a third party any of the work entrusted to him or her under the contract without the contract giver's prior evaluation and approval of the arrangements. Arrangements made between the contract accepter and any third party should ensure that the manufacturing and analytical information is made available in the same way as between the original contract giver and contract accepter.

7.10 The contract accepter should refrain from any activity that may adversely affect the quality of the product manufactured and/or analyzed for the contract giver.

The Contract

7.11 There must be a written contract between the contract giver and the contract accepter which clearly establishes the responsibilities of each party.

7.12 The contract must clearly state the way in which the authorized person, in releasing each batch of product for sale or issuing the Certificate of Analysis, exercises his or her full responsibility and ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the marketing authorization.

7.13 Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis, and GMP.

7.14 All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.

7.15 The contract should describe clearly who is responsible for purchasing, testing, and releasing materials and for undertaking production and quality controls, including in-process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the contract accepter should take samples at the premises of the manufacturer.

7.16 Manufacturing, analytical, distribution records, and reference samples should be kept by, or be available to, the contract giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the contract giver.

7.17 The contract should describe the handling of starting materials, intermediate and bulk products, and finished products if they are rejected. It should also describe the procedure to be followed if the contract analysis shows that the tested product must be rejected.

8. Self-Inspection and Quality Audits

8.1 Principle. The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and quality control. The self-inspection program should be designed to detect any shortcomings in the implementation of

GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, for example, in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively. All recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up program.

Items for Self-Inspection

8.2 Written instructions for self-inspection should be established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items:

(a) Personnel
(b) Premises including personnel facilities
(c) Maintenance of buildings and equipment
(d) Storage of starting materials and finished products
(e) Equipment
(f) Production and in-process controls
(g) Quality control
(h) Documentation
(i) Sanitation and hygiene
(j) Validation and revalidation programs
(k) Calibration of instruments or measurement systems
(l) Recall procedures
(m) Complaints management
(n) Labels control
(o) Results of previous self-inspections and any corrective steps taken

Self-Inspection Team

8.3 Management should appoint a self-inspection team consisting of experts in their respective fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

Frequency of Self-Inspection

8.4 The frequency at which self-inspections are conducted may depend on company requirements but should preferably be at least once a year. The frequency should be stated in the procedure.

Self-Inspection Report

8.5 A report should be made at the completion of a self-inspection. The report should include

(a) Self-inspection results
(b) Evaluation and conclusions and
(c) Recommended corrective actions

Follow-Up Action

8.6 There should be an effective follow-up program. The company management should evaluate both the self-inspection report and the corrective actions as necessary.

Quality Audit

8.7 It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors (see Section 7, "Contract Production and Analysis").

Suppliers' Audits and Approval

8.8 The person responsible for quality control should have responsibility together with other relevant departments for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.

8.9 Before suppliers are approved and included in the approved suppliers' list or specifications, they should be evaluated. The evaluation should take into account a supplier's history and the nature of the materials to be supplied. If an audit is required, it should determine the supplier's ability to conform with GMP standards.

9. Personnel

9.1 Principle. The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason, there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written descriptions.

General

9.2 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive so as to present any risk to quality.

9.3 All responsible staff should have their specific duties recorded in written descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be

no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of GMP. The manufacturer should have an organization chart.

9.4 All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs. All personnel should be motivated to support the establishment and maintenance of high-quality standards.

9.5 Steps should be taken to prevent unauthorized people from entering production, storage, and quality control areas. Personnel who do not work in these areas should not use them as a passageway.

Key Personnel

9.6 Key personnel include the head of production, the head of quality control, and the authorized person. Normally, key posts should be occupied by full-time personnel. The heads of production and quality control should be independent of each other. In large organizations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated.

9.7 Key personnel responsible for supervising the manufacture and quality control of pharmaceutical products should possess the qualifications of a scientific education and practical experience required by national legislation. Their education should include the study of an appropriate combination of

(a) Chemistry (analytical or organic) or biochemistry
(b) Chemical engineering
(c) Microbiology
(d) Pharmaceutical sciences and technology
(e) Pharmacology and toxicology
(f) Physiology and
(g) Other related sciences

They should also have adequate practical experience in the manufacture and quality assurance of pharmaceutical products. In order to gain such experience, a preparatory period may be required, during which they should exercise their duties under professional guidance. The scientific education and practical experience of experts should be such as to enable them to exercise independent professional judgment, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and quality control of pharmaceutical products.

9.8 The heads of the production and quality control generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, depending on national regulations,

(a) To ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality
(b) To approve the instructions relating to production operations, including the in-process controls, and to ensure their strict implementation
(c) To ensure that the production records are evaluated and signed by a designated person
(d) To check the maintenance of the department, premises, and equipment
(e) To ensure that the appropriate process validations and calibrations of control equipment are performed and recorded and the reports made available and
(f) To ensure that the required initial and continuing training of production personnel is carried out and adapted according to need

9.9 The head of the production generally has the following responsibilities:

(a) Authorization of written procedures and other documents, including amendments
(b) Monitoring and control of the manufacturing environment
(c) Plant hygiene
(d) Process validation and calibration of analytical apparatus
(e) Training, including the application and principles of quality assurance
(f) Approval and monitoring of suppliers of materials
(g) Approval and monitoring of contract manufacturers
(h) Designation and monitoring of storage conditions for materials and products
(i) Performance and evaluation of in-process controls
(j) Retention of records
(k) Monitoring of compliance with GMP requirements and
(l) Inspection, investigation, and taking of samples in order to monitor factors that may affect product quality

9.10 The head of the quality control generally has the following responsibilities:

(a) To approve or reject starting materials, packaging materials, and intermediate, bulk, and finished products in relation to their specifications
(b) To evaluate batch records
(c) To ensure that all necessary testing is carried out
(d) To approve sampling instructions, specifications, test methods, and other quality control procedures
(e) To approve and monitor analyses carried out under contract
(f) To check the maintenance of the department, premises, and equipment
(g) To ensure that the appropriate validations, including those of analytical procedures, and calibrations of control equipment are carried out and

(h) To ensure that the required initial and continuing training of quality control personnel is carried out and adapted according to need

Other duties of the quality control are summarized in Sections 17.3 and 17.4.

9.11 The authorized person is responsible for compliance with technical or regulatory requirements related to the quality of finished products and the approval of the release of the finished product for sale.

9.12 The authorized person will also be involved in other activities, including

(a) Implementation (and, when needed, establishment) of the quality system
(b) Participation in the development of the company's quality manual
(c) Supervision of the regular internal audits or self-inspections
(d) Oversight of the quality control department
(e) Participation in external audit (vendor audit) and
(f) Participation in validation programs

9.13 The function of the approval of the release of a finished batch or a product can be delegated to a designated person with appropriate qualifications and experience who will release the product in accordance with an approved procedure. This is normally done by quality assurance by means of batch review.

9.14 The person responsible for approving a batch for release should always ensure that the following requirements have been met:

(a) The marketing authorization and the manufacturing authorization requirements for the product have been met for the batch concerned.
(b) The principles and guidelines of GMP, as laid down in the guidelines published by WHO, have been followed.
(c) The principal manufacturing and testing processes have been validated, if different.
(d) All the necessary checks and tests have been performed and account taken of the production conditions and manufacturing records.
(e) Any planned changes or deviations in manufacturing or quality control have been notified in accordance with a well-defined reporting system before any product is released. Such changes may need notification to, and approval by, the drug regulatory authority.
(f) Any additional sampling, inspection, tests, and checks have been carried out or initiated, as appropriate, to cover planned changes and deviations.
(g) All necessary production and quality control documentation has been completed and endorsed by supervisors trained in appropriate disciplines.
(h) Appropriate audits, self-inspections, and spot-checks are carried out by experienced and trained staff.
(i) Approval has been given by the head of quality control.
(j) All relevant factors have been considered, including any not specifically associated with the output batch directly under review (e.g., subdivision of output batches from a common input, factors associated with continuous production runs).

10. Training

10.1 The manufacturer should provide training in accordance with a written program for all personnel whose duties take them into manufacturing areas or into control laboratories (including the technical, maintenance, and cleaning personnel) and for other personnel as required.

10.2 Besides basic training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given and its practical effectiveness periodically assessed. Approved training programs should be available. Training records should be kept.

10.3 Personnel working in areas where contamination is a hazard, for example, clean areas or areas where highly active, toxic, infectious, or sensitizing materials are handled, should be given specific training.

10.4 The concept of quality assurance and all the measures which aid its understanding and implementation should be fully discussed during the training sessions.

10.5 Visitors or untrained personnel should preferably not be taken into the production and quality control areas. If this is unavoidable, they should be given relevant information in advance (particularly about personal hygiene) and the prescribed protective clothing. They should be closely supervised.

10.6 Consultant and contract staff should be qualified for the services they provide. Evidence of this should be included in the training records.

11. Personal Hygiene

11.1 All personnel, prior to and during employment, as appropriate, should undergo health examinations. Personnel conducting visual inspections should also undergo periodic eye examinations.

11.2 All personnel should be trained in the practices of personal hygiene. A high level of personal hygiene should be observed by all those concerned with manufacturing processes. In particular, personnel should be instructed to wash their hands before entering production areas. Signs to this effect should be posted and instructions observed.

11.3 Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle starting materials, packaging materials, in-process materials, or drug products until the condition is no longer judged to be a risk.

11.4 All employees should be instructed and encouraged to report to their immediate supervisor any conditions (relating to plant, equipment, or personnel) that they consider may adversely affect the products.

11.5 Direct contact should be avoided between the operator's hands and starting materials, primary packaging materials, and intermediate or bulk product.

11.6 To ensure protection of the product from contamination, personnel should wear clean body coverings appropriate to the duties they perform, including appropriate hair covering. Used clothes, if reusable, should be stored in separate closed containers until properly laundered and, if necessary, disinfected or sterilized.

11.7 Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material, and personal medicines should not be permitted in production, laboratory, and storage areas or in any other areas where they might adversely influence product quality.

11.8 Personal hygiene procedures including the use of protective clothing should apply to all persons entering production areas, whether they are temporary or fulltime employees or nonemployees, for example, contractors' employees, visitors, senior managers, and inspectors.

12. Premises

12.1 Principle. Premises must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out.

General

12.2 The layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

12.3 Where dust is generated (e.g., during sampling, weighing, mixing and processing operations, packaging of powder), measures should be taken to avoid cross-contamination and facilitate cleaning.

12.4 Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.

12.5 Premises used for the manufacture of finished products should be suitably designed and constructed to facilitate good sanitation.

12.6 Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products.

12.7 Premises should be cleaned and, where applicable, disinfected according to detailed written procedures. Records should be maintained.

12.8 Electrical supply, lighting, temperature, humidity, and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage or the accurate functioning of equipment.

12.9 Premises should be designed and equipped so as to afford maximum protection against the entry of insects, birds, or other animals. There should be a procedure for rodent and pest control.

12.10 12.10. Premises should be designed to ensure the logical flow of materials and personnel.

Ancillary Areas

12.11 Rest and refreshment rooms should be separate from manufacturing and control areas.

12.12 Facilities for changing and storing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not communicate directly with production or storage areas.

12.13 Maintenance workshops should if possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

12.14 Animal housing should be well isolated from other areas, with separate entrance (animal access) and air-handling facilities.

Storage Areas

12.15 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products with proper separation and segregation: Starting and packaging materials; intermediates, bulk, and finished products; products in quarantine; and released, rejected, returned, or recalled products.

12.16 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean, dry, sufficiently lit, and maintained within acceptable temperature limits. Where special storage conditions are required (e.g., temperature, humidity), these should be provided, controlled, monitored, and recorded where appropriate.

12.17 Receiving and dispatch bays should be separated and protect materials and products from the weather. Receiving areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.

12.18 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.

12.19 Segregation should be provided for the storage of rejected, recalled, or returned materials or products.

12.20 Highly active and radioactive materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire, or explosion should be stored in safe and secure areas.

12.21 Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labeling and special attention should be paid to sampling and the safe and secure storage of these materials.

12.22 There should normally be a separate sampling area for starting materials. (If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.)

Weighing Areas

12.23 The weighing of starting materials and the estimation of yield by weighing should be carried out in separate weighing areas designed for that use, for example, with provisions for dust control. Such areas may be part of either storage or production areas.

Production Areas

12.24 In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitizing materials (e.g., penicillins) or biological preparations (e.g., live microorganisms). The production of certain other highly active products, such as some antibiotics, hormones, cytotoxic substances, and certain nonpharmaceutical products, should not be conducted in the same facilities. In exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations (including cleaning validation) are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of pharmaceutical products.

12.25 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

12.26 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different pharmaceutical products or their components, to avoid cross-contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

12.27 Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors, and ceilings) should be smooth and free from cracks and open joints, should not shed particulate matter, and should permit easy and effective cleaning and, if necessary, disinfection.

12.28 Pipework, light fittings, ventilation points, and other services should be designed and sited to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

12.29 Drains should be of adequate size and designed and equipped to prevent backflow. Open channels should be avoided where possible, but if they are necessary they should be shallow to facilitate cleaning and disinfection.

12.30 Production areas should be effectively ventilated, with air-control facilities (including filtration of air to a sufficient level to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity) appropriate to the products handled, to the operations undertaken, and to the external environment. These areas should be regularly monitored during both production and nonproduction periods to ensure compliance with their design specifications.

12.31 Premises for the packaging of pharmaceutical products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

12.32 Production areas should be well lit, particularly where visual online controls are carried out.

Quality Control Areas

12.33 Quality control laboratories should be separated from production areas. Areas where biological, microbiological, or radioisotope test methods are employed should be separated from each other.

12.34 Quality control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples, reference standards (if necessary, with cooling), solvents, reagents, and records.

12.35 The design of the laboratories should take into account the suitability of construction materials, prevention of fumes, and ventilation. There should be separate air supply to laboratories and production areas. Separate air-handling units and other provisions are needed for biological, microbiological, and radioisotope laboratories.

12.36 A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture, and other external factors or where it is necessary to isolate the instruments.

13. Equipment

13.1 Equipment must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. The layout and design of equipment must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

13.2 Equipment should be installed in such a way as to minimize any risk of error or of contamination.

13.3 Fixed pipework should be clearly labeled to indicate the contents and, where applicable, the direction of flow.

13.4 All service piping and devices should be adequately marked and special attention paid to the provision of noninterchangeable connections or adaptors for dangerous gases and liquids.

13.5 Balances and other measuring equipment of an appropriate range and precision should be available for production and control operations and should be calibrated on a scheduled basis.

13.6 Production equipment should be thoroughly cleaned on a scheduled basis.

13.7 Laboratory equipment and instruments should be suited to the testing procedures undertaken.

13.8 Washing, cleaning, and drying equipment should be chosen and used so as not to be a source of contamination.

13.9 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive, or absorptive to an extent that would affect the quality of the product.

13.10 Defective equipment should be removed from production and quality control areas. If this is not possible, it should be clearly labeled as defective to prevent use.

13.11 Closed equipment should be used whenever appropriate. Where open equipment is used or equipment is opened, precautions should be taken to minimize contamination.

13.12 Nondedicated equipment should be cleaned according to validated cleaning procedures between production of different pharmaceutical products to prevent cross-contamination.

13.13 Current drawings of critical equipment and support systems should be maintained.

14. Materials

14.1 Principle. The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (starting and packaging).

14.2 Materials include starting materials, packaging materials, gases, solvents, process aids, reagents, and labeling materials.

General

14.3 No materials used for operations such as cleaning, lubrication of equipment, and pest control should come into direct contact with the product. Where possible, such materials should be of a suitable grade (e.g., food grade) to minimize health risks.

14.4 All incoming materials and finished products should be quarantined immediately after receipt or processing, until they are released for use or distribution.

14.5 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation by a first-expire, first-out rule.

14.6 Water used in the manufacture of pharmaceutical products should be suitable for its intended use.

Starting Materials

14.7 The purchase of starting materials is an important operation that should involve staff who have a particular and thorough knowledge of the products and suppliers.

14.8 Starting materials should be purchased only from approved suppliers and, where possible, directly from the producer. It is also recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all critical aspects of the production and control of the starting material in question, including handling, labeling, and packaging requirements as well as complaints and rejection procedures, are contractually agreed between the manufacturer and the supplier.

14.9 For each consignment, the containers should be checked for at least integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels.

14.10 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labeled, if required, with the prescribed information. Where additional labels are attached to containers, the original information should not be lost.

14.11 Damage to containers and any other problem that might adversely affect the quality of a material

should be recorded and reported to the quality control department and investigated.

14.12 If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing, and release.

14.13 Starting materials in the storage area should be appropriately labeled. Labels should bear at least the following information:

(a) The designated name of the product and the internal code reference where applicable
(b) The batch number given by the supplier and, on receipt, the control or batch number given by the manufacturer, if any, documented so as to ensure traceability
(c) The status of the contents (e.g., on quarantine, on test, released, rejected, returned, recalled) and
(d) Where appropriate, an expiry date or a date beyond which retesting is necessary

When fully validated computerized storage systems are used, not all of the above information need be in a legible form on the label.

14.14 There should be appropriate procedures or measures to ensure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified.

14.15 Only starting materials released by the quality control department and within their shelf life should be used.

14.16 Starting materials should be dispensed only by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labeled containers.

14.17 Each dispensed material and its weight or volume should be independently checked and the check recorded.

14.18 Materials dispensed for each batch of the final product should be kept together and conspicuously labeled as such.

Packaging Materials

14.19 The purchase, handling, and control of primary and printed packaging materials should be as for starting materials.

14.20 Particular attention should be paid to printed packaging materials. They should be stored in secure conditions so as to exclude the possibility of unauthorized access. Roll-feed labels should be used wherever possible. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by designated personnel following an approved and documented procedure.

14.21 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

14.22 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and its disposal recorded.

14.23 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity, and conformity with the packaging instructions.

Intermediate and Bulk Products

14.24 Intermediate and bulk products should be kept under appropriate conditions.

14.25 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

Finished Products

14.26 Finished products should be held in quarantine until their final release, after which they should be stored as usable stock under conditions established by the manufacturer.

14.27 The evaluation of finished products and the documentation necessary for release of a product for sale are described in Section 17, "Good Practices in Quality Control."

Rejected, Recovered, Reprocessed, and Reworked Materials

14.28 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed in a timely manner. Whatever action is taken should be approved by authorized personnel and recorded.

14.29 The reworking or recovery of rejected products should be exceptional. It is permitted only if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. A record should be kept of the reworking or recovery. A reworked batch should be given a new batch number.

14.30 The introduction of all or part of earlier batches, conforming to the required quality, into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded.

14.31 The need for additional testing of any finished product that has been reprocessed, reworked, or into which a recovered product has been incorporated should be considered by the quality control department.

Recalled Products

14.32 Recalled products should be identified and stored separately in a secure area until a decision is taken on their fate. The decision should be made as soon as possible.

Returned Goods

14.33 Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; in such cases they may be considered for resale or relabeling or alternative action taken only after they have been critically assessed by the quality control function in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse. Any action taken should be appropriately recorded.

Reagents and Culture Media

14.34 There should be records for the receipt and preparation of reagents and culture media.

14.35 Reagents made up in the laboratory should be prepared according to written procedures and appropriately labeled. The label should indicate the concentration, standardization factor, shelf life, the date when re-standardization is due, and the storage conditions. The label should be signed and dated by the person preparing the reagent.

14.36 Both positive and negative controls should be applied to verify the suitability of culture media each time they are prepared and used. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

Reference Standards

14.37 Whenever official reference standards exist, these should preferably be used.

14.38 Official reference standards should be used only for the purpose described in the appropriate monograph.

14.39 Reference standards prepared by the producer should be tested, released, and stored in the same way as official standards. They should be kept under the responsibility of a designated person in a secure area.

14.40 Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization.

14.41 Reference standards should be properly labeled with at least the following information:

(a) Name of the material
(b) Batch or lot number and control number
(c) Date of preparation
(d) Shelf life
(e) Potency and
(f) Storage conditions

14.42 All in-house reference standards should be standardized against an official reference standard, when available, initially and at regular intervals thereafter.

14.43 All reference standards should be stored and used in a manner that will not adversely affect their quality.

Waste Materials

14.44 Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.

14.45 Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

Miscellaneous

14.46 Rodenticides, insecticides, fumigating agents, and sanitizing materials should not be permitted to contaminate equipment, starting materials, packaging materials, in-process materials, or finished products.

15. Documentation

15.1 Principle. Good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control, to ensure that all personnel concerned with manufacture know what to do and when to do it, to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a drug for sale, to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review, and statistical analysis. The design and use of documents depend upon the manufacturer. In some cases, some or all of the documents described below may be brought together, but they will usually be separate.

General

15.2 Documents should be designed, prepared, reviewed, and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorizations.

15.3 Documents should be approved, signed, and dated by the appropriate responsible persons. No

document should be changed without authorization and approval.

15.4 Documents should have unambiguous contents: The title, nature, and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

15.5 Documents should be regularly reviewed and kept up-to-date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version. Superseded documents should be retained for a specific period of time.

15.6 Where documents require the entry of data, these entries should be clear, legible, and indelible. Sufficient space should be provided for such entries.

15.7 Any alteration made to a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

15.8 Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records should be retained for at least one year after the expiry date of the finished product.

15.9 Data (and records for storage) may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formulae and detailed standard operating procedures relating to the system in use should be available, and the accuracy of the records should be checked. If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions; access should be restricted by passwords or other means, and the entry of critical data should be independently checked. Batch records stored electronically should be protected by back-up transfer on magnetic tape, microfilm, paper printouts, or other means. It is particularly important that, during the period of retention, the data are readily available.

Documents Required

Labels

15.10 Labels applied to containers, equipment, or premises should be clear, unambiguous, and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colors to indicate status (e.g., quarantined, accepted, rejected, clean).

15.11 All finished drug products should be identified by labeling, as required by the national legislation, bearing at least the following information:

(a) The name of the drug product
(b) A list of the active ingredients (if applicable, with the INNs), showing the amount of each present and a statement of the net contents (e.g., number of dosage units, weight, volume)
(c) The batch number assigned by the manufacturer
(d) The expiry date in an uncoded form
(e) Any special storage conditions or handling precautions that may be necessary
(f) Directions for use, and warnings and precautions that may be necessary and
(g) The name and address of the manufacturer or the company or the person responsible for placing the product on the market

15.12 For reference standards, the label and/or accompanying document should indicate potency or concentration, date of manufacture, expiry date, date the closure is first opened, storage conditions, and control number, as appropriate.

Specifications and Testing Procedures

15.13 Testing procedures described in documents should be validated in the context of available facilities and equipment before they are adopted for routine testing.

15.14 There should be appropriately authorized and dated specifications, including tests on identity, content, purity, and quality, for starting and packaging materials and for finished products; where appropriate, they should also be available for intermediate or bulk products. Specifications for water, solvents, and reagents (e.g., acids and bases) used in production should be included.

15.15 Each specification should be approved, signed, and dated and maintained by quality control, quality assurance unit, or documentation center. Specifications for starting materials, intermediates, and bulk, finished products, and packaging materials are referred to in Sections 15.18–15.21.

15.16 Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia.

15.17 Pharmacopoeias, reference standards, reference spectra, and other reference materials should be available in the quality control laboratory.

Specifications for Starting and Packaging Materials

15.18 Specifications for starting, primary, and printed packaging materials should provide, if applicable, a description of the materials, including

(a) The designated name (if applicable, the INN) and internal code reference
(b) The reference, if any, to a pharmacopoeial monograph and
(c) Qualitative and quantitative requirements with acceptance limits

Depending on the company's practice, other data may be added to the specification, such as

(a) The supplier and the original producer of the materials
(b) A specimen of printed materials
(c) Directions for sampling and testing, or a reference to procedures
(d) Storage conditions and precautions and
(e) The maximum period of storage before reexamination

Packaging material should conform to specifications and should be compatible with the material and/or with the drug product it contains. The material should be examined for compliance with the specification and for defects as well as for the correctness of identity markings.

15.19 Documents describing testing procedures should state the required frequency for re-assaying each starting material, as determined by its stability.

Specifications for Intermediate and Bulk Products

15.20 Specifications for intermediate and bulk products should be available. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for Finished Products

15.21 Specifications for finished products should include
(a) The designated name of the product and the code reference, where applicable
(b) The designated name(s) of the active ingredient(s) [if applicable, with the INN(s)]
(c) The formula or a reference to the formula
(d) A description of the dosage form and package details
(e) Directions for sampling and testing or a reference to procedures
(f) The qualitative and quantitative requirements, with acceptance limits
(g) The storage conditions and precautions, where applicable, and
(h) The shelf life

Master Formulae

15.22 A formally authorized master formula should exist for each product and batch size to be manufactured.

15.23 The master formula should include
(a) The name of the product, with a product reference code relating to its specification;
(b) A description of the dosage form, strength of the product, and batch size;
(c) A list of all starting materials to be used (if applicable, with the INNs), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing)
(d) A statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable
(e) A statement of the processing location and the principal equipment to be used
(f) The methods, or reference to the methods, to be used for preparing and operating the critical equipment, for example, cleaning (especially after a change in product), assembling, calibrating, sterilizing, use
(g) Detailed stepwise processing instructions (e.g., checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures)
(h) The instructions for any in-process controls with their limits
(i) Where necessary, the requirements for storage of the products, including the container, the labeling, and any special storage conditions, and
(j) Any special precautions to be observed

Packaging Instructions

15.24 Formally authorized packaging instructions should exist for each product, pack size, and type. These should normally include, or make reference to,
(a) The name of the product
(b) A description of its pharmaceutical form, strength, and, where applicable, method of application
(c) The pack size expressed in terms of the number, weight, or volume of the product in the final container
(d) A complete list of all the packaging materials required for a standard batch size, including quantities, sizes, and types, with the code or reference number relating to the specifications for each packaging material
(e) Where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked
(f) Special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before and after packaging operations
(g) A description of the packaging operation, including any significant subsidiary operations, and equipment to be used and
(h) Details of in-process controls with instructions for sampling and acceptance limits

Batch Processing Records

15.25 A batch processing record should be kept for each batch processed. It should be based on the relevant

parts of the currently approved specifications on the record. The method of preparation of such records should be designed to avoid errors. (Copying or validated computer programs are recommended. Transcribing from approved documents should be avoided.)

15.26 Before any processing begins, a check should be made that the equipment and workstation are clear of previous products, documents, or materials not required for the planned process and that the equipment is clean and suitable for use. This check should be recorded.

15.27 During processing, the following information should be recorded at the time each action is taken, and after completion the record should be dated and signed by the person responsible for the processing operations:

(a) The name of the product
(b) The number of the batch being manufactured
(c) Dates and times of commencement, of significant intermediate stages, and of completion of production
(d) The name of the person responsible for each stage of production
(e) The initials of the operator(s) of different significant steps of production and, where appropriate, of the person(s) who checked each of these operations (e.g., weighing)
(f) The batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added)
(g) Any relevant processing operation or event and the major equipment used
(h) The in-process controls performed, the initials of the person(s) carrying them out, and the results obtained
(i) The amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield and
(j) Notes on special problems including details, with signed authorization for any deviation from the master formula

Batch Packaging Records

15.28 A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the approved packaging instructions, and the method of preparing such records should be designed to avoid errors. (Copying or validated computer programs are recommended. Transcribing from approved documents should be avoided.)

15.29 Before any packaging operation begins, checks should be made that the equipment and workstation are clear of previous products, documents, or materials not required for the planned packaging operations and that equipment is clean and suitable for use. These checks should be recorded.

15.30 The following information should be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by signature or electronic password:

(a) The name of the product, the batch number, and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained, and the reconciliation
(b) The date(s) and time(s) of the packaging operations
(c) The name of the responsible person carrying out the packaging operation
(d) The initials of the operators of the different significant steps
(e) The checks made for identity and conformity with the packaging instructions, including the results of in-process controls
(f) Details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area
(g) Whenever possible, samples of the printed packaging materials used, including specimens bearing the approval for the printing of and regular check (where appropriate) of the batch number, expiry date, and any additional overprinting
(h) Notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person
(i) The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed, or returned to stock and the quantities of product obtained to permit an adequate reconciliation

Standard Operating Procedures and Records

15.31 Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached should be available for

(a) Equipment assembly and validation
(b) Analytical apparatus and calibration
(c) Maintenance, cleaning, and sanitization

(d) Personnel matters including qualification, training, clothing, and hygiene
(e) Environmental monitoring
(f) Pest control
(g) Complaints
(h) Recalls and
(i) Returns

15.32 There should be standard operating procedures and records for the receipt of each delivery of starting material and primary and printed packaging material.

15.33 The records of the receipts should include
(a) The name of the material on the delivery note and the containers
(b) The "in-house" name and/or code of the material if different from (a)
(c) The date of receipt
(d) The supplier's name and, if possible, manufacturer's name
(e) The manufacturer's batch or reference number
(f) The total quantity and number of containers received
(g) The batch number assigned after receipt and
(h) Any relevant comment (e.g., state of the containers)

15.34 There should be standard operating procedures for the internal labeling, quarantine, and storage of starting materials, packaging materials, and other materials, as appropriate.

15.35 Standard operating procedures should be available for each instrument and piece of equipment (e.g., use, calibration, cleaning, maintenance) and placed in close proximity to the equipment.

15.36 There should be standard operating procedures for sampling, which specify the person(s) authorized to take samples.

15.37 The sampling instructions should include
(a) The method of sampling and the sampling plan
(b) The equipment to be used
(c) Any precautions to be observed to avoid contamination of the material or any deterioration in its quality
(d) The amount(s) of sample(s) to be taken
(e) Instructions for any required subdivision of the sample
(f) The type of sample container(s) to be used, and whether they are for aseptic sampling or for normal sampling, and labeling and
(g) Any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material

15.38 There should be a standard operating procedure describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk, or finished product is identified with a specific batch number.

15.39 The standard operating procedures for batch numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.

15.40 The standard operating procedure for batch numbering should ensure that the same batch numbers will not be used repeatedly; this applies also to reprocessing.

15.41 Batch-number allocation should be immediately recorded, for example, in a logbook. The record should include at least the date of allocation, product identity, and size of batch.

15.42 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.

15.43 Analysis records should include at least the following data:
(a) The name of the material or product and, where applicable, dosage form
(b) The batch number and, where appropriate, the manufacturer and/or supplier
(c) References to the relevant specifications and testing procedures
(d) Test results, including observations and calculations, and reference to any specifications (limits)
(e) Date(s) and reference number(s) of testing
(f) The initials of the persons who performed the testing
(g) The date and initials of the persons who verified the testing and the calculations, where appropriate, and
(h) A clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person

15.44 Written release and rejection procedures should be available for materials and products and in particular for the release for sale of the finished product by an authorized person.

15.45 Records should be maintained of the distribution of each batch of a product in order, for example, to facilitate the recall of the batch if necessary.

15.46 Records should be kept for major and critical equipment, as appropriate, of any validations, calibrations, maintenance, cleaning, or repair operations, including dates and the identities of the people who carried these operations out.

15.47 The use of major and critical equipment and the areas where products have been processed should be appropriately recorded in chronological order.

15.48 There should be written procedures assigning responsibility for cleaning and sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used, and facilities and equipment to be cleaned. Such written procedures should be followed.

16. Good Practices in Production

16.1 Principle. Production operations must follow clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.

General

16.2 All handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labeling, dispensing, processing, packaging, and distribution, should be done in accordance with written procedures or instructions and, where necessary, recorded.

16.3 Any deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be done in accordance with an approved procedure. The authorization of the deviation should be approved in writing by a designated person, with the involvement of the quality control department, when appropriate.

16.4 Checks on yields and reconciliation of quantities should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

16.5 Operations on different products should not be carried out simultaneously or consecutively in the same room or area unless there is no risk of mix-up or cross-contamination.

16.6 At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate, the rooms and packaging lines being used should be labeled or otherwise identified with an indication of the product or material being processed, its strength (where applicable), and the batch number. Where applicable, this indication should also mention the stage of production. In some cases, it may be useful to record also the name of the previous product that has been processed.

16.7 Access to production premises should be restricted to authorized personnel.

16.8 Normally, nonmedicinal products should not be produced in areas or with equipment destined for the production of pharmaceutical products.

16.9 In-process controls are usually performed within the production area. The performance of such in-process controls should not have any negative effect on the quality of the product or another product (e.g., cross-contamination or mix-up).

Prevention of Cross-Contamination and Bacterial Contamination During Production

16.10 When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust. Provision should be made for proper air control (e.g., supply and extraction of air of suitable quality).

16.11 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, particles, vapors, sprays, or organisms from materials and products in process; from residues on equipment; from intruding insects; and from operators' clothing, skin, etc. The significance of this risk varies with the type of contaminant and of the product being contaminated. Among the most hazardous contaminants are highly sensitizing materials, biological preparations such as living organisms, certain hormones, cytotoxic substances, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection or applied to open wounds and those given in large doses and/or over a long time.

16.12 Cross-contamination should be avoided by taking appropriate technical or organizational measures, for example,

(a) Carrying out production in dedicated and self-contained areas (which may be required for products such as penicillins, live vaccines, live bacterial preparations, and certain other biologicals)
(b) Conducting campaign production (separation in time) followed by appropriate cleaning in accordance with a validated cleaning procedure
(c) Providing appropriately designed airlocks, pressure differentials, and air supply and extraction systems
(d) Minimizing the risk of contamination caused by recirculation or reentry of untreated or insufficiently treated air
(e) Wearing protective clothing where products or materials are handled
(f) Using cleaning and decontamination procedures of known effectiveness
(g) Using a "closed system" in production
(h) Testing for residues and
(i) Using cleanliness status labels on equipment

16.13 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to standard operating procedures.

16.14 Production areas where susceptible products are processed should undergo periodic environmental monitoring (e.g., for microbiological monitoring and particulate matter where appropriate).

Processing Operations

16.15 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels, or documents not required for the current operation.

16.16 Any necessary in-process controls and environmental controls should be carried out and recorded.

16.17 Means should be instituted of indicating failures of equipment or of services (e.g., water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified. After use, production equipment should be cleaned without delay according to detailed written procedures and stored under clean and dry conditions in a separate area or in a manner that will prevent contamination.

16.18 Time limits for storage of equipment after cleaning and before use should be stated and based on data.

16.19 Containers for filling should be cleaned before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

16.20 Any significant deviation from the expected yield should be recorded and investigated.

16.21 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

16.22 Pipes used for conveying distilled or deionized water and, where appropriate, other water pipes should be sanitized and stored according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

16.23 Measuring, weighing, recording, and control equipment and instruments should be serviced and calibrated at prespecified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated, preferably on a label attached to the instrument.

16.24 Repair and maintenance operations should not present any hazard to the quality of the products.

Packaging Operations

16.25 When the program for packaging operations is being set up, particular attention should be given to minimizing the risk of cross-contamination, mix-ups, or substitutions. Different products should not be packaged in close proximity unless there is physical segregation or an alternative system that will provide equal assurance.

16.26 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines, and other equipment are clean and free from any products, materials, or documents used previously and which are not required for the current operation. The line clearance should be performed according to an appropriate procedure and checklist, and recorded.

16.27 The name and batch number of the product being handled should be displayed at each packaging station or line.

16.28 Normally, filling and sealing should be followed as quickly as possible by labeling. If labeling is delayed, appropriate procedures should be applied to ensure that no mix-ups or mislabeling could occur.

16.29 The correct performance of any printing (e.g., of code numbers or expiry dates) done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand, which should be rechecked at regular intervals.

16.30 Special care should be taken when cut labels are used and when overprinting is carried out off-line, and in hand-packaging operations. Roll-feed labels are normally preferable to cut labels in helping to avoid mix-ups. Online verification of all labels by automated electronic means can be helpful in preventing mix-ups, but checks should be made to ensure that any electronic code readers, label counters, or similar devices are operating correctly. When labels are attached manually, in-process control checks should be performed more frequently.

16.31 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

16.32 Regular online control of the product during packaging should include at least checks on

(a) The general appearance of the packages
(b) Whether the packages are complete
(c) Whether the correct products and packaging materials are used
(d) Whether any overprinting is correct and
(e) The correct functioning of line monitors

Samples taken away from the packaging line should not be returned.

16.33 Products that have been involved in an unusual event during packaging should be reintroduced into the process only after special inspection, investigation, and approval by authorized personnel. A detailed record should be kept of this operation.

16.34 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated, satisfactorily accounted for, and recorded before release.

16.35 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure requiring checks to be performed before returning unused materials should

be followed if uncoded printed materials are returned to stock.

17. Good Practices in Quality Control

17.1 Quality control is the part of GMP concerned with sampling, specifications, and testing, and with the organization, documentation, and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. Quality control is not confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

17.2 The independence of quality control from production is considered fundamental.

17.3 Each manufacturer (the holder of a manufacturing authorization) should have a quality control function. The quality control function should be independent of other departments and under the authority of a person with appropriate qualification and experience, who has one or several control laboratories at his or her disposal. Adequate resources must be available to ensure that all the quality control arrangements are effectively and reliably carried out. The basic requirements for quality control are as follows:

(a) Adequate facilities, trained personnel, and approved procedures must be available for sampling, inspecting, and testing starting materials, packaging materials, and intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes.

(b) Samples of starting materials, packaging materials, intermediate products, bulk products, and finished products must be taken by methods and personnel approved of by the quality control department.

(c) Qualification and validation must be performed.

(d) Records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting, and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated.

(e) The finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container, and correctly labeled.

(f) Records must be made of the results of inspecting and testing the materials and intermediate, bulk, and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures.

(g) No batch of product is to be released for sale or supply prior to certification by the authorized person(s) that it is in accordance with the requirements of the marketing authorization. In certain countries, by law, the batch release is a task of the authorized person from production together with the authorized person from quality control.

(h) Sufficient samples of starting materials and products must be retained to permit future examination of the product if necessary; the retained product must be kept in its final pack unless the pack is exceptionally large.

17.4 Quality control as a whole will also have other duties, such as to establish, validate, and implement all quality control procedures; to evaluate, maintain, and store the reference standards for substances; to ensure the correct labeling of containers of materials and products; to ensure that the stability of the active pharmaceutical ingredients and products is monitored; to participate in the investigation of complaints related to the quality of the product; and to participate in environmental monitoring. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

17.5 Assessment of finished products should embrace all relevant factors, including the production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product, and an examination of the finished pack.

17.6 Quality control personnel must have access to production areas for sampling and investigation as appropriate.

Control of Starting Materials and Intermediate, Bulk, and Finished Products

17.7 All tests should follow the instructions given in the relevant written test procedure for each material or product. The result should be checked by the supervisor before the material or product is released or rejected.

17.8 Samples should be representative of the batches of material from which they are taken in accordance with the approved written procedure.

17.9 Sampling should be carried out so as to avoid contamination or other adverse effects on quality. The containers that have been sampled should be

marked accordingly and carefully resealed after sampling.

17.10 Care should be taken during sampling to guard against contamination or mix-up of, or by, the material being sampled. All sampling equipment that comes into contact with the material should be clean. Some particularly hazardous or potent materials may require special precautions.

17.11 Sampling equipment should be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment.

17.12 Each sample container should bear a label indicating
(a) The name of the sampled material
(b) The batch or lot number
(c) The number of the container from which the sample has been taken
(d) The number of the sample
(e) The signature of the person who has taken the sample and
(f) The date of sampling

17.13 Out-of-specification results obtained during testing of materials or products should be investigated in accordance with an approved procedure. Records should be maintained.

Test Requirements

Starting and Packaging Materials

17.14 Before releasing a starting or packaging material for use, the quality control manager should ensure that the materials have been tested for conformity with specifications for identity, strength, purity, and other quality parameters.

17.15 An identity test should be conducted on a sample from each container of starting material (see also Section 14.14).

17.16 Each batch (lot) of printed packaging materials must be examined following receipt.

17.17 In lieu of testing by the manufacturer, a Certificate of Analysis may be accepted from the supplier, provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results (see Sections 8.8 and 8.9) and through on-site audits of the supplier's capabilities. (This does not affect Section 17.15.) Certificates must be originals (not photocopies) or otherwise have their authenticity assured. Certificates must contain at least the following information:
(a) Identification (name and address) of the issuing supplier
(b) Signature of the competent official, and statement of his or her qualifications
(c) The name of the material tested
(d) The batch number of the material tested
(e) The specifications and methods used
(f) The test results obtained and
(g) The date of testing

In-Process Control

17.18 In-process control records should be maintained and form a part of the batch records (see Section 15.25).

Finished Products

17.19 For each batch of drug product, there should be an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

17.20 Products failing to meet the established specifications or any other relevant quality criteria should be rejected.

Batch Record Review

17.21 Production and quality control records should be reviewed as part of the approval process of batch release. Any divergence or failure of a batch to meet its specifications should be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.

17.22 Retention samples from each batch of finished product should be kept for at least one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. If exceptionally large packages are produced, smaller samples might be stored in appropriate containers. Samples of active starting materials should be retained for at least 1 year beyond the expiry date of the corresponding finished product. Other starting materials (other than solvents, gases, and water) should be retained for a minimum of two years if their stability allows. Retention samples of materials and products should be of a size sufficient to permit at least two full reexaminations.

Stability Studies

17.23 Quality control should evaluate the quality and stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products.

17.24 Quality control should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.

17.25 A written program for ongoing stability determination should be developed and implemented to include elements such as
(a) A complete description of the drug involved in the study
(b) The complete set of testing parameters and methods, describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability

(c) Provision for the inclusion of a sufficient number of batches;
(d) The testing schedule for each drug
(e) Provision for special storage conditions
(f) Provision for adequate sample retention and
(g) A summary of all the data generated, including the evaluation and the conclusions of the study

17.26 Stability should be determined prior to marketing and following any significant changes in processes, equipment, packaging materials, etc.

WHO INSPECTIONS SUMMARY

- Types of GMP Inspection
  - Routine inspection
  - Concise inspection
  - Follow-up inspection
  - Special inspection
  - Quality systems review
- Routine Inspection
  - Full inspection of all components of GMP
  - Newly established manufacturer
  - Renewal of a license
  - Changes:
    - New product or product lines
    - Modifications to manufacturing methods
  - Key personnel, premises, or equipment
  - History of noncompliance with GMP
  - Not inspected in the last 3–5 years
- Concise Inspection
  - Consistent record of compliance with GMP
  - Focus on limited number of GMP requirements
  - Selected as indicators
  - Identify significant changes
  - Indicate attitude toward GMP
  - Noncompliance
  - Should trigger comprehensive inspection
- Follow-up Inspection
  - Reassessment or reinspection
  - Monitor result of corrective actions
  - 6 weeks to 6 months after initial inspection
  - Nature of defects
  - Work undertaken
  - Specific GMP requirements
  - Not observed
  - Not adequately implemented
- Special Inspection
  - Spot-check focusing on
    - One product, a group of related products
    - Specific operations, for example, mixing, labeling
  - Complaints or recalls
  - Adverse drug reactions
  - Marketing approval or export certificate
  - Information or investigation
  - Specific information
  - Advice on regulatory requirements
- Quality Systems Review
  - Assess the quality assurance (QA) system
  - Description of the QA system (e.g., manual)
  - Policy and standards to be observed
  - Management structure
  - Implementation
  - Procedures
  - Quality standards set for products
  - Correctly defined manufacturing processes
  - Records kept
  - QC and QA functions are performed
- Frequency of Inspections
  - Depends on type of inspection
  - Inspectorate resources (e.g., workload, number of inspectors)
  - New facilities—before licensed
  - All companies—regular schedule
  - Ideally annual
    - Large companies
    - Several visits over a period, for example, 5 years
    - Validity of manufacturing license or GMP certificate
- Duration of Inspections
  - Depends on type of inspection
  - Inspectorate resources (e.g., workload, number of inspectors)
  - Size of the company
  - Purpose of the visit
  - Days to weeks
  - Number of inspectors
  - Including specialist support
- Announced and Unannounced Inspections
  - Announced
    - Comprehensive inspection
  - Unannounced
    - Routine inspection (depending on country policy)
    - Concise inspection
    - Follow-up inspection
    - Special inspection
- Regulatory Actions
  - Based on national regulations
  - Correction of unsatisfactory situations
  - Closing down of a factory
  - Withholding of authorizations
  - Product recall
- Group Session
  - The inspectorate received a complaint that an injectable product [water for injection (WFI), 10 mL ampoule] is possibly contaminated with microorganisms. You have to organize an inspection of the company in question.
  - What type of inspection would be performed?
  - Will the inspection be announced or unannounced?
  - Who will be part of the inspection team?
  - What will you consider in preparation for the inspection?

- Possible Issues
  - Purpose of the inspection
  - Notification (or not) of the company in advance
  - Makeup of the team
  - Program for the inspection
  - Sterility test, leak test, and visual inspection
  - Validation and qualification
  - Documentation review

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Appendix A

GMP AUDIT TEMPLATE

The Guidelines for cGMP Compliance:

- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/vol4-chap1_2013-01_en.pdf
- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2014-03_chapter_2.pdf
- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/chapter4_01-2011_en.pdf
- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2014-11_vol4_chapter_6.pdf
- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2014-08_gmp_chap8.pdf
- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/pdfs-en/cap9_en.pdf
- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2014-08_gmp_part1.pdf
- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2011_site_master_file_en.pdf
- http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002873.pdf
- http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002871.pdf
- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/mra_batch-certificate_05-2011.pdf
- https://ec.europa.eu/health/sites/health/files/files/gmp/2013_01_28_template.pdf
- http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/11/WC500177735.pdf
- http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52015XC0321(02)&from=EN
- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/template_imp_batch_certification.docx
- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2008_11_25_gmp-an1_en.pdf
- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/pdfs-en/2018_annex2_en.pdf
- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/annex11_01-2011_en.pdf
- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2015-10_annex15.pdf
- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/v4_an16_201510_en.pdf
- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/pdfs-en/2018_annex17_en.pdf
- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/pdfs-en/2005_12_14_annex19_en.pdf
- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/pdfs-en/2018_annex17_en.pdf

		Compliance 1 2 3[a]	Remarks	EU-Guide
1	**PERSONNEL**			
1.1	Qualified personnel available?	☐☐☐		2.1
1.2	Organization charts available?	☐☐☐		2.2
1.3	Job descriptions available?	☐☐☐		2.2
1.4	Responsibilities clearly defined?	☐☐☐		2.2
	Key Personnel			
	Responsible persons designated for			
1.5	• Production?	☐☐☐		2.5
1.6	• Quality control?	☐☐☐		2.6
1.7	Are they independent of each other?	☐☐☐		2.3
1.8	Are joint functions clearly defined?	☐☐☐		2.7
1.9	Are the responsible persons working full time?	☐☐☐		2.3
1.10	Do the responsible persons have the appropriate formulation, knowledge, and experience?	☐☐☐		2.1/2.2
1.11	Do the relevant departments have enough personnel?	☐☐☐		2.1
	Training			
1.12	Continuous training programs for the production and QC staff?	☐☐☐		2.8
1.13	Initial job training for all employees?	☐☐☐		2.9
1.14	Teaching aids (videos, slides, and brochures) available?	☐☐☐		2.9
1.15	External training courses for the staff?	☐☐☐		2.9
1.16	Training records?	☐☐☐		2.9
1.17	Special training in sensitive areas (sterile production and toxic substances)?	☐☐☐		2.10
1.18	Information for visitors to the manufacturing area?	☐☐☐		2.11
2	**HYGIENE**			
	Personnel Hygiene			
	Detailed written hygiene programs for			
2.1	• Clothing?	☐☐☐		2.13
2.2	• Use of washrooms?	☐☐☐		2.13
2.3	• Behavior in production areas?	☐☐☐		2.13
2.4	Precautions against sick personnel or personnel with open wounds in production?	☐☐☐		2.14
	Medical examination:			
2.5	• On recruitment?	☐☐☐		2.15
2.6	• Regular reexaminations?	☐☐☐		2.15
	Duty of notification after			
2.7	• Trips to tropical countries?	☐☐☐		2.15
2.8	• Cases of contagious illness in the family?	☐☐☐		2.15
2.9	Instructions for appropriate working clothes?	☐☐☐		2.16
2.10	Absence of food and drink (chewing gum!) in the working area?	☐☐☐		2.17
2.11	Measures against contact with open product (gloves etc.)?	☐☐☐		2.18
2.12	Instructions for hand washing in production?	☐☐☐		2.19
2.13	Change of clothes when entering and leaving the production area?	☐☐☐		5.19
2.14	Change rooms and toilets easily within reach?	☐☐☐		3.31
2.15	Toilets and restrooms sufficiently separated from production areas?	☐☐☐		3.30/3.31
2.16	Workshops separate from production areas?	☐☐☐		3.32
2.17	Laboratory animal rooms totally segregated from production rooms?	☐☐☐		3.33
3	**WAREHOUSE**			
	Rooms, General			
3.1	Suitable for the intended use?	☐☐☐		3
3.2	• Adequate size?	☐☐☐		3
3.3	• Clean?	☐☐☐		3
3.4	Located and designed to exclude external contamination?	☐☐☐		3.1
3.5	Appropriate level of maintenance?	☐☐☐		3.2

(*Continued*)

		Compliance 1 2 3[a]	Remarks	EU-Guide
3.6	Maintenance works possible without contamination risk?	☐☐☐		3.2
3.7	Appropriate lighting and air-conditioning?	☐☐☐		3.3
3.8	Recording of temperature and humidity?	☐☐☐		3.3
3.9	Protection against the entry of insects or other animals?	☐☐☐		3.4
3.10	Controlled access for authorized personnel only?	☐☐☐		3.5
	Rooms, Special Requirements			
	Type of warehousing:			
3.11	Separation of goods sufficient?	☐☐☐		3.18
3.12	Provision for different storage temperatures?	☐☐☐		3.19
3.13	Goods receiving zone weather protected?	☐☐☐		3.20
3.14	Cleaning zone for incoming goods?	☐☐☐		3.20
3.15	Separate quarantine area with controlled access?	☐☐☐		3.21
3.16	Separate, protected sampling area?	☐☐☐		3.22
	Separate and safe storage of			
3.17	• Returned goods?	☐☐☐		3.23
3.18	• Rejected goods?	☐☐☐		3.23
3.19	Separate and safe storage of highly active, toxic, or dangerous substances?	☐☐☐		3.24
3.20	Safe storage of narcotics?	☐☐☐		3.24
3.21	Safe storage of printed packaging materials?	☐☐☐		3.25
3.22	Security measurements against theft?	☐☐☐		3.25
3.23	Smoke detectors?	☐☐☐		3.25
3.24	Fire extinguishing system?	☐☐☐		3.25
	Operations			
3.25	Reception, sampling, and labeling according to written procedures?	☐☐☐		5.2
3.26	Is a sampling plan available?	☐☐☐		Suppl. 4
3.27	Cleaning of incoming containers?	☐☐☐		5.3
3.28	Investigation and recording of damaged deliveries?	☐☐☐		5.4
3.29	First In First Out (FIFO) principle?	☐☐☐		5.7
3.30	Inventory system?	☐☐☐		5.8
3.31	Can the location of materials be detected at all times?	☐☐☐		
3.32	Incoming goods: containers and seals intact?	☐☐☐		5.27
3.33	Incoming goods: conformity with bill of delivery?	☐☐☐		5.27
	Labeling of incoming containers with			
3.34	• Internal name and code?	☐☐☐		5.29
3.35	• Allocated batch number?	☐☐☐		5.29
3.36	• Quarantine status?	☐☐☐		5.29
3.37	• Expiry date or reanalysis date?	☐☐☐		5.29
3.38	Identity test for each incoming container?	☐☐☐		5.29
3.39	Are the sampled containers marked?	☐☐☐		5.30
3.40	Are reference samples taken?	☐☐☐		5.30
3.41	Safe storage of printed packaging materials?	☐☐☐		5.41
3.42	Lot tracing of all packaging materials possible?	☐☐☐		5.42
3.43	Are excessive packaging materials destroyed?	☐☐☐		5.43

Release of starting materials by physical/inventory checks on raw materials, packaging materials, and finished goods:

Item	Stocks: Physical	Stocks: Inventory	Storage conditions

(*Continued*)

		Compliance 1 2 3[a]	Remarks	EU-Guide
4	**DISPENSING/ASSEMBLING**			
	Rooms, General			
4.1	Suitable for the intended use?	☐☐☐		3
4.2	• Adequate size?	☐☐☐		3
4.3	• Clean?	☐☐☐		3
4.4	Located and designed to exclude external contamination?	☐☐☐		3.1
4.5	Appropriate level of maintenance?	☐☐☐		3.2
4.6	Maintenance works possible without contamination risk?	☐☐☐		3.2
4.7	Appropriate lighting and air-conditioning?	☐☐☐		3.3
4.8	Recording of temperature and humidity?	☐☐☐		
4.9	Protection against the entry of insects or other animals?	☐☐☐		3.4
4.10	Controlled access for authorized personnel only?	☐☐☐		3.5
	Rooms, Special Requirements			
4.11	Segregated from production and warehouse?	☐☐☐		3.13
4.12	Separate weighing cabins?	☐☐☐		3.13
4.13	Separate air handling unit (AHU) for each cabin?	☐☐☐		3.12
	Air pressure gradient from weighing cabin → corridor:			3.3
4.14	Dust extraction systems available?	☐☐☐		5.11
	Operations			
4.15	Balances regularly calibrated?	☐☐☐		3.41
4.16	Only pharmaceutical raw materials in this area?	☐☐☐		5.17
4.17	Check on remains from previous materials before entering of new materials into a weighing cabin?	☐☐☐		5.9/5.35
4.18	Only one material in one cabin?	☐☐☐		5.9
4.19	Are dispensed materials correctly labeled?	☐☐☐		5.29
4.20	Only released products in the dispensing?	☐☐☐		5.31
4.21	Cleaning SOPs for the dispensing?	☐☐☐		4.28
4.22	Previously dispensed material recorded on weighing protocol?	☐☐☐		4.8
4.23	Safety measures against mix-ups during assembling (e.g., cage pallets)?	☐☐☐		5.32/5.34
5	**SOLIDS MANUFACTURING**			
	Field of activity:			
	• Granulation	☐		
	• Compression	☐		
	• Encapsulation	☐		
	• Film and sugar coating	☐		
	• Visual inspection (capsules, tablets, etc.)	☐		
	• Premix (human)	☐		
	Rooms, General			
5.1	Suitable for the intended use?	☐☐☐		3
5.2	• Adequate size?	☐☐☐		3
5.3	• Clean?	☐☐☐		3
5.4	Located and designed to exclude external contamination?	☐☐☐		3.1
5.5	Appropriate level of maintenance?	☐☐☐		3.2
5.6	Maintenance works possible without contamination risk?	☐☐☐		3.2
5.7	Appropriate lighting and air-conditioning?	☐☐☐		3.3
5.8	Recording of temperature and humidity?	☐☐☐		
5.9	Protection against the entry of insects or other animals?	☐☐☐		3.4
5.10	Controlled access for authorized personnel only?	☐☐☐		3.5
	Rooms, Special Requirements			
5.11	Separate manufacturing area for penicillins/cephalosporins or highly sensitizing substances?	☐☐☐		3.6
5.12	Only for processing of pharmaceuticals?	☐☐☐		3.6
5.13	Logical flow of materials?	☐☐☐		3.7
5.14	Walls, floors, and ceilings: smooth surface and free of cracks?	☐☐☐		3.8
5.15	Easy cleaning possible?	☐☐☐		3.10

(*Continued*)

		Compliance 1 2 3[a]	Remarks	EU-Guide
5.16	Adequate drains with traps and grilles?	☐☐☐		3.11
5.17	Appropriate air handling system?	☐☐☐		3.12
	Air pressure gradient from working bay → corridor: Classification according to EC guide?			
5.18	Appropriate dust extraction system?	☐☐☐		3.14
5.19	Appropriate lighting?	☐☐☐		3.16
5.20	Separate rest rooms?	☐☐☐		3.30
5.21	Changing rooms designed to avoid contamination?	☐☐☐		3.31
5.22	Toilets segregated from manufacturing areas?	☐☐☐		3.31
	Equipment			
5.23	Suitable for the intended use?	☐☐☐		3.34
5.24	Well maintained?	☐☐☐		3.34
5.25	Written and validated cleaning procedures?	☐☐☐		3.36
5.26	Maintenance without contamination risk (separate area)?	☐☐☐		3.35
5.27	Equipment in contact with product: suitable materials quality?	☐☐☐		3.39
5.28	Machinery equipped with measuring and control devices?	☐☐☐		3.40
5.29	Calibration at fixed intervals according to written procedures?	☐☐☐		3.41
5.30	Calibration records available?	☐☐☐		3.41
5.31	Contents and flow direction marked on pipes?	☐☐☐		3.42
5.32	Pipes for distilled and demineralized water regularly monitored and sanitized?	☐☐☐		3.43
5.33	Not functioning equipment in the production area (if yes: clearly marked)?	**Y N**		3.44
5.34	Status of cleanliness indicated?	☐☐☐		5.13
5.35	Previous product indicated?	☐☐☐		5.13
	Operations			
5.36	Are written and validated procedures for all manufacturing steps available?	☐☐☐		5.2
5.37	Are all manufacturing steps recorded with actual parameters?	☐☐☐		5.2
5.38	Check of each single container of the starting materials (contents, weight, and identity)?	☐☐☐		5.3
5.39	Limits for yields?	☐☐☐		5.8
5.40	Only one batch of one product processed?	☐☐☐		5.9
5.41	Protection against microbial contamination?	☐☐☐		5.10
5.42	Appropriate measures against generation of dust (e.g., closed systems)?	☐☐☐		5.11
	Correct labeling of containers, materials, equipment, and rooms with			5.12
5.43	• Product name and batch no.?	☐☐☐		5.12
5.44	• Quarantine status?	☐☐☐		5.12
5.45	Deviations from standard procedures recorded and signed by the supervisor?	☐☐☐		5.14
5.46	Special procedures for the production of antibiotics, hormones, etc.?	☐☐☐		5.19
5.47	• Campaign production?	☐☐☐		5.19
5.48	• Special monitoring?	☐☐☐		5.19
5.49	• Validated decontamination procedure?	☐☐☐		5.19
5.50	Double check on weight?	☐☐☐		5.34
5.51	Line clearance before start of production?	☐☐☐		5.35
5.52	Investigation of deviations in yields?	☐☐☐		5.39
5.53	Validated procedures for reworking of rejected batches?	☐☐☐		5.62
5.54	Detailed procedures for the addition of previous batches?	☐☐☐		5.63
5.55	Special release procedure (QA) for those batches?	☐☐☐		5.64
5.56	Use of protective clothing (hair cover, shoes, masks, and gloves)?	☐☐☐		2.16
5.57	Clothing regulation for visitors?	☐☐☐		2.11
	In-Process Control (IPC)			5.38
	Who performs IPC?			

(*Continued*)

		Compliance 1 2 3[a]	Remarks	EU-Guide
5.58	Are IPC methods approved by QC?	☐☐☐		6.18
	Performance of IPCs:	During start-up?	Frequency	Automatic data recording?
		Yes **No**		**Yes** **No**
	Tablets/Kernels			
5.59	Individual weights	☐☐		☐☐
5.60	Disintegration	☐☐		☐☐
5.61	Thickness	☐☐		☐☐
5.62	Hardness	☐☐		☐☐
5.63	Friability/Abrasion	☐☐		☐☐
	Sugar-/Film-Coated Tablets			
5.64	Weights	☐☐		☐☐
5.65	Disintegration	☐☐		☐☐
5.66	Residual absolute humidity	☐☐		☐☐
	Capsules			
5.67	Individual weights	☐☐		☐☐
5.68	Disintegration	☐☐		☐☐
	Validation			
5.69	Validation according to fixed procedures?	☐☐☐		5.21
5.70	New procedures released only after validation?	☐☐☐		5.22
	Validation of changes of			
5.71	• Processes?	☐☐☐		5.23
5.72	• Starting materials?	☐☐☐		5.23
5.73	• Equipment?	☐☐☐		5.23
5.74	Revalidation at fixed intervals?	☐☐☐		5.24
5.75	Procedures for the retrospective validation of old procedures?	☐☐☐		
6	**LIQUIDS MANUFACTURING**			
	Operations carried out:			
	• Dispensing (if different from solid)	☐☐☐		
	• Syrups and suspensions	☐☐☐		
	• Drops	☐☐☐		
	• Ointment manufacture	☐☐☐		
	• Ointment filling	☐☐☐		
	• Ampoule solution manufacture	☐☐☐		
	• Sterile or aseptic ampoule filling	☐☐☐		
	• Sterile freeze drying	☐☐☐		
	• Sterile powder filling	☐☐☐		
	Rooms, General			
6.1	Suitable for the intended use?	☐☐☐		3
6.2	• Adequate size?	☐☐☐		3
6.3	• Clean?	☐☐☐		3
6.4	Located and designed to exclude external contamination?	☐☐☐		3.1
6.5	Appropriate level of maintenance?	☐☐☐		3.2
6.6	Maintenance works possible without contamination risk?	☐☐☐		3.2
6.7	Appropriate lighting and air-conditioning?	☐☐☐		3.3
6.8	Recording of temperature and humidity?	☐☐☐		
6.9	Protection against the entry of insects or other animals?	☐☐☐		3.4
6.10	Controlled access for authorized personnel only?	☐☐☐		3.5
	Rooms, Special Requirements			
6.11	Separate manufacturing area for penicillins/cephalosporins or highly sensitizing substances?	☐☐☐		3.6
6.12	Only for processing of pharmaceuticals?	☐☐☐		3.6
6.13	Logical flow of materials?	☐☐☐		3.7
6.14	Walls, floors, and ceilings: smooth surface and free of cracks?	☐☐☐		3.8

(*Continued*)

		Compliance 1 2 3[a]	Remarks	EU-Guide
6.15	Easy cleaning possible?	☐☐☐		3.10
6.16	Adequate drains with traps and grilles?	☐☐☐		3.11
6.17	Appropriate air-handling system with filtered air where open products are exposed to the environment?	☐☐☐		3.12
	Air pressure gradient from working bay → corridor:			
	Classification according to EC guide?			
6.18	Appropriate lighting?	☐☐☐		3.16
6.19	Separate rest rooms?	☐☐☐		3.30
6.20	Changing rooms designed to avoid contamination?	☐☐☐		3.31
6.21	Toilets segregated from manufacturing areas?	☐☐☐		3.31
	Equipment			
6.22	Suitable for the intended use?	☐☐☐		3.34
6.23	Well maintained?	☐☐☐		3.34
6.24	Tanks, containers, pipework, and pumps designed for easy cleaning and sanitation (dead legs!)?	☐☐☐		Suppl. 2
6.25	Written and validated cleaning procedures?	☐☐☐		3.36
6.26	Maintenance without contamination risk (separate area)?	☐☐☐		3.35
6.27	Equipment in contact with product: suitable materials quality?	☐☐☐		3.39
6.28	Machinery equipped with measuring and control devices?	☐☐☐		3.40
6.29	Calibration at fixed intervals according to written procedures?	☐☐☐		3.41
6.30	Calibration records available?	☐☐☐		3.41
6.31	Contents and flow direction marked on pipes?	☐☐☐		3.42
6.32	Pipes for distilled and demineralized water regularly monitored and sanitized?	☐☐☐		3.43
6.33	Not functioning equipment in the production area (if yes: clearly marked)?	**Y N**		3.44
6.34	Status of cleanliness indicated?	☐☐☐		5.13
6.35	Previous product indicated?	☐☐☐		5.13
	Operations			
6.36	Are written and validated procedures for all manufacturing steps available?	☐☐☐		5.2
6.37	Are all manufacturing steps recorded with actual parameters?	☐☐☐		5.2
6.38	Check of each single container of the starting materials (contents, weight, and identity)?	☐☐☐		5.3
6.39	Limits for yields?	☐☐☐		5.8
6.40	Only one batch of one product processed?	☐☐☐		5.9
6.41	Protection against microbial contamination?	☐☐☐		5.10
	Correct labeling of containers, materials, equipment, and rooms with			5.12
6.42	• Product name and batch no.?	☐☐☐		5.12
6.43	• Quarantine status?	☐☐☐		5.12
6.44	Deviations from standard procedures recorded and signed by the supervisor?	☐☐☐		5.14
6.45	Special procedures for the production of antibiotics, hormones, etc.?	☐☐☐		5.19
6.46	• Campaign production?	☐☐☐		5.19
6.47	• Special monitoring?	☐☐☐		5.19
6.48	• Validated decontamination procedure?	☐☐☐		5.19
6.49	Double check on weight?	☐☐☐		5.34
6.50	Line clearance before start of production?	☐☐☐		5.35
6.51	Investigation of deviations in yields?	☐☐☐		5.39
6.52	Specification of maximum storage time and storage conditions if products are not immediately filled or packaged?	☐☐☐		Suppl. 9
6.53	Validated procedures for reworking of rejected batches?	☐☐☐		5.62
6.54	Detailed procedures for the addition of previous batches?	☐☐☐		5.63
6.55	Special release procedure (QA) for those batches?	☐☐☐		5.64
6.56	Use of protective clothing (hair cover, shoes, masks, and gloves)?	☐☐☐		2.16
6.57	Clothing regulation for visitors?	☐☐☐		2.11

(*Continued*)

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Water			
6.58	Loop system for purified water?	☐☐☐		Suppl. 4
6.59	Antimicrobial treatment of purified water?	☐☐☐		Suppl. 4
6.60	Loop system for water for injection?	☐☐☐		Suppl. 4
	Storage temperature of water for injection:			Suppl. 4
6.61	Loop system constructed to avoid dead legs?	☐☐☐		Suppl. 4
6.62	Regular microbiological monitoring?	☐☐☐		Suppl. 4
6.63	Regular endotoxin control?	☐☐☐		Suppl. 4
	Special Requirements for Sterile and Aseptic Products			**Suppl.**
	Rooms and Equipment			
6.64	Access of staff and materials to clean areas *only* through air locks?	☐☐☐		1
6.66	Rooms classified according to EC Guide?	☐☐☐		3
	Classification for products to be sterilized:			
6.67	• Solution preparation (EC: class C, with special precautions class D):	Class:		5
6.68	• Filling (EC: under LF in class C):	Class:		5
	Classification for aseptic products:			
6.69	• Handling of starting materials that can be sterile filtered (EC: class C):	Class:		6
6.70	• Handling of starting materials that cannot be sterile filtered (EC: class A in class B):	Class:		6
6.71	• Handling and filling of bulk (EC: class A in Class B):	Class:		6
6.72	All rooms easy to clean and disinfect?	☐☐☐		17
6.73	Doors, windows, frames, lighting, etc. without edges?	☐☐☐		18
6.74	Suspended ceilings (if yes: sealed?)?	☐☐☐		19
6.75	Traps constructed to avoid microbiological contamination?	☐☐☐		21
6.76	Appropriately constructed changing rooms?	☐☐☐		22
6.77	Measures against opening of both doors of air locks?	☐☐☐		23
6.78	Overpressure gradient from cleanest areas to others?	☐☐☐		24
6.79	AHU validated and regularly revalidated?	☐☐☐		25
6.80	Control instruments for pressure gradient?	☐☐☐		26
6.81	Warning system for errors in air supply?	☐☐☐		26
6.82	Recording of pressure gradients?	☐☐☐		26
6.83	Do conveyor belts leave sterile areas?	☐☐☐		28
6.84	Maintenance works outside clean areas possible?	☐☐☐		28
6.85	Cleaning and disinfection procedure after maintenance works?	☐☐☐		29
6.86	Regular revalidation of all equipment and systems?	☐☐☐		30
6.87	Water prepared, circulated, and stored to exclude microbiological contamination?	☐☐☐		31
6.88	Cleaning and disinfection of rooms according to validated SOPs?	☐☐☐		32
	• Disinfection methods?			
6.89	Microbiological monitoring of cleaning and disinfection agents?	☐☐☐		33
6.90	Microbiological monitoring program of production areas?	☐☐☐		35
6.91	Results recorded and considered for the release?	☐☐☐		35
	Personnel and Hygiene			
6.92	Minimal number of personnel in clean areas?	☐☐☐		7
6.93	Special and regular training?	☐☐☐		8
6.94	Regular medical examinations?	☐☐☐		10
6.95	Appropriate clean room clothes (material and design)?	☐☐☐		12
6.96	Protective clothes worn correctly?	☐☐☐		12
6.97	Prohibition of cosmetics, jewelry, and watches?	☐☐☐		13
6.98	New clean room clothes for each working cycle?	☐☐☐		15
6.99	Appropriate washing and sterilization of clothes?	☐☐☐		16
	Operations			
6.100	Validation (media filling) at regular intervals?	☐☐☐		38

(*Continued*)

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Monitoring of water preparation system, frequency:			
6.101	• Microbiological:			40
6.102	• Chemical:			40
6.103	• Particles:			40
6.104	• Endotoxins:			40
6.105	Microbiological monitoring of starting materials?	☐☐☐		42
6.106	Maximum storage times defined for sterilized equipment?	☐☐☐		45
6.107	Maximum storage time defined between solution preparation and filtration?	☐☐☐		46
6.108	Material transfer to clean areas through double door autoclaves?	☐☐☐		48
	Sterilization Processes			
6.109	All processes validated?	☐☐☐		50
6.110	Sterilized and nonsterilized materials clearly separated?	☐☐☐		54
	Trays and boxes clearly labeled with			
6.111	• Product name and code	☐☐☐		54
6.112	• Batch no.	☐☐☐		54
6.113	• Status: sterilized or nonsterilized	☐☐☐		54
	Sterilizers			
6.114	Recording of temperature, pressure, and time?	☐☐☐		55
6.115	Coldest point determined?	☐☐☐		55
6.116	Independent counter check probe?	☐☐☐		55
6.117	Heat-up time for each product determined?	☐☐☐		56
6.118	Sterile cooling media?	☐☐☐		57
6.119	Tightness tests for vacuum autoclaves?	☐☐☐		58
6.120	Clean steam for steam autoclaves?	☐☐☐		58
6.121	Circulated air with overpressure?	☐☐☐		61
6.122	Recirculated air: sterile filtered?	☐☐☐		61
6.123	Ethylene oxide autoclaves: humidity, temperature, and time recorded?	☐☐☐		69
6.124	Ethylene oxide autoclaves: use of bioindicators?	☐☐☐		70
	Filtration			
6.125	Double filtration?	☐☐☐		75
6.126	Integrity testing of filters immediately after use?	☐☐☐		77
6.127	Are results a part of the batch protocol?	☐☐☐		77
6.128	Optical control of each single container of ampoules, vials, and infusions?	☐☐☐		82
	IPC			
6.129	Written IPC procedures and SOPs?	☐☐☐		
	Particle testing of			
6.130	• Rooms?	☐☐☐		
6.131	• Primary packaging materials?	☐☐☐		
6.132	• System of warning and action limits?	☐☐☐		
	Microbiological monitoring of			
6.133	• Rooms?			
6.134	• Personnel?			
6.135	• Equipment?			
6.136	Residual O_2 of ampoules, infusions, and syrups?	☐☐☐		
6.137	Endotoxin testing of water and packaging materials?	☐☐☐		
6.138	Calibration of equipment?	☐☐☐		
6.139	Regular revalidation of equipment?	☐☐☐		
7	**PACKAGING**			
	Operations carried out:			
	• Blistering	☐		
	• Foil packaging	☐		
	• Filling into tablet glasses	☐		

(*Continued*)

		Compliance 1 2 3[a]	Remarks	EU-Guide
	• Effervescent packaging	☐		
	• Powder filling	☐		
	• Syrup/drops filling	☐		
	• Ointment filling	☐		
	Rooms			
7.1	Suitable for the intended use?	☐☐☐		3
7.2	• Adequate size?	☐☐☐		3
7.3	• Clean?	☐☐☐		3
7.4	Located and designed to exclude external contamination?	☐☐☐		3.1
7.5	Appropriate level of maintenance?	☐☐☐		3.2
7.6	Maintenance works possible without contamination risk?	☐☐☐		3.2
7.7	Appropriate lighting and air-conditioning?	☐☐☐		3.3
7.8	Recording of temperature and humidity?	☐☐☐		
7.9	Protection against the entry of insects or other animals?	☐☐☐		3.4
7.10	Controlled access for authorized personnel only?	☐☐☐		3.5
7.11	Adequate separation of the packaging lines?	☐☐☐		3.15
	Operations			
7.12	Only *one* product per line?	☐☐☐		5.44
7.13	Check list for clearance before processing a new product/new batch?	☐☐☐		5.45
7.14	Adequate labeling of the lines (product name and code)?	☐☐☐		5.46
7.15	Check of all materials delivered to the line (quantity, identity, conformity with order)?	☐☐☐		5.47
7.16	Cleaning of primary packaging materials?	☐☐☐		5.48
7.17	Immediate labeling after filling?	☐☐☐		5.49
7.18	Careful check of all printing processes (code and expiry date)?	☐☐☐		5.50
7.19	Special safety measures for off-line printing?	☐☐☐		5.51
7.20	Regular checks of all control devices (code reader, counter, etc.)?	☐☐☐		5.52
7.21	Printings clear and durable?	☐☐☐		5.53
7.22	Balancing of printed packaging materials and bulk?	☐☐☐		5.56
7.23	Destruction of excessive coded packaging material after completion of an order?	☐☐☐		5.57
7.24	Are the finished products kept in quarantine until final release?	☐☐☐		5.58
7.25	Appropriate storage after release?	☐☐☐		5.60
	IPC			
7.26	Checks on identity of bulk and packaging materials?	☐☐☐		5.47
	Regular line checks on			
7.27	• Aspect of the packages?	☐☐☐		5.54a
7.28	• Completeness?	☐☐☐		5.54b
7.29	• Conformity of quantity and quality of materials with packaging order?	☐☐☐		5.54c
7.30	• Correct imprint?	☐☐☐		5.54d
7.31	• Correct function of control devices?	☐☐☐		5.54d
	Are the following IPC checks performed?			
7.32	• Leaking	☐☐☐		
7.33	• Release torque of screw caps	☐☐☐		
7.34	• pH, density, drop weight, viscosity, and sedimentation	☐☐☐		
8	**DOCUMENTATION**			
	Specifications			
8.1	Specifications for raw/packaging materials available?	☐☐☐		4.10
	Do they include			
8.2	• Internal name and code?	☐☐☐		4.11
8.3	• Name of supplier and/or manufacturer?	☐☐☐		4.11
8.4	• Reference sample (printed packaging material)?	☐☐☐		4.11
8.5	• Sampling procedure?	☐☐☐		4.11

(*Continued*)

		Compliance 1 2 3[a]	Remarks	EU-Guide
8.6	• Qualitative/quantitative specifications with limits?	☐☐☐		4.11
8.7	• Storage conditions?	☐☐☐		4.11
8.8	• Maximum storage period?	☐☐☐		4.11
	Goods Receiving			
8.9	Written procedures for the reception of deliveries?	☐☐☐		4.19
	Do the records of receipt include			
8.10	• Product name on labels and delivery note?	☐☐☐		4.20
8.11	• Internal name and code?	☐☐☐		4.20
8.12	• Receiving date?	☐☐☐		4.20
8.13	• Name of supplier and/or manufacturer?	☐☐☐		4.20
8.14	• Batch number of supplier?	☐☐☐		4.20
8.15	• Total quantity and number of containers?	☐☐☐		4.20
8.16	• Allocated internal batch number?	☐☐☐		4.20
8.17	SOPs for labeling, quarantine, and storage conditions of all incoming goods available?	☐☐☐		4.21
	SOPs include			
8.18	• authorized sampling personnel?	☐☐☐		4.22
8.19	• methods, equipment, and quantities?	☐☐☐		4.22
8.20	• safety measures?	☐☐☐		4.22
	Master Formulae			
8.21	Are master formulae for each product and batch size available?	☐☐☐		4.3
8.22	Is the master formula approved and signed by the authorized persons?	☐☐☐		4.3
	The master formula includes			
8.23	• Product name and code?	☐☐☐		4.14a
8.24	• Description of galenical form, dosage, and batch size?	☐☐☐		4.14b
8.25	• All active ingredients with name, code, and weight?	☐☐☐		4.14c
8.26	• All excipients used during manufacture with name, code, and weight?	☐☐☐		4.14c
8.27	• Yields with limits?	☐☐☐		4.14d
	Does the working procedure include			
8.28	• The production line?	☐☐☐		4.15a
8.29	• Equipment to be used?	☐☐☐		4.15a
8.30	• Reference to methods for cleaning, assembling, and calibration of machines?	☐☐☐		4.15b
8.31	• Detailed stepwise manufacturing prescription?	☐☐☐		4.15c
8.32	• IPCs to be performed with limits?	☐☐☐		4.15d
8.33	• Precautions to be followed?	☐☐☐		4.15e
8.34	Are batch records kept for each batch processed?	☐☐☐		4.17
	Do batch records include			
8.35	• Protocol of line clearance?	☐☐☐		4.17
8.36	• Name of the product and batch no.?	☐☐☐		4.17a
8.37	• Date and time of start and end of production?	☐☐☐		4.17b
8.38	• Name and initials of responsible workers for each step?	☐☐☐		4.17c, d
8.39	• Batch and analytical no. and actual weight of all starting materials?	☐☐☐		4.17e
8.40	• Equipment used?	☐☐☐		4.17f
8.41	• Results of IPCs with initials of person who carries them out?	☐☐☐		4.17g
8.42	• Yields of the relevant manufacturing steps?	☐☐☐		4.17h
8.43	• Detailed notes on problems and process deviations?	☐☐☐		4.17i
8.44	Records on reprocessing of batches?	☐☐☐		
	Packaging Instructions			
8.45	Packaging instructions for each product, package size, and presentation?	☐☐☐		4.16
	Do they include			
8.46	• Product name?	☐☐☐		4.16a

(*Continued*)

		Compliance 1 2 3[a]	Remarks	EU-Guide
8.47	• Description of galenical form and strength?	☐☐☐		4.16b
8.48	• Package size?	☐☐☐		4.17c
8.49	• List of all packaging materials with code for a standard batch size?	☐☐☐		4.17d
8.50	• Samples of printed packaging materials?	☐☐☐		4.17e
8.51	• Special precautions?	☐☐☐		4.17f
8.52	• Description of the process and equipment?	☐☐☐		4.17g
8.53	• IPCs to be performed with sampling instruction?	☐☐☐		4.17h
8.54	Are packaging batch records kept for each batch or part batch?	☐☐☐		4.18
	Do the packaging batch records include			
8.55	• Protocol of line clearance?	☐☐☐		4.18
8.56	• Name of the product?	☐☐☐		4.18a
8.57	• Date and time when operations have been performed?	☐☐☐		4.18b
8.58	• Name of the responsible person?	☐☐☐		4.18c
8.59	• Initials of workers carrying out operations?	☐☐☐		4.18d
8.60	• Notes on identity checks and conformity with packaging instructions?	☐☐☐		4.18e
8.61	• Results of IPCs?	☐☐☐		4.18e
8.62	• Details of operations and equipment used?	☐☐☐		4.18f
8.63	• Samples of printed packaging materials with codes (MFD, EXP, batch no., etc.)?	☐☐☐		4.18g
8.64	• Record of problems and process deviations?	☐☐☐		4.18h
8.65	• Quantities of packaging materials delivered, used, destroyed, or returned?	☐☐☐		4.18i
8.66	• No. of packs consumed?	☐☐☐		4.18j
	Testing			
	Do the written testing procedures include			
8.67	• Test methods?	☐☐☐		4.23
8.68	• Equipment for testing?	☐☐☐		4.23
8.69	Tests documented?	☐☐☐		4.23
	Others			
8.70	Procedures for release and rejection of materials and finished products?	☐☐☐		4.24
8.71	Final release by authorized person?	☐☐☐		4.24
8.72	Records about distribution of each batch?	☐☐☐		4.25
	Procedures and protocols about			
8.73	• Validation?	☐☐☐		4.26
8.74	• Setup and calibration of equipment?	☐☐☐		4.26
8.75	• Maintenance, cleaning, and disinfection?	☐☐☐		4.26
8.76	• Training records?	☐☐☐		4.26
8.77	• Environmental monitoring of production areas?	☐☐☐		4.26
8.78	• Pest control?	☐☐☐		4.26
8.79	• Complaints?	☐☐☐		4.26
8.80	• Recalls?	☐☐☐		4.26
8.81	• Returned goods?	☐☐☐		4.26
8.82	Instructions for use of manufacturing and testing equipment?	☐☐☐		4.27
	Log books for major equipment including date and name of persons who performed			
8.83	• Validation?	☐☐☐		4.28
8.84	• Calibration?	☐☐☐		4.28
8.85	• Maintenance, cleaning, and repair works?	☐☐☐		4.28
8.86	Chronological records of use of major equipment and manufacturing areas?	☐☐☐		4.29
9	**QUALITY CONTROL**			**6**
	General Requirements			
9.1	Independent QC department available?	☐☐☐		6.1
9.2	Head of QC well qualified and sufficiently experienced?	☐☐☐		6.1

(*Continued*)

		Compliance 1 2 3[a]	Remarks	EU-Guide
9.3	Qualified personnel available?	☐☐☐		2.1
9.4	Organization charts available?	☐☐☐		2.2
9.5	Job descriptions available?	☐☐☐		2.2
9.6	Responsibilities clearly defined?	☐☐☐		2.2
9.7	Continuous training programs for QC staff?	☐☐☐		2.2
9.8	Initial job training for all employees?	☐☐☐		2.9
9.9	Training records?	☐☐☐		
9.10	QC personnel admitted to the production rooms for sampling, etc.?	☐☐☐		
	QC Laboratories			
9.11	Suitable for the intended use?	☐☐☐		3.26
9.12	Laboratories of adequate size?	☐☐☐		3.26
9.13	Appropriate level of maintenance?	☐☐☐		3.1
9.14	Adequate separation from the production area?	☐☐☐		3.26
9.15	Controlled access of authorized personnel only?	☐☐☐		3.5
9.16	Special laboratory to handle biological samples available?	☐☐☐		3.29
9.17	Special laboratory to handle radioactive material available?	☐☐☐		3.29
9.18	Separate recreation rooms for the personnel available?	☐☐☐		3.30
9.19	Animal laboratories present?	☐☐☐		3.33
9.20	Animal laboratories separated from other areas?	☐☐☐		3.33
9.21	Animal laboratories equipped with a separate air-handling system?	☐☐☐		3.33
	QC Documentation			
9.22	Do procedures exist for			
	• Self inspection?	☐☐☐		
	• Release or rejection of products or raw material?	☐☐☐		
	• Product complaints?	☐☐☐		
	• Product recalls?	☐☐☐		
	• Local stability testing?	☐☐☐		
	• Storage of reference samples?	☐☐☐		
	• Validation of analytical procedures?	☐☐☐		
9.23	Specifications available for	☐☐☐		6.7
	• Raw materials?	☐☐☐		
	• Bulk products?	☐☐☐		
	• Packaging materials?	☐☐☐		
9.24	Analytical procedures for every product?	☐☐☐		
9.25	Are Basel methods followed?	☐☐☐		
9.26	Validation of locally developed test methods?	☐☐☐		
9.27	Sampling procedures available for			6.7
	• Raw materials?	☐☐☐		
	• Bulk products?	☐☐☐		
	• Packaging materials?	☐☐☐		
9.28	Suppliers' certificates available?	☐☐☐		6.7
9.29	Calibration program for analytical instruments installed?	☐☐☐		6.7
9.30	Maintenance program for analytical instruments?	☐☐☐		6.7
9.31	Retention system for QC records?	☐☐☐		6.8
9.32	Batch documents stored for expiry + 1 year or 5 years (EEC 75/319, article 22) minimum?	☐☐☐		6.8
9.33	Are original data such as notebooks stored in addition to the batch documents?	☐☐☐		6.10
9.34	Can the original data be traced back easily and quickly from the analytical report number or batch number?	☐☐☐		6.10

(*Continued*)

		Compliance 1 2 3[a]	Remarks	EU-Guide
9.35	Are trend analyses being performed for			6.9
	• Analytical results?	☐☐☐		
	• Yields?	☐☐☐		
	• Environmental monitoring data?	☐☐☐		
	Sampling			
9.36	Written procedures for taking samples?	☐☐☐		6.11
9.37	Do procedures define			
	• Method of sampling?	☐☐☐		
	• Necessary equipment?	☐☐☐		
	• Quantity of the sample?	☐☐☐		
	• Subdivision of the sample?	☐☐☐		
	• Sample container?	☐☐☐		
	• Labeling of samples?	☐☐☐		
	• Storage conditions?	☐☐☐		
	• Cleaning and storage of sampling equipment?	☐☐☐		
	• Identification of containers sampled?	☐☐☐		
9.38	Are samples representative of the batch they are taken from (sampling plan)?	☐☐☐		6.12
9.39	Are critical steps being surveilled and validated by additional sampling (e.g., at the beginning or end of a process)?	☐☐☐		6.12
9.40	Sample containers labeled with			6.13
	• Name of the content?	☐☐☐		
	• Batch number?	☐☐☐		
	• Date of sampling?	☐☐☐		
	• Batch containers sampled?	☐☐☐		
9.41	Are samples taken by QC/QA?	☐☐☐		
9.42	Reference samples retained for validity +1 year?	☐☐☐		6.14
9.43	Storage of reference samples under the recommended storage conditions?	☐☐☐		6.14
9.44	Finished products stored in the final packaging?	☐☐☐		6.14
9.45	Quantity of the reference sample makes one (better two) complete reanalysis possible?	☐☐☐		6.14
9.46	Sample room secure?	**Yes No**		6.14
9.47	Sample room neatly organized and not overcrowded?	**Yes No**		6.14
	Testing			
9.48	Are the applied analytical methods validated?	☐☐☐		6.15
9.49	Analytical methods in compliance with the registration?	☐☐☐		6.16
9.50	Are all results recorded and checked for correctness?	☐☐☐		6.16
9.51	Are all calculations checked?	☐☐☐		6.16
9.52	Do the testing protocols contain			6.17
	• Name and galenical form of material?	☐☐☐		
	• Batch number?	☐☐☐		
	• Supplier if applicable?	☐☐☐		
	• Specification reference?	☐☐☐		
	• Method reference?	☐☐☐		
	• Analytical results?	☐☐☐		
	• Reference to analytical certificates?	☐☐☐		
	• Date of the analysis?	☐☐☐		
	• Name of the analyst?	☐☐☐		
	• Name of the person verifying the data?	☐☐☐		
	• Statement of release or rejection?	☐☐☐		
	• Date and signature of the release person?	☐☐☐		
9.53	Are all IPC methods in production approved by QC?	☐☐☐		6.18
9.54	Are written methods available for the preparation of reagents and volumetric solutions?	☐☐☐		6.19
9.55	Is a record maintained of standardization of volumetric solutions?	☐☐☐		6.2

(*Continued*)

		Compliance 1 2 3[a]	Remarks	EU-Guide
9.56	Are reagents for prolonged use labeled with			6.20
	• Date of the preparation?	☐☐☐		
	• Signature of the preparator?	☐☐☐		
9.57	Are unstable reagents labeled with			6.20
	• Expiry date?	☐☐☐		
	• Storage conditions?	☐☐☐		
9.58	Are volumetric solutions labeled with			6.20
	• The last date of standardization?	☐☐☐		
	• Last current factor?	☐☐☐		
9.59	Are reference standards labeled with			6.21
	• Name and potency?	☐☐☐		
	• Supplier's reference?	☐☐☐		
	• Date of receipt?	☐☐☐		
	• Date of expiry?	☐☐☐		
9.60	Are reference standards stored properly and under the control of a designated person?	☐☐☐		
9.61	Are animals used for testing of components, materials, or products			
	• Quarantined before use?	☐☐☐		
	• Checked for suitability?	☐☐☐		
	• Are records maintained showing the history of their use?	☐☐☐		
10	**COMPLAINTS AND PRODUCT RECALLS**			**8**
	Complaints			8.1
10.1	Does a written complaint procedure exist?	☐☐☐		8.2
10.2	Are product complaints carefully reviewed?	☐☐☐		8.1
10.3	Is a person designated to handle complaints and to decide on measures to be taken?	☐☐☐		8.1
10.4	Is each complaint concerning a product recorded with all original details?	☐☐☐		8.3
10.5	Are product complaints thoroughly investigated?	☐☐☐		8.3
10.6	Is a responsible QC person involved in the study?	☐☐☐		8.3
10.7	Is it considered that other batches might be concerned as well?	☐☐☐		8.4
10.8	Are decisions and measures as a result recorded?	☐☐☐		8.5
10.9	Is this record added to the corresponding batch documents?	☐☐☐		8.5
10.10	Are the complaint records regularly revised with respect to specific or recurring problems?	☐☐☐		8.6
10.11	Are the authorities informed of serious quality problems with a product?	☐☐☐		8.7
	Recalls			8.8
10.12	Does a written recall procedure exist?	☐☐☐		8.9
10.13	Is a person nominated responsible for the execution and coordination of a recall?	☐☐☐		8.8
10.14	Is the responsible person independent of the marketing and sales organization?	☐☐☐		8.8
10.15	Are the competent authorities informed of an imminent recall?	☐☐☐		8.11
10.16	Does the person responsible for a recall have access to the distribution records?	☐☐☐		8.12
10.17	Do the distribution records contain sufficient information on customers with	☐☐☐		8.12
	• Addresses?			
	• Phone numbers inside or outside working hours?	☐☐☐		
	• Batches and amounts delivered?	☐☐☐		
	• Medical samples?	☐☐☐		
10.18	Are recalled products stored separately in a secure area?	☐☐☐		8.13
10.19	Is a final record made, including a reconciliation between the delivered and recovered quantities?	☐☐☐		8.14

(*Continued*)

		Compliance 1 2 3[a]	Remarks	EU-Guide
10.20	Is the effectiveness of the arrangements for recalls checked critically from time to time?	☐☐☐		8.15
11	**SELF-INSPECTION**			**9**
11.1	Does a self-inspection procedure exist that defines frequency and program?	☐☐☐		9.1
11.2	Are self-inspections carried out to check compliance with GMP rules?	☐☐☐		9.1
11.3	Are self-inspections conducted in an independent and detailed way?	☐☐☐		9.2
	by designated competent persons from the company or external experts?	☐☐☐		
11.4	Are self-inspections recorded?	☐☐☐		9.3
11.5	Do reports contain	☐☐☐		9.3
	• The observations made during a self-inspection?			
	• Proposals for corrective measures?	☐☐☐		
11.6	Are actions subsequently taken recorded?	☐☐☐		9.3
12	**CONTRACT MANUFACTURE AND ANALYSIS**			**7**
12.1	Is a written contract between contract giver and contract acceptor available?	☐☐☐		7.1
12.2	Are responsibilities and duties clearly defined?	☐☐☐		7
12.3	Are all arrangements in accordance with the marketing authorization of the product concerned?	☐☐☐		7.2
	The Contract Giver			
12.4	Competence of the acceptor to carry out the work successfully and according to GMP assessed?	☐☐☐		7.3
12.5	Acceptor provided with all the information necessary to carry out the contract work?	☐☐☐		7.4
12.6	Acceptor informed of safety aspects?	☐☐☐		7.4
12.7	Conformance of products supplied by the acceptor ensured?	☐☐☐		7.5
12.8	Product released by a qualified person on the acceptor's side?	☐☐☐		7.5
	The Contract Acceptor			
12.9	Does the acceptor have	☐☐☐		7.6
	• Adequate premises and equipment?			
	• Knowledge and experience?	☐☐☐		
	• Competent personnel?	☐☐☐		
	• A manufacturing authorization?	☐☐☐		
12.10	Does the acceptor ensure that all products or materials delivered to him or her are suitable?	☐☐☐		7.7
12.11	There must be no work passed to a third party without the permission of the giver.	☐☐☐		7.8
12.12	If a third party is involved, it must have the necessary manufacturing and analytical information.	☐☐☐		7.8
	The Contract			
12.13	Does the written contract specify the responsibilities?	☐☐☐		7.10
12.14	Have technical aspects been drawn up by competent persons?	☐☐☐		7.10
12.15	Release of material and check for compliance with the marketing authorization defined?	☐☐☐		7.11
12.16	Is it defined who is responsible for			7.12
	• Purchasing of materials?	☐☐☐		
	• IPC controls?	☐☐☐		
	• Testing and release of materials?	☐☐☐		
	• Manufacturing and quality control?	☐☐☐		
	• Sampling?	☐☐☐		
	• Storage of batch documentation?	☐☐☐		
12.17	Are manufacturing, analytical, and distribution records available to the contract giver?	☐☐☐		7.13

(*Continued*)

		Compliance 1 2 3[a]	Remarks	EU-Guide
12.18	Does the contract permit the giver to visit the facilities of the acceptor?	☐☐☐		7.14
12.19	In the case of contract analysis: Does the contract acceptor understand that he or she is subject to inspection by the competent authorities?	☐☐☐		7.15
13	**AUDIT OF SUPPLIERS**			**2.7**
13.1	Supplier audits performed for	☐☐☐		
	• Excipients?			
	• Active substances?	☐☐☐		
	• Packaging material?	☐☐☐		

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

GLOSSARY

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

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

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

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

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

Batch (or Lot): A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Batch Number (or Lot Number): A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined. .

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

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

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

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

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

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

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

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

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

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

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

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

Deviation: Departure from an approved instruction or established standard.

Drug (Medicinal) Product: The dosage form in the final immediate packaging intended for marketing. (See ICH Guidance Q1A.)

Drug Substance: See Active Pharmaceutical Ingredient.

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

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

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

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

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

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

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

Lot: See Batch.

Lot Number: See Batch Number.

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

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

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

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

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

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

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

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

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

Pharmaceutical Product: Any material or product intended for human or veterinary use presented in its finished dosage form, or as a starting material for use in such a dosage form, that is subject to control by

pharmaceutical legislation in the exporting state and/or the importing state.

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

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

Process Control: See In-Process Control.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Signature (Signed): See definition for signed.

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

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

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

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

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

Validation: A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria. Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material,

activity, or system actually leads to the expected results (see also Qualification).

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

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

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

Appendix B

DISSOLUTION TESTING OF SEMISOLID DOSAGE FORMS

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (min)	Date Updated
Prochlorperazine	Suppository	I (Suppository, dissolution baskets, Palmieri type)	100	0.1 N HCl at 38°C	900	10, 20, 30, and 45	08/17/2006
Acetaminophen	Suppository	II (Paddle)	50	Phosphate buffer, pH 5	900	15, 30, 45, 60, and 90	08/17/2006
Mesalamine	Suppository	II (Paddle) with option to use a sinker	75 (for 500 mg) and 125 (for 1000 mg)	For 500-mg strength: 0.2 M phosphate buffer, pH 7.5 at 37°C; For 1000-mg strength: 0.2 M phosphate buffer, pH 7.5 at 40°C	900	30, 60, 90, 120, and 150	01/30/2006

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Appendix C

APPROVED INGREDIENTS

Ingredient	Route	Dosage FoRM	Quantity	Unit
1,2,6-HEXANETRIOL	TOPICAL		0.05	%W/W
1,2,6-HEXANETRIOL	TOPICAL	EMULSION, CREAM	7.5	%
1,3-DIMETHYLOL-5,5-DIMETHYL-HYDANTOIN	TOPICAL	LOTION	46.4	%
2-AMINO-2-METHYL-1-PROPANOL	TOPICAL	LOTION	0.3	%
2-AMINO-2-METHYL-1-PROPANOL	TOPICAL	EMULSION, CREAM	1	%
2-ETHYLHEXYL SALICYLATE	TRANSDERMAL	SPRAY	68.85	%
ACACIA	BUCCAL	UM	7.07	MG
ACACIA	BUCCAL	GUM, CHEWING	14	MG
ACESULFAME	BUCCAL	GUM, CHEWING	2.4	MG
ACESULFAME POTASSIUM			1.6	MG
ACESULFAME POTASSIUM			1.5	MG
ACESULFAME POTASSIUM			3	MG
ACESULFAME POTASSIUM	BUCCAL	GUM	2.35	MG
ACESULFAME POTASSIUM	BUCCAL	GUM, CHEWING	7.35	MG
ACETIC ACID			0.025	%
ACETONE	TOPICAL	LOTION	10	%
ACRYLATES COPOLYMER		EMULSION, SUSTAINED RELEASE	13.6	%W/W
ACRYLATES COPOLYMER			382.22	MG
ACRYLATES COPOLYMER	EMULSION, SUSTAINED RELEASE	TOPICAL	13.6	%W/W
ACRYLATES COPOLYMER	TOPICAL	GEL	10	%
ACRYLATES COPOLYMER	TOPICAL	EMULSION, CREAM	13.6	%
ACRYLATES COPOLYMER	TOPICAL	GEL	0.8	%W/W
ACRYLATES COPOLYMER	TRANSDERMAL	FILM, CONTROLLED RELEASE	382.22	MG
ACRYLIC ACID-ISOOCTYL ACRYLATE COPOLYMER			56.4	MG
ACRYLIC ACID/ISOOCTYLACRYLATE COPOLYMER	TRANSDERMAL	FILM, CONTROLLED RELEASE	24.5	MG
ACRYLIC ADHESIVE 788			10.17	MG
ACRYLIC ADHESIVE 788			20.08	MG
ADCOTE 72A103			16	MG
ADCOTE 72A103	TRANSDERMAL	PATCH, CONTROLLED RELEASE	3.99	MG
ADCOTE 72A103	TRANSDERMAL	FILM, CONTROLLED RELEASE	16	MG
ADHESIVE TAPE	TRANSDERMAL	FILM, CONTROLLED RELEASE	127.85	MG
AEROTEX RESIN 3730			1.9	MG
AEROTEX RESIN 3730	TRANSDERMAL	FILM, CONTROLLED RELEASE	1.9	MG
ALCOHOL			60.43	%W/W
ALCOHOL			358.7	MG
ALCOHOL	RECTAL	GEL	22.45	%
ALCOHOL	TOPICAL	LOTION	80.5	%
ALCOHOL	TOPICAL	GEL	84.95	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
ALCOHOL	TOPICAL	GEL	94.78	%W/W
ALCOHOL	TRANSDERMAL	GEL	74.1	%
ALCOHOL	TRANSDERMAL	FILM, CONTROLLED RELEASE	358.7	MG
ALCOHOL	TRANSDERMAL	GEL	74.1	%
ALCOHOL	TRANSDERMAL	GEL	65.8	%W/W
ALCOHOL	TRANSDERMAL	GEL, METERED	73.5	%
ALCOHOL, DEHYDRATED	TOPICAL	LOTION	8.8	%
ALCOHOL, DEHYDRATED	TOPICAL	GEL	94.7808	%
ALCOHOL, DEHYDRATED	TRANSDERMAL	GEL	46.28	%
ALCOHOL, DEHYDRATED	TRANSDERMAL	FILM, CONTROLLED RELEASE	250	MG
ALCOHOL, DENATURED			1.8	%
ALCOHOL, DENATURED	TOPICAL	LOTION	25	%
ALCOHOL, DENATURED	TOPICAL	GEL	96.9385	%
ALCOHOL, DENATURED	TOPICAL	GEL	96.94	%W/W
ALGELDRATE			5	%W/W
ALLANTOIN			2	%
ALLANTOIN	TOPICAL	GEL	0.2	%
ALLANTOIN	TOPICAL	EMULSION, CREAM	1	%
ALLANTOIN	TOPICAL	GEL	0.2	%W/W
ALLANTOIN	VAGINAL	EMULSION, CREAM	2	%
ALMOND OIL	TOPICAL	EMULSION, CREAM	2	%
ALPHA-TERPINEOL	TOPICAL	LOTION	11	%
ALPHA-TOCOPHEROL	TOPICAL	OINTMENT	0.002	%
ALPHA-TOCOPHEROL	BUCCAL	FILM	0.07	MG
ALPHA-TOCOPHEROL ACETATE	BUCCAL	FILM	0.088	MG
ALPHA-TOCOPHEROL ACETATE, DL-			0.002	%W/W
ALUMINUM ACETATE			0.009	%W/W
ALUMINUM ACETATE	TOPICAL	EMULSION, CREAM	0.0001	%
ALUMINUM ACETATE	TOPICAL	LOTION	10	%
ALUMINUM DIACETATE	RECTAL	SUPPOSITORY	75	MG
ALUMINUM HYDROXIDE			0.25	%W/W
ALUMINUM HYDROXIDE			0.25	%W/W
ALUMINUM HYDROXIDE		TOPICAL	0.25	%W/W
ALUMINUM HYDROXIDE		TOPICAL	0.25	%W/W
ALUMINUM HYDROXIDE			5	%W/W
ALUMINUM HYDROXIDE	TOPICAL	EMULSION, CREAM	5	%
ALUMINUM HYDROXIDE GEL	TOPICAL	EMULSION, CREAM	5	%
ALUMINUM HYDROXIDE GEL F 500	TOPICAL	EMULSION, CREAM	2	%
ALUMINUM HYDROXIDE GEL F 5000	TOPICAL	EMULSION, CREAM	3	%
ALUMINUM MONOSTEARATE			0.01	%W/W
ALUMINUM MONOSTEARATE	TOPICAL	EMULSION, CREAM	0.01	%
ALUMINUM POLYESTER			9.78	MG
ALUMINUM POLYESTER			81	MG
ALUMINUM POLYESTER	TRANSDERMAL	FILM, CONTROLLED RELEASE	81	MG
ALUMINUM POTASSIUM SULFATE	VAGINAL	SUPPOSITORY	17.2	MG
ALUMINUM STARCH OCTENYLSUCCINATE			10	%W/W
ALUMINUM STARCH OCTENYLSUCCINATE	TOPICAL	EMULSION, CREAM	10	%
ALUMINUM STEARATE			0.01	%W/W
ALUMINUM STEARATE	TOPICAL	EMULSION, CREAM	0.01	%
ALUMINUM STEARATE	TOPICAL	OINTMENT	0.01	%
ALUMINUM SULFATE			0.015	%W/W
ALUMINUM SULFATE		TOPICAL	0.015	%W/W
ALUMINUM SULFATE	TOPICAL	EMULSION, CREAM	0.131	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
ALUMINUM SULFATE ANHYDROUS			0.13	%W/W
AMERCHOL C			0.1	%W/W
AMERCHOL-CAB	TOPICAL	OINTMENT	10	%
AMINOMETHYLPROPANOL			1	%W/W
AMMONIA SOLUTION			5.72	%W/W
AMMONIA SOLUTION	TOPICAL	GEL	1.13	%W/W
AMMONIA SOLUTION	TOPICAL	GEL	1.2	%W/W
AMMONIA SOLUTION	TOPICAL	GEL		ADJPH
AMMONIUM GLYCYRRHIZATE			0.3	MG
AMMONIUM HYDROXIDE	TOPICAL	EMULSION, CREAM	5.72	%
AMMONIUM LAURYL SULFATE			39.75	%W/W
AMMONYX	TOPICAL	SPONGE	37500	MG
AMPHOTERIC-9			0.66	%W/W
AMPHOTERIC-9	TOPICAL	EMULSION, CREAM	0.66	%
ANHYDROUS CITRIC ACID			0.01	%W/W
ANHYDROUS CITRIC ACID		EMULSION, SUSTAINED RELEASE	0.18	%W/W
ANHYDROUS CITRIC ACID		TOPICAL	0.01	%W/W
ANHYDROUS CITRIC ACID			5.56	MG
ANHYDROUS CITRIC ACID			2.96	MG
ANHYDROUS CITRIC ACID			0.08	%W/W
ANHYDROUS CITRIC ACID			0.05	%W/W
ANHYDROUS CITRIC ACID	BUCCAL	FILM	1.04	MG
ANHYDROUS CITRIC ACID	EMULSION, SUSTAINED RELEASE	TOPICAL	0.18	%W/W
ANHYDROUS CITRIC ACID	TOPICAL	GEL	0.05	%W/W
ANHYDROUS TRISODIUM CITRATE		EMULSION, SUSTAINED RELEASE	0.12	%W/W
ANHYDROUS TRISODIUM CITRATE			1.34	MG
ANHYDROUS TRISODIUM CITRATE			0.28	%W/W
ANHYDROUS TRISODIUM CITRATE	EMULSION, SUSTAINED RELEASE	TOPICAL	0.12	%W/W
ANOXID SBN			0.16	%W/W
ANOXID SBN	TOPICAL	EMULSION, CREAM	0.1562	%
ANTIFOAM	TOPICAL	LOTION	0.031	%
APRICOT KERNEL OIL PEG-6 ESTERS			2.94	%W/W
APRICOT KERNEL OIL PEG-6 ESTERS			2.94	%
APRICOT KERNEL OIL PEG-6 ESTERS	TOPICAL	EMULSION, CREAM	2.94	%
APRICOT KERNEL OIL PEG-6 ESTERS	VAGINAL	EMULSION, CREAM	2.94	%
AQUAPHOR			1	%W/W
AQUAPHOR	TOPICAL	EMULSION, CREAM	1	%
ARLACEL			5.5	%W/W
ARLACEL			1.5	%W/W
ARLACEL	TOPICAL	EMULSION, CREAM	1.5	%
ARLATONE 289	TOPICAL	EMULSION, CREAM	1.9	%
ASCORBIC ACID	RECTAL	SUPPOSITORY	3	MG
ASCORBIC ACID	TOPICAL	GEL	0.3	%
ASCORBIC ACID	TOPICAL	GEL	0.3	%W/W
ASCORBYL PALMITATE			0.02	%W/W
ASCORBYL PALMITATE	RECTAL	SUPPOSITORY	5.6	MG
ASCORBYL PALMITATE	TOPICAL	EMULSION, CREAM	0.02	%
BALSAM, CANADA	TOPICAL	LOTION	0.5	%
BALSAM, PERU	RECTAL	SUPPOSITORY	100	MG
BARIUM SULFATE	VAGINAL	DRUG DELIVERY SYSTEM	5.9	MG
BEESWAX	TOPICAL	EMULSION, CREAM	5	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
BEESWAX	TOPICAL	OINTMENT	20	%
BEESWAX, SYNTHETIC			3.5	%W/W
BEESWAX, SYNTHETIC		TOPICAL	3.5	%W/W
BEESWAX, SYNTHETIC			3.5	%W/W
BEESWAX, SYNTHETIC	TOPICAL	EMULSION, CREAM	3.5	%
BENTONITE			9.86	MG
BENTONITE	TOPICAL	LOTION	5	%
BENTONITE	TRANSDERMAL	PATCH, CONTROLLED RELEASE	2.47	MG
BENTONITE	TRANSDERMAL	FILM, CONTROLLED RELEASE	9.86	MG
BENTONITE	VAGINAL	SUPPOSITORY	288.1	MG
BENZALKONIUM CHLORIDE	OPHTHALMIC	GEL	0.008	%
BENZALKONIUM CHLORIDE	OPHTHALMIC	GEL	0.008	%
BENZALKONIUM CHLORIDE	TOPICAL	LOTION	0.1	%
BENZOIC ACID			0.2	%W/W
BENZOIC ACID		EMULSION, SUSTAINED RELEASE	0.19	%W/W
BENZOIC ACID		TOPICAL	0.2	%W/W
BENZOIC ACID			0.1	%W/W
BENZOIC ACID			0.25	%W/W
BENZOIC ACID			0.1	%
BENZOIC ACID			0.25	%
BENZOIC ACID	EMULSION, SUSTAINED RELEASE	TOPICAL	0.19	%W/W
BENZOIC ACID	RECTAL	GEL	0.28	%
BENZOIC ACID	TOPICAL	GEL	0.1	%
BENZOIC ACID	TOPICAL	LOTION	0.2	%
BENZOIC ACID	TOPICAL	EMULSION, CREAM	0.25	%
BENZOIC ACID	TOPICAL	GEL	0.1	%W/W
BENZOIC ACID	VAGINAL	EMULSION, CREAM	0.25	%
BENZOIC ACID	VAGINAL	SPONGE	3	MG
BENZOIC ACID	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	0.19	%
BENZYL ALCOHOL			2	%W/W
BENZYL ALCOHOL			2.3	%W/W
BENZYL ALCOHOL		AUGMENTED	1	%W/W
BENZYL ALCOHOL		EMULSION, SUSTAINED RELEASE	2	%W/W
BENZYL ALCOHOL		TOPICAL	2	%W/W
BENZYL ALCOHOL		TOPICAL	2.3	%W/W
BENZYL ALCOHOL			2.7	%W/W
BENZYL ALCOHOL			1	%
BENZYL ALCOHOL	AUGMENTED	TOPICAL	1	%W/W
BENZYL ALCOHOL	EMULSION, SUSTAINED RELEASE	TOPICAL	2	%W/W
BENZYL ALCOHOL	RECTAL	GEL	3.1	%
BENZYL ALCOHOL	TOPICAL	CREAM, AUGMENTED	1	%
BENZYL ALCOHOL	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	1	%
BENZYL ALCOHOL	TOPICAL	LOTION	1.3	%
BENZYL ALCOHOL	TOPICAL	OINTMENT	2.2	%
BENZYL ALCOHOL	TOPICAL	EMULSION, CREAM	2.7	%
BENZYL ALCOHOL	TOPICAL	GEL	50	%
BENZYL ALCOHOL	TOPICAL	GEL	2	%W/W
BENZYL ALCOHOL	VAGINAL	CREAM, AUGMENTED	1	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
BENZYL ALCOHOL	VAGINAL	EMULSION, CREAM	1	%
BENZYL ALCOHOL	VAGINAL	CREAM, AUGMENTED	1	%
BENZYL ALCOHOL	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	1	%
BETADEX	TOPICAL	GEL	1	%
BETADEX	TOPICAL	GEL	1	%W/W
BISMUTH SUBGALLATE	RECTAL	SUPPOSITORY	115	MG
BORIC ACID			1.3	%W/W
BORIC ACID	OPHTHALMIC	GEL	0.5	%
BORIC ACID	OPHTHALMIC	GEL	0.5	%
BUTYL ALCOHOL, TERTIARY	TOPICAL	GEL	0.1186	%
BUTYL STEARATE			3.68	%W/W
BUTYL STEARATE	TOPICAL	EMULSION, CREAM	3.7	%
BUTYLATED HYDROXYANISOLE			0.0052	%W/W
BUTYLATED HYDROXYANISOLE		TOPICAL	0.0052	%W/W
BUTYLATED HYDROXYANISOLE			0.08	MG
BUTYLATED HYDROXYANISOLE			5.2	%W/W
BUTYLATED HYDROXYANISOLE			0.03	%
BUTYLATED HYDROXYANISOLE	RECTAL	SUPPOSITORY	0.213	MG
BUTYLATED HYDROXYANISOLE	TOPICAL	OINTMENT	0.005	%
BUTYLATED HYDROXYANISOLE	TOPICAL	GEL	0.05	%
BUTYLATED HYDROXYANISOLE	TOPICAL	EMULSION, CREAM	0.1	%
BUTYLATED HYDROXYANISOLE	TOPICAL	GEL	0.05	%W/W
BUTYLATED HYDROXYANISOLE	VAGINAL	OINTMENT	0.02	%
BUTYLATED HYDROXYANISOLE	VAGINAL	EMULSION, CREAM	0.125	%
BUTYLATED HYDROXYANISOLE	VAGINAL	SUPPOSITORY	1	MG
BUTYLATED HYDROXYTOLUENE			0.05	%W/W
BUTYLATED HYDROXYTOLUENE		AUGMENTED	0.2	%W/W
BUTYLATED HYDROXYTOLUENE		EMULSION, SUSTAINED RELEASE	0.1	%W/W
BUTYLATED HYDROXYTOLUENE		TOPICAL	0.05	%W/W
BUTYLATED HYDROXYTOLUENE			0.06	MG
BUTYLATED HYDROXYTOLUENE			0.1	%W/W
BUTYLATED HYDROXYTOLUENE			0.1	%W/W
BUTYLATED HYDROXYTOLUENE			0.05	%
BUTYLATED HYDROXYTOLUENE	AUGMENTED	TOPICAL	0.2	%W/W
BUTYLATED HYDROXYTOLUENE	BUCCAL	GUM, CHEWING	0.21	MG
BUTYLATED HYDROXYTOLUENE	EMULSION, SUSTAINED RELEASE	TOPICAL	0.1	%W/W
BUTYLATED HYDROXYTOLUENE	RECTAL	SUPPOSITORY	0.213	MG
BUTYLATED HYDROXYTOLUENE	TOPICAL	LOTION	0.02	%
BUTYLATED HYDROXYTOLUENE	TOPICAL	OINTMENT	0.025	%
BUTYLATED HYDROXYTOLUENE	TOPICAL	CREAM, AUGMENTED	0.05	%
BUTYLATED HYDROXYTOLUENE	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	0.1	%
BUTYLATED HYDROXYTOLUENE	TOPICAL	EMULSION, CREAM	0.1	%
BUTYLATED HYDROXYTOLUENE	TOPICAL	GEL	2	%
BUTYLATED HYDROXYTOLUENE	TOPICAL	GEL	0.1	%W/W
BUTYLATED HYDROXYTOLUENE	TRANSDERMAL	GEL	0.05	%
BUTYLATED HYDROXYTOLUENE	VAGINAL	EMULSION, CREAM	0.05	%
BUTYLENE GLYCOL			8.12	MG
BUTYLENE GLYCOL	TRANSDERMAL	PATCH, CONTROLLED RELEASE	2.03	MG
BUTYLENE GLYCOL	TRANSDERMAL	FILM, CONTROLLED RELEASE	8.12	MG

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
BUTYLPARABEN		EMULSION, SUSTAINED RELEASE	0.05	%W/W
BUTYLPARABEN			0.4	%W/W
BUTYLPARABEN	EMULSION, SUSTAINED RELEASE	TOPICAL	0.05	%W/W
BUTYLPARABEN	TOPICAL	LOTION	0.15	%
BUTYLPARABEN	TOPICAL	EMULSION, CREAM	0.4	%
C13-14 ISOPARAFFIN/LAURETH-7/ POLYACRYLAMIDE	TOPICAL	GEL	5	%W/W
CALCIUM ACETATE			0.002	%W/W
CALCIUM ACETATE		TOPICAL	0.002	%W/W
CALCIUM ACETATE			0.092	%W/W
CALCIUM ACETATE	TOPICAL	EMULSION, CREAM	0.092	%
CALCIUM CARBONATE			4.83	MG
CALCIUM CARBONATE	BUCCAL	GUM, CHEWING	145.7	MG
CALCIUM CHLORIDE	TOPICAL	EMULSION, CREAM	0.25	%
CALCIUM HYDROXIDE	TOPICAL	EMULSION, CREAM	1.4	%
CAPRYLIC/CAPRIC TRIGLYCERIDE	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	10	%
CAPRYLIC/CAPRIC TRIGLYCERIDE	TOPICAL	EMULSION, CREAM	10.8	%
CAPRYLIC/CAPRIC/STEARIC TRIGLYCERIDE	TOPICAL	OINTMENT	70	%
CARAMEL			0.26	%W/W
CARAMEL	TOPICAL	EMULSION, CREAM	0.26	%
CARBOMER 1342	TOPICAL	CREAM, AUGMENTED	0.2	%
CARBOMER 1342	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	0.2	%
CARBOMER 1342	TOPICAL	LOTION	0.2	%
CARBOMER 1342	TOPICAL	EMULSION, LOTION	0.3	%
CARBOMER 1342	TRANSDERMAL	GEL	1.5	%
CARBOMER 1342	TRANSDERMAL	FILM, CONTROLLED RELEASE	24.3	MG
CARBOMER 1382	TOPICAL	GEL	0.9	%W/W
CARBOMER 934	TOPICAL	LOTION	0.5	%
CARBOMER 934	TOPICAL	OINTMENT	0.5	%
CARBOMER 934	TOPICAL	EMULSION, CREAM	1	%
CARBOMER 934	TOPICAL	GEL	1.498	%
CARBOMER 934	VAGINAL	GEL	2	%
CARBOMER 934P	TOPICAL	LOTION	0.56	%
CARBOMER 934P	TOPICAL	CREAM, AUGMENTED	1	%
CARBOMER 934P	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	1	%
CARBOMER 934P	TOPICAL	EMULSION, CREAM	1	%
CARBOMER 934P	TOPICAL	GEL	2	%
CARBOMER 934P	VAGINAL	GEL	2	%
CARBOMER 940	TOPICAL	EMULSION, CREAM	0.6	%
CARBOMER 940	TOPICAL	CREAM, AUGMENTED	1	%
CARBOMER 940	TOPICAL	OINTMENT, AUGMENTED	2.25	%
CARBOMER 940	TOPICAL	GEL	3.5	%
CARBOMER 940	TOPICAL	LOTION	58	%
CARBOMER 940	TRANSDERMAL	GEL	1.2	%
CARBOMER 941	TOPICAL	LOTION	0.15	%
CARBOMER 941	TOPICAL	GEL	0.2	%
CARBOMER 974P	TOPICAL	GEL	0.8	%
CARBOMER 980	TOPICAL	GEL	0.85	%
CARBOMER 980	TOPICAL	EMULSION, CREAM	1.2	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
CARBOMER 980	TRANSDERMAL	GEL	7.5	%
CARBOMER 981	TOPICAL	GEL	0.85	%
CARBOMER COPOLYMER TYPE A (ALLYL PENTAERYTHRITOL CROSSLINKED)			0.2	%W/W
CARBOMER COPOLYMER TYPE A (ALLYL PENTAERYTHRITOL CROSSLINKED)		TOPICAL	0.2	%W/W
CARBOMER COPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)		AUGMENTED	0.2	%W/W
CARBOMER COPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)		EMULSION, SUSTAINED RELEASE	0.2	%W/V
CARBOMER COPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)			0.2	%W/W
CARBOMER COPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)			0.3	%W/W
CARBOMER COPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)			24.3	MG
CARBOMER COPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)	AUGMENTED	TOPICAL	0.2	%W/W
CARBOMER COPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)	EMULSION, SUSTAINED RELEASE	TOPICAL	0.2	%W/V
CARBOMER COPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL	GEL	0.8	%W/W
CARBOMER COPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)	TRANSDERMAL	GEL	0.3	%W/W
CARBOMER HOMOPOLYMER TYPE A (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL	GEL	0.85	%W/W
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)			1.2	%W/W
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)		TOPICAL	1.2	%W/W
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)			1	%W/W
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)	OPHTHALMIC	GEL	0.48	%
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)	OPHTHALMIC	GEL	0.48	%
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL OR ALLYL SUCROSE CROSSLINKED)		AUGMENTED	1	%W/V
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL OR ALLYL SUCROSE CROSSLINKED)		EMULSION, SUSTAINED RELEASE	1	%W/V
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL OR ALLYL SUCROSE CROSSLINKED)			0.5	%W/W
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL OR ALLYL SUCROSE CROSSLINKED)			1	%W/W
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL OR ALLYL SUCROSE CROSSLINKED)	AUGMENTED	TOPICAL	1	%W/V
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL OR ALLYL SUCROSE CROSSLINKED)	EMULSION, SUSTAINED RELEASE	TOPICAL	1	%W/V
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL OR ALLYL SUCROSE CROSSLINKED)	TOPICAL	GEL	1.51	%W/W

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL OR ALLYL SUCROSE CROSSLINKED)	VAGINAL	GEL	2	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)			1.2	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)			1.2	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)		AUGMENTED	1	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)		EMULSION, SUSTAINED RELEASE	1.2	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)		TOPICAL	1.2	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)		TOPICAL	1.2	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)			0.6	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)			1.2	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	AUGMENTED	TOPICAL	1	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	EMULSION, SUSTAINED RELEASE	TOPICAL	1.2	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	OPHTHALMIC	GEL	4	%
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	OPHTHALMIC	GEL	4	%
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL	GEL	0.7	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL	GEL	0.78	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL	GEL	1.6	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL	GEL	2	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL	GEL	3.5	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TRANSDERMAL	GEL	1.5	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TRANSDERMAL	GEL	1.5	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TRANSDERMAL	GEL, METERED	1	%
CARBOXY VINYL COPOLYMER	TOPICAL	GEL	30	%
CARBOXYMETHYLCELLULOSE	BUCCAL	FILM	10.95	MG
CARBOXYMETHYLCELLULOSE	TOPICAL	PATCH	6.14	MG
CARBOXYMETHYLCELLULOSE SODIUM	TOPICAL	JELLY	3.5	%
CARBOXYMETHYLCELLULOSE SODIUM (0.7 CARBOXYMETHYL SUBSTITUTION PER SACCHARIDE; 38 MPA.S AT 2%)	BUCCAL	FILM	17.64	MG
CARBOXYMETHYLCELLULOSE SODIUM, UNSPECIFIED FORM			0.4	%
CARBOXYMETHYLCELLULOSE SODIUM, UNSPECIFIED FORM			0.2	%
CARBOXYMETHYLCELLULOSE SODIUM, UNSPECIFIED FORM			700	MG
CARBOXYPOLYMETHYLENE	TOPICAL	LOTION	0.3	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
CARBOXYPOLYMETHYLENE	TOPICAL	GEL	1	%
CARBOXYPOLYMETHYLENE	TOPICAL	GEL	1	%W/W
CARNAUBA WAX	BUCCAL	GUM, CHEWING	0.55	MG
CARRAGEENAN			33	MG
CARRAGEENAN	TOPICAL	LOTION	0.5	%
CARRAGEENAN	TRANSDERMAL	FILM, CONTROLLED RELEASE	33	MG
CARRAGEENAN SALT	TOPICAL	LOTION	0.271	%
CASTOR OIL	NASAL	GEL	107	MG/SPR
CASTOR OIL	TOPICAL	EMULSION, CREAM	12.5	%
CASTOR OIL	TOPICAL	OINTMENT	14.9	%
CERASYNT-SE	RECTAL	SUPPOSITORY	35	MG
CERASYNT-SE	TOPICAL	LOTION	3	%
CERESIN			7	%
CERESIN	TOPICAL	OINTMENT	7.31	%
CERESIN	VAGINAL	CREAM	7	%W/W
CETEARETH-12			5	%W/W
CETEARETH-12			5	%W/W
CETEARETH-12	TOPICAL	EMULSION, CREAM	5	%
CETEARETH-15			1.25	%W/W
CETEARETH-15	TOPICAL	EMULSION, CREAM	1.5	%
CETEARETH-30		AUGMENTED	1	%W/W
CETEARETH-30		EMULSION, SUSTAINED RELEASE	3	%W/W
CETEARETH-30			3	%W/W
CETEARETH-30	AUGMENTED	TOPICAL	1	%W/W
CETEARETH-30	EMULSION, SUSTAINED RELEASE	TOPICAL	3	%W/W
CETEARETH-30	TOPICAL	CREAM, AUGMENTED	1	%
CETEARETH-30	TOPICAL	LOTION	2.3	%
CETEARETH-30	TOPICAL	EMULSION, CREAM	3	%
CETEARYL ALCOHOL	TOPICAL	OINTMENT	1.2	%
CETEARYL ALCOHOL	TOPICAL	LOTION	4	%
CETEARYL ALCOHOL	TOPICAL	EMULSION, LOTION	5	%
CETEARYL ALCOHOL	TOPICAL	EMULSION, CREAM	12	%
CETEARYL ALCOHOL	VAGINAL	CREAM, AUGMENTED	10	%
CETEARYL ALCOHOL	VAGINAL	EMULSION, CREAM	12	%
CETEARYL ALCOHOL/CETEARETH-20			0.5	%W/W
CETEARYL ALCOHOL/CETEARETH-20			2	%W/W
CETEARYL ALCOHOL/CETEARETH-20		AUGMENTED	4.72	%W/W
CETEARYL ALCOHOL/CETEARETH-20		TOPICAL	0.5	%W/W
CETEARYL ALCOHOL/CETEARETH-20		TOPICAL	2	%W/W
CETEARYL ALCOHOL/CETEARETH-20			8	%W/W
CETEARYL ALCOHOL/CETEARETH-20	AUGMENTED	TOPICAL	4.72	%W/W
CETEARYL ALCOHOL/CETEARETH-20	TOPICAL	CREAM, AUGMENTED	4.72	%
CETEARYL ALCOHOL/CETEARETH-20	TOPICAL	EMULSION, CREAM	8	%
CETEARYL ETHYLHEXANOATE			1	%W/W
CETEARYL ETHYLHEXANOATE		TOPICAL	1	%W/W
CETEARYL ETHYLHEXANOATE			3	%W/W
CETEARYL OCTANOATE	TOPICAL	EMULSION, CREAM	3	%
CETETH-10	TOPICAL	LOTION	2.5	%
CETETH-2			2.5	%W/W
CETETH-2	TOPICAL	LOTION	0.8	%
CETETH-2	TOPICAL	EMULSION, CREAM	2.5	%
CETETH-20			15	%W/W
CETETH-20		AUGMENTED	6	%W/W

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
CETETH-20		EMULSION, SUSTAINED RELEASE	3	%W/W
CETETH-20		TOPICAL	15	%W/W
CETETH-20			4.01	%W/W
CETETH-20			3	%W/W
CETETH-20			1	%W/W
CETETH-20	AUGMENTED	TOPICAL	6	%W/W
CETETH-20	EMULSION, SUSTAINED RELEASE	TOPICAL	3	%W/W
CETETH-20	TOPICAL	EMULSION, LOTION	1	%
CETETH-20	TOPICAL	LOTION	2	%
CETETH-20	TOPICAL	EMULSION, CREAM	4.005	%
CETETH-20	TOPICAL	CREAM, AUGMENTED	6	%
CETETH-23			2	%W/W
CETETH-23			2	%W/W
CETETH-23	TOPICAL	EMULSION, CREAM	2	%
CETOSTEARYL ALCOHOL			12	%W/W
CETOSTEARYL ALCOHOL		AUGMENTED	8	%W/W
CETOSTEARYL ALCOHOL		EMULSION, SUSTAINED RELEASE	11.5	%W/W
CETOSTEARYL ALCOHOL		TOPICAL	12	%W/W
CETOSTEARYL ALCOHOL			1.09	%W/W
CETOSTEARYL ALCOHOL			11.4	%W/W
CETOSTEARYL ALCOHOL			6	%W/W
CETOSTEARYL ALCOHOL			5	%W/W
CETOSTEARYL ALCOHOL			12	%
CETOSTEARYL ALCOHOL	AUGMENTED	TOPICAL	8	%W/W
CETOSTEARYL ALCOHOL	EMULSION, SUSTAINED RELEASE	TOPICAL	11.5	%W/W
CETOSTEARYL ALCOHOL	VAGINAL	CREAM, AUGMENTED	10	%
CETRIMONIUM CHLORIDE	TOPICAL	LOTION	0.2	%
CETYL ALCOHOL			6	%W/W
CETYL ALCOHOL			6.7	%W/W
CETYL ALCOHOL		AUGMENTED	4	%W/W
CETYL ALCOHOL		EMULSION, SUSTAINED RELEASE	7.2	%W/W
CETYL ALCOHOL		TOPICAL	6	%W/W
CETYL ALCOHOL		TOPICAL	6.7	%W/W
CETYL ALCOHOL			3.23	%W/W
CETYL ALCOHOL			12	%W/W
CETYL ALCOHOL			0.75	%
CETYL ALCOHOL			4	%
CETYL ALCOHOL	AUGMENTED	TOPICAL	4	%W/W
CETYL ALCOHOL	EMULSION, SUSTAINED RELEASE	TOPICAL	7.2	%W/W
CETYL ALCOHOL	TOPICAL	CREAM, AUGMENTED	4	%
CETYL ALCOHOL	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	6	%
CETYL ALCOHOL	TOPICAL	OINTMENT	7	%
CETYL ALCOHOL	TOPICAL	EMULSION, CREAM	12	%
CETYL ALCOHOL	TOPICAL	LOTION	68.4	%
CETYL ALCOHOL	VAGINAL	EMULSION, CREAM	15	%
CETYL ALCOHOL	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	5	%
CETYL ESTERS	TOPICAL	LOTION	3	%
CETYL ESTERS	TOPICAL	EMULSION, CREAM	10.3	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
CETYL ESTERS	VAGINAL	CREAM, AUGMENTED	3	%
CETYL ESTERS	VAGINAL	EMULSION, CREAM	3	%
CETYL ESTERS WAX			2	%W/W
CETYL ESTERS WAX		TOPICAL	2	%W/W
CETYL ESTERS WAX			10.3	%W/W
CETYL ESTERS WAX			3	%
CETYL ESTERS WAX	VAGINAL	CREAM, AUGMENTED	3	%
CETYL ESTERS WAX	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	9	%
CETYL PALMITATE			0.35	%W/W
CETYL PALMITATE		TOPICAL	0.35	%W/W
CETYL PALMITATE			0.31	%W/W
CETYL PALMITATE			3.3	%
CETYL PALMITATE	TOPICAL	EMULSION, CREAM	9.45	%
CETYL PALMITATE	VAGINAL	EMULSION, CREAM	3.3	%
CETYLPYRIDINIUM CHLORIDE	IONTOPHORESIS	DRUG DELIVERY SYSTEM	1.2	MG
CETYLPYRIDINIUM CHLORIDE	TRANSDERMAL	DRUG DELIVERY SYSTEM	1.2	MG
CHEMODERM 6401B		EMULSION, SUSTAINED RELEASE	0.1	%W/W
CHEMODERM 6401B	EMULSION, SUSTAINED RELEASE	TOPICAL	0.1	%W/W
CHEMODERM 6401B	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	0.1	%
CHLOROCRESOL			0.075	%W/W
CHLOROCRESOL		AUGMENTED	0.1	%W/W
CHLOROCRESOL		TOPICAL	0.075	%W/W
CHLOROCRESOL			0.75	%W/W
CHLOROCRESOL	AUGMENTED	TOPICAL	0.1	%W/W
CHLOROCRESOL	TOPICAL	CREAM, AUGMENTED	0.1	%
CHLOROCRESOL	TOPICAL	EMULSION, CREAM	0.75	%
CHLOROXYLENOL			0.15	%W/W
CHLOROXYLENOL	TOPICAL	EMULSION, CREAM	0.15	%
CHOLESTEROL			1	%W/W
CHOLESTEROL			0.5	%
CHOLESTEROL	TOPICAL	EMULSION, CREAM	1	%
CHOLESTEROL	TOPICAL	LOTION	1.5	%
CHOLESTEROL	TOPICAL	OINTMENT	5	%
CHOLESTEROL	VAGINAL	EMULSION, CREAM	0.5	%
CHOLETH	VAGINAL	EMULSION, CREAM	1	%
CHOLETH-24			5	%W/W
CITRIC ACID	IONTOPHORESIS	SOLUTION	0.02	%
CITRIC ACID	IONTOPHORESIS	PATCH, CONTROLLED RELEASE	0.2	MG
CITRIC ACID	IONTOPHORESIS	DRUG DELIVERY SYSTEM	1.4	MG
CITRIC ACID	TOPICAL	OINTMENT	0.012	%
CITRIC ACID	TOPICAL	CREAM, AUGMENTED	0.05	%
CITRIC ACID	TOPICAL	GEL	0.05	%
CITRIC ACID	TOPICAL	PATCH, CONTROLLED RELEASE	0.2	MG
CITRIC ACID	TOPICAL	LOTION	0.85	%
CITRIC ACID	TOPICAL	EMULSION, CREAM	5	%
CITRIC ACID	TRANSDERMAL	DRUG DELIVERY SYSTEM	1.4	MG

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
CITRIC ACID	VAGINAL	SPONGE	7.5	MG
CITRIC ACID MONOHYDRATE			0.03	%W/W
CITRIC ACID MONOHYDRATE			0.05	%W/W
CITRIC ACID MONOHYDRATE			0.05	%W/W
CITRIC ACID MONOHYDRATE			0.055	%W/W
CITRIC ACID MONOHYDRATE		AUGMENTED	0.05	%W/W
CITRIC ACID MONOHYDRATE		EMULSION, SUSTAINED RELEASE	0.1	%W/W
CITRIC ACID MONOHYDRATE		TOPICAL	0.03	%W/W
CITRIC ACID MONOHYDRATE		TOPICAL	0.05	%W/W
CITRIC ACID MONOHYDRATE		TOPICAL	0.05	%W/W
CITRIC ACID MONOHYDRATE		TOPICAL	0.055	%W/W
CITRIC ACID MONOHYDRATE			0.11	%W/W
CITRIC ACID MONOHYDRATE			0.11	%W/W
CITRIC ACID MONOHYDRATE			0.44	%W/W
CITRIC ACID MONOHYDRATE			0.18	%W/W
CITRIC ACID MONOHYDRATE			0.05	%W/W
CITRIC ACID MONOHYDRATE			0.49	%
CITRIC ACID MONOHYDRATE	AUGMENTED	TOPICAL	0.05	%W/W
CITRIC ACID MONOHYDRATE	BUCCAL	FILM	0.69	MG
CITRIC ACID MONOHYDRATE	EMULSION, SUSTAINED RELEASE	TOPICAL	0.1	%W/W
CITRIC ACID MONOHYDRATE	TOPICAL	EMULSION, CREAM	0.05	%
CITRIC ACID MONOHYDRATE	TOPICAL	GEL	0.1	%
CITRIC ACID MONOHYDRATE	TOPICAL	GEL	0.56	%W/W
CITRIC ACID MONOHYDRATE	VAGINAL	EMULSION, CREAM	0.494	%
CITRIC ACID, HYDROUS	TOPICAL	EMULSION, LOTION	0.05	%
CITRIC ACID, HYDROUS	TOPICAL	EMULSION, CREAM	0.1	%
COCAMIDE DIETHANOLAMINE	TOPICAL	EMULSION, CREAM	4	%
COCAMIDE DIETHANOLAMINE	TOPICAL	SPONGE	20.2	MG
COCO DIETHANOLAMIDE			4	%W/W
COCO-CAPRYLATE/CAPRATE	TOPICAL	GEL	2.5	%W/W
COCOA BUTTER	RECTAL	SUPPOSITORY	2070.6	MG
COCOA BUTTER	TOPICAL	LOTION	0.1	%
COCONUT OIL	TOPICAL	EMULSION, CREAM	6	%
COCONUT OIL	TOPICAL	OINTMENT	25	%
COCONUT OIL, FRACTIONED	TOPICAL	OINTMENT	0.02	%
COCONUT OIL/PALM KERNEL OIL GLYCERIDES, HYDROGENATED	RECTAL	SUPPOSITORY	1734.9	MG
COCONUT OIL/PALM KERNEL OIL GLYCERIDES, HYDROGENATED	VAGINAL	SUPPOSITORY	2375	MG
COLLAGEN	TOPICAL	GEL	0.024	%
COLLAGEN	TOPICAL	GEL	0.024	%W/W
CROSPOVIDONE	TOPICAL	LOTION	0.185	%
CROSPOVIDONE	VAGINAL	SUPPOSITORY	116.1	MG
CROSPOVIDONE, UNSPECIFIED			1	%W/W
CROSPOVIDONE, UNSPECIFIED			3.63	MG
CROSPOVIDONE, UNSPECIFIED			60	MG
CROSPOVIDONE, UNSPECIFIED			47.5	MG
CYCLOMETHICONE			5	%W/W
CYCLOMETHICONE		AUGMENTED	7.6	%W/W
CYCLOMETHICONE		TOPICAL	5	%W/W
CYCLOMETHICONE			5.26	%W/W
CYCLOMETHICONE			13	%W/W
CYCLOMETHICONE	AUGMENTED	TOPICAL	7.6	%W/W
CYCLOMETHICONE	TOPICAL	LOTION	4	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
CYCLOMETHICONE	TOPICAL	CREAM, AUGMENTED	7.6	%
CYCLOMETHICONE	TOPICAL	EMULSION, CREAM	13	%
CYCLOMETHICONE 5		AUGMENTED	13	%W/W
CYCLOMETHICONE 5	AUGMENTED	TOPICAL	13	%W/W
CYCLOMETHICONE/DIMETHICONE COPOLYOL	TOPICAL	GEL	2.3	%
CYCLOMETHICONE/DIMETHICONE COPOLYOL	TOPICAL	GEL	2.3	%W/W
D&C YELLOW NO. 10			0.003	%
D&C YELLOW NO. 10	BUCCAL	GUM, CHEWING	1.01	MG
D&C YELLOW NO. 10	ORAL	GUM, CHEWING	0.1	MG
D&C YELLOW NO. 10	RECTAL	SUPPOSITORY	0.11	MG
D&C YELLOW NO. 10	TOPICAL	GEL	0.001	%
D&C YELLOW NO. 10	TOPICAL	GEL	0.001	%W/W
D&C YELLOW NO. 10 ALUMINUM LAKE	BUCCAL	GUM	2.4	MG
D&C YELLOW NO. 10 ALUMINUM LAKE	BUCCAL	GUM, CHEWING	1.9	MG
DAUBERT 1-5 PESTR (MATTE) 164Z			507.5	MG
DAUBERT 1–5 PESTR (MATTE) 164Z	TRANSDERMAL	FILM, CONTROLLED RELEASE	507.5	MG
DEHYDAG WAX SX			8.5	%W/W
DEHYDROACETIC ACID	TOPICAL	LOTION	11.6	%
DEHYMULS E	TOPICAL	OINTMENT	7.5	%
DENATONIUM BENZOATE	TOPICAL	GEL	0.0006	%
DENATONIUM BENZOATE	TOPICAL	GEL	0.001	%W/W
DEXTRIN			0.03	%W/W
DEXTRIN		TOPICAL	0.03	%W/W
DEXTRIN			0.029	%W/W
DEXTRIN	TOPICAL	EMULSION, CREAM	0.029	%
DIAZOLIDINYL UREA		EMULSION, SUSTAINED RELEASE	0.2	%W/W
DIAZOLIDINYL UREA			0.2	%W/W
DIAZOLIDINYL UREA	EMULSION, SUSTAINED RELEASE	TOPICAL	0.2	%W/W
DIAZOLIDINYLUREA	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	0.2	%
DIAZOLIDINYLUREA	TOPICAL	EMULSION, CREAM	0.3	%
DICHLOROBENZYL ALCOHOL		EMULSION, SUSTAINED RELEASE	0.1	%W/W
DICHLOROBENZYL ALCOHOL	EMULSION, SUSTAINED RELEASE	TOPICAL	0.1	%W/W
DICHLOROBENZYL ALCOHOL	TOPICAL	EMULSION, CREAM	0.1	%
DICHLORODIFLUOROMETHANE			8	%W/W
DICHLORODIFLUOROMETHANE			20	%
DICHLOROTETRAFLUOROETHANE			80	%
DIETHANOLAMINE			0.3	%W/W
DIETHANOLAMINE	TOPICAL	EMULSION, CREAM	0.3	%
DIETHYLAMINOETHYL STEARAMIDE PHOSPHATE			0.54	%
DIETHYLENE GLYCOL MONOETHYL ETHER			15	%W/W
DIETHYLENE GLYCOL MONOETHYL ETHER		EMULSION, SUSTAINED RELEASE	15	%W/W
DIETHYLENE GLYCOL MONOETHYL ETHER		TOPICAL	15	%W/W
DIETHYLENE GLYCOL MONOETHYL ETHER			15	%W/W
DIETHYLENE GLYCOL MONOETHYL ETHER	EMULSION, SUSTAINED RELEASE	TOPICAL	15	%W/W
DIETHYLENE GLYCOL MONOETHYL ETHER	TOPICAL	GEL	25	%
DIETHYLENE GLYCOL MONOETHYL ETHER	TOPICAL	GEL	49.91	%W/W
DIETHYLENE GLYCOL MONOETHYL ETHER	TOPICAL	GEL	250	MG
DIETHYLENE GLYCOL MONOETHYL ETHER	TRANSDERMAL	GEL	5	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
DIETHYLENE GLYCOL MONOETHYL ETHER	TRANSDERMAL	GEL	5	%
DIHYDROXYALUMINUM AMINOACETATE			32.2	MG
DIISOPROPANOLAMINE			0.12	%W/W
DIISOPROPANOLAMINE		EMULSION, SUSTAINED RELEASE	0.12	%W/W
DIISOPROPANOLAMINE		TOPICAL	0.12	%W/W
DIISOPROPANOLAMINE			0.12	%W/W
DIISOPROPANOLAMINE	EMULSION, SUSTAINED RELEASE	TOPICAL	0.12	%W/W
DIISOPROPANOLAMINE	TOPICAL	EMULSION, CREAM	0.12	%
DIISOPROPANOLAMINE	TOPICAL	GEL	0.2	%
DIISOPROPANOLAMINE	TOPICAL	GEL	1.5	%W/W
DIISOPROPYL ADIPATE			5	%W/W
DIISOPROPYL ADIPATE	TOPICAL	LOTION	20	%
DIISOPROPYL ADIPATE	TRANSDERMAL	GEL	1.5	%
DIMETHICONE			0.95	%W/W
DIMETHICONE			5	%W/W
DIMETHICONE			564	MG
DIMETHICONE 100	TOPICAL	GEL	0.1	%W/W
DIMETHICONE 20		AUGMENTED	0.5	%W/W
DIMETHICONE 20	AUGMENTED	TOPICAL	0.5	%W/W
DIMETHICONE 350			0.8	%W/W
DIMETHICONE 350		TOPICAL	0.8	%W/W
DIMETHICONE 350			1	%W/W
DIMETHICONE 350	TOPICAL	EMULSION, CREAM	1	%
DIMETHICONE 360	TOPICAL	EMULSION, CREAM	5	%
DIMETHICONE 360	TRANSDERMAL	FILM, CONTROLLED RELEASE	564	MG
DIMETHICONE COPOLYOL	TOPICAL	GEL	1	%
DIMETHICONOL/TRIMETHYLSILOXYSILICATE CROSSPOLYMER (40/60 W/W; 1000000 PA.S)			70.6	MG
DIMETHICONOL/TRIMETHYLSILOXYSILICATE CROSSPOLYMER (40/60 W/W; 1000000 PA.S)			57.14	MG
DIMETHICONOL/TRIMETHYLSILOXYSILICATE CROSSPOLYMER (40/60 W/W; 1000000 PA.S)			164	MG/PATCH
DIMETHICONOL/TRIMETHYLSILOXYSILICATE CROSSPOLYMER (45/55 W/W; 100000 PA.S)			114.7	MG
DIMETHYL ISOSORBIDE			5.44	%W/W
DIMETHYL ISOSORBIDE			15	%W/W
DIMETHYL ISOSORBIDE	TOPICAL	EMULSION, CREAM	15	%
DIMETHYL SULFOXIDE	TOPICAL	DRESSING	16.5	MG
DIOCTYLPHTHALATE	TRANSDERMAL	FILM, CONTROLLED RELEASE	600.12	MG
DIPROPYLENE GLYCOL			5.37	MG
DIPROPYLENE GLYCOL			12	MG
DIPROPYLENE GLYCOL			1.58	MG
DIPROPYLENE GLYCOL	TRANSDERMAL	PATCH, CONTROLLED RELEASE	0.218	MG
DIPROPYLENE GLYCOL	TRANSDERMAL	FILM, CONTROLLED RELEASE	12	MG
DISODIUM LAURETH SULFOSUCCINATE	TOPICAL	GEL	0.04	%
DISODIUM LAURETH SULFOSUCCINATE	TOPICAL	GEL	0.04	%W/W
DISODIUM LAURYL SULFOSUCCINATE	TOPICAL	GEL	0.04	%W/W
DL-GLUTAMIC ACID	VAGINAL	EMULSION, CREAM	0.1	%
DL-LIMONENE	TOPICAL	LOTION	10	%
DL-TARTARIC ACID	RECTAL	SUPPOSITORY	21.5	MG

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
DL-TARTARIC ACID	VAGINAL	SUPPOSITORY	32.3	MG
DOCUSATE SODIUM	TOPICAL	GEL	3	%
DOCUSATE SODIUM	TOPICAL	GEL	0.2	%W/W
DURO-TAK 387-2516			37.4	MG
DURO-TAK 80-1196			172	MG
DURO-TAK 80–1196	TRANSDERMAL	FILM, CONTROLLED RELEASE	172	MG
DURO-TAK 87-2194			208.28	MG
DURO-TAK 87-2287			537.7	MG
DURO-TAK 87-2287			121.1	MG
DURO-TAK 87–2194	TRANSDERMAL	FILM, CONTROLLED RELEASE	208.28	MG
DURO-TAK 87–2287	PERCUTANEOUS	PATCH, CONTROLLED RELEASE	165	CM
DURO-TAK 87–2287	TRANSDERMAL	FILM, CONTROLLED RELEASE	121.1	MG
DURO-TAK 87–2296	TRANSDERMAL	PATCH, CONTROLLED RELEASE	43	MG
DURO-TAK 87–2888	TRANSDERMAL	PATCH	175.9	MG
DYE BROWN LAKE BLEND	BUCCAL	GUM, CHEWING	0.17	MG
DYE FDC BROWN R LB-56069	BUCCAL	GUM, CHEWING	0.14	MG
EDAMINE	TOPICAL	EMULSION, CREAM	0.18	%
EDETATE CALCIUM DISODIUM	URETERAL	SOLUTION	0.01	%
EDETATE CALCIUM DISODIUM	URETHRAL	SOLUTION	0.01	%
EDETATE DISODIUM			0.05	%W/W
EDETATE DISODIUM		AUGMENTED	0.1	%W/W
EDETATE DISODIUM		EMULSION, SUSTAINED RELEASE	0.05	%W/W
EDETATE DISODIUM		TOPICAL	0.05	%W/W
EDETATE DISODIUM			0.11	%W/W
EDETATE DISODIUM			0.05	%W/W
EDETATE DISODIUM			0.1	%W/W
EDETATE DISODIUM			0.05	%
EDETATE DISODIUM			14	MG
EDETATE DISODIUM	AUGMENTED	TOPICAL	0.1	%W/W
EDETATE DISODIUM	EMULSION, SUSTAINED RELEASE	TOPICAL	0.05	%W/W
EDETATE DISODIUM	IONTOPHORESIS	PATCH, CONTROLLED RELEASE	0.1	MG
EDETATE DISODIUM	OPHTHALMIC	GEL	0.055	%
EDETATE DISODIUM	OPHTHALMIC	GEL	0.055	%
EDETATE DISODIUM	TOPICAL	OINTMENT	0.0065	%
EDETATE DISODIUM	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	0.05	%
EDETATE DISODIUM	TOPICAL	CREAM, AUGMENTED	0.1	%
EDETATE DISODIUM	TOPICAL	LOTION	0.1	%
EDETATE DISODIUM	TOPICAL	PATCH, CONTROLLED RELEASE	0.1	MG
EDETATE DISODIUM	TOPICAL	GEL	0.17	%
EDETATE DISODIUM	TOPICAL	EMULSION, CREAM	1	%
EDETATE DISODIUM	TOPICAL	GEL	0.17	%W/W
EDETATE DISODIUM	TRANSDERMAL	GEL	0.06	%
EDETATE DISODIUM	TRANSDERMAL	GEL	0.06	%
EDETATE DISODIUM	VAGINAL	EMULSION, CREAM	0.05	%
EDETATE DISODIUM	VAGINAL	GEL	0.05	%
EDETATE DISODIUM	VAGINAL	CREAM	0.05	%W/W

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
EDETATE DISODIUM	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	0.05	%
EDETATE DISODIUM	VAGINAL	GEL	0.05	%
EDETATE DISODIUM ANHYDROUS			0.02	%W/W
EDETATE DISODIUM ANHYDROUS		TOPICAL	0.02	%W/W
EDETATE DISODIUM ANHYDROUS	VAGINAL	CREAM	0.05	%W/W
EDETATE SODIUM	TOPICAL	LOTION	0.05	%
EDETIC ACID	RECTAL	SUPPOSITORY	1.7	MG
EDETIC ACID	TOPICAL	LOTION	0.11	%
EMULSIFYING WAX			12	%W/W
EMULSIFYING WAX			12	%W/W
EMULSIFYING WAX		TOPICAL	12	%W/W
EMULSIFYING WAX		TOPICAL	12	%W/W
EMULSIFYING WAX			24.8	%W/W
ENTSUFON SODIUM			40.3	%W/W
ERYTHRITOL			10.35	MG
ESSENCE BOUQUET 9200	TOPICAL	LOTION	0.2	%
ETHYL ACETATE			36138	MG
ETHYL ACETATE	TRANSDERMAL	FILM, CONTROLLED RELEASE	36138	MG
ETHYL OLEATE			8.64	MG
ETHYL OLEATE	TRANSDERMAL	FILM, CONTROLLED RELEASE	8.64	MG
ETHYLCELLULOSE	TOPICAL	PATCH	2.53	MG
ETHYLCELLULOSE	TRANSDERMAL	FILM, CONTROLLED RELEASE	80.4	MG
ETHYLCELLULOSE, UNSPECIFIED			80.4	MG
ETHYLENE VINYL ACETATE COPOLYMER	TRANSDERMAL	FILM, CONTROLLED RELEASE	735	MG
ETHYLENE VINYLACETATE COPOLYMER, 28% VINYLACETATE	VAGINAL	SPONGE	1677	MG
ETHYLENE VINYLACETATE COPOLYMER, 9% VINYLACETATE	VAGINAL	SPONGE	197	MG
ETHYLENE-PROPYLENE COPOLYMER			31.67	MG
ETHYLENE-PROPYLENE COPOLYMER	TRANSDERMAL	FILM, CONTROLLED RELEASE	31.67	MG
ETHYLENE-VINYL ACETATE COPOLYMERS			11.65	MG
ETHYLENE-VINYL ACETATE COPOLYMERS			735	MG
ETHYLENEDIAMINE			0.18	%W/W
ETHYLENEDIAMINE DIHYDROCHLORIDE			0.25	%W/W
ETHYLENEDIAMINE DIHYDROCHLORIDE	TOPICAL	EMULSION, CREAM	0.25	%
ETHYLHEXYL HYDROXYSTEARATE		EMULSION, SUSTAINED RELEASE	12	%W/W
ETHYLHEXYL HYDROXYSTEARATE			12	%W/W
ETHYLHEXYL HYDROXYSTEARATE	EMULSION, SUSTAINED RELEASE	TOPICAL	12	%W/W
FAT, HARD	RECTAL	SUPPOSITORY	1920	MG
FATTY ACID PENTAERYTHRIOL ESTER	TOPICAL	OINTMENT	1	%
FD&C BLUE NO. 1			0.036	MG
FD&C GREEN NO. 3			0.003	%
FD&C GREEN NO. 3	RECTAL	SUPPOSITORY	0.015	MG
FD&C RED NO. 4	TOPICAL	LOTION	0.0007	%
FD&C RED NO. 40	BUCCAL	GUM, CHEWING	2	MG
FD&C RED NO. 40	TOPICAL	SPONGE	50	MG
FD&C YELLOW NO. 10	TOPICAL	LOTION	0.0008	%
FD&C YELLOW NO. 5			0.004	%W/W

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
FD&C YELLOW NO. 5			0.004	%
FD&C YELLOW NO. 5	TOPICAL	EMULSION, CREAM	0.004	%
FD&C YELLOW NO. 5	VAGINAL	EMULSION, CREAM	0.004	%
FD&C YELLOW NO. 6			0.02	MG
FD&C YELLOW NO. 6	TOPICAL	GEL	0.0013	%
FD&C YELLOW NO. 6	TOPICAL	LOTION	0.0016	%
FD&C YELLOW NO. 6	TOPICAL	GEL	0.001	%W/W
FERRIC OXIDE	TOPICAL	LOTION	0.15	%
FERRIC OXIDE RED	BUCCAL	FILM	0.03	MG
FERRIC OXIDE YELLOW	BUCCAL	FILM	0.27	MG
FLAVOR CINNAMON	BUCCAL	GUM, CHEWING	26	MG
FLAVOR CINNAMON SD 516	BUCCAL	GUM, CHEWING	9.6	MG
FLAVOR CINNAMON VEKO 3726	BUCCAL	GUM, CHEWING	27	MG
FLAVOR CITRUS/FRUIT FREEZE 1100609500	BUCCAL	GUM, CHEWING	2.25	MG
FLAVOR DF-1530			0.77	%
FLAVOR FRUIT 84.6422	BUCCAL	GUM, CHEWING	11	MG
FLAVOR HAVERSTROO ZD 49284	BUCCAL	GUM, CHEWING	11	MG
FLAVOR LEMON LIME			6	MG
FLAVOR LEMON LIME SD 935			4.5	MG
FLAVOR MENTHOL VERALOCK	BUCCAL	GUM, CHEWING	3.84	MG
FLAVOR MINT 287	BUCCAL	GUM	27.03	MG
FLAVOR MINT 287	BUCCAL	GUM, CHEWING	28	MG
FORMALDEHYDE			0.27	%W/W
FORMALDEHYDE	TOPICAL	EMULSION, CREAM	0.27	%
FORMALDEHYDE SOLUTION			0.27	%W/W
FORMALDEHYDE SOLUTION	TOPICAL	EMULSION, CREAM	0.27	%
FRAGRANCE 6.007	TOPICAL	LOTION	0.2	%
FRAGRANCE 9128-Y			0.07	%W/W
FRAGRANCE 9128-Y	TOPICAL	EMULSION, CREAM	0.07	%
FRAGRANCE 93498G	TOPICAL	LOTION	0.0069	%
FRAGRANCE CHEMODERM 6401-B		AUGMENTED	0.25	%W/W
FRAGRANCE CHEMODERM 6401-B	AUGMENTED	TOPICAL	0.25	%W/W
FRAGRANCE CHEMODERM 6401-B	TOPICAL	CREAM, AUGMENTED	0.25	%
FRAGRANCE CHEMODERM 6411	TOPICAL	EMULSION, CREAM	0.1	%
FRAGRANCE CS-28197	TOPICAL	EMULSION, CREAM	0.1	%
FRAGRANCE GIVAUDAN ESS 9090/1 C	TOPICAL	SPONGE	1.01	MG
FRAGRANCE NJ-1085	TOPICAL	LOTION	0.1	%
FRAGRANCE P O FL-147			0.27	%W/W
FRAGRANCE PERA DERM D	TOPICAL	LOTION	0.12	%
FRAGRANCE RBD-9819			0.1	%W/W
FRAGRANCE RBD-9819			0.06	%W/W
FRAGRANCE RBD-9819	TOPICAL	LOTION	0.084	%
FRAGRANCE RBD-9819	TOPICAL	EMULSION, CREAM	0.125	%
FRAGRANCE UNGERER N5195	TOPICAL	LOTION	8.1	%
GELATIN, UNSPECIFIED	BUCCAL	GUM, CHEWING	4.27	MG
GLUCONOLACTONE	TOPICAL	SPONGE	2500	MG
GLUTAMIC ACID, DL-			0.1	%
GLYCERIN			1.5	%W/W
GLYCERIN			4	%W/W
GLYCERIN			5	%W/W
GLYCERIN			20	%W/W
GLYCERIN		AUGMENTED	4	%W/W
GLYCERIN		EMULSION, SUSTAINED RELEASE	3	%W/W
GLYCERIN		TOPICAL	1.5	%W/W
GLYCERIN		TOPICAL	4	%W/W

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
GLYCERIN		TOPICAL	5	%W/W
GLYCERIN		TOPICAL	20	%W/W
GLYCERIN			2.11	%W/W
GLYCERIN			20	%W/W
GLYCERIN			6	%W/W
GLYCERIN			5	%W/W
GLYCERIN			2520	MG
GLYCERIN			306.2	MG
GLYCERIN	AUGMENTED	TOPICAL	4	%W/W
GLYCERIN	BUCCAL	GUM, CHEWING	28.8	MG
GLYCERIN	EMULSION, SUSTAINED RELEASE	TOPICAL	3	%W/W
GLYCERIN	IONTOPHORESIS	PATCH, CONTROLLED RELEASE	168.1	MG
GLYCERIN	OPHTHALMIC	GEL	0.88	%
GLYCERIN	OPHTHALMIC	GEL	0.88	%
GLYCERIN	RECTAL	SUPPOSITORY	128	MG
GLYCERIN	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	2	%
GLYCERIN	TOPICAL	CREAM, AUGMENTED	4	%
GLYCERIN	TOPICAL	EMULSION, CREAM	20	%
GLYCERIN	TOPICAL	GEL	20	%
GLYCERIN	TOPICAL	LOTION	50	%
GLYCERIN	TOPICAL	PATCH, CONTROLLED RELEASE	168.1	MG
GLYCERIN	TOPICAL	GEL	20	%W/W
GLYCERIN	TRANSDERMAL	GEL	25	%
GLYCERIN	TRANSDERMAL	FILM, CONTROLLED RELEASE	306.2	MG
GLYCERIN	TRANSDERMAL	GEL	1.3	%W/W
GLYCERIN	TRANSDERMAL	GEL	5	%W/W
GLYCERIN	VAGINAL	EMULSION, CREAM	5	%
GLYCERIN	VAGINAL	GEL	14.51	%
GLYCERIN	VAGINAL	SUPPOSITORY	227.9	MG
GLYCERIN	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	17	%W/W
GLYCERIN	VAGINAL	GEL	14.51	%
GLYCERYL CITRATE	TOPICAL	EMULSION, CREAM	0.05	%
GLYCERYL ISOSTEARATE		EMULSION, SUSTAINED RELEASE	2.7	%W/W
GLYCERYL ISOSTEARATE			2	%W/W
GLYCERYL ISOSTEARATE			2.7	%
GLYCERYL ISOSTEARATE	EMULSION, SUSTAINED RELEASE	TOPICAL	2.7	%W/W
GLYCERYL ISOSTEARATE	TOPICAL	EMULSION, CREAM	2	%
GLYCERYL ISOSTEARATE	VAGINAL	EMULSION, CREAM	2.7	%
GLYCERYL ISOSTEARATE	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	2.7	%W/W
GLYCERYL LAURATE			0.83	MG
GLYCERYL LAURATE	TRANSDERMAL	FILM, CONTROLLED RELEASE	0.36	MG
GLYCERYL MONO AND DIPALMITOSTEARATE			7	%W/W
GLYCERYL MONO AND DIPALMITOSTEARATE			13.5	%W/W
GLYCERYL MONO AND DIPALMITOSTEARATE			9.5	%W/W
GLYCERYL MONO AND DIPALMITOSTEARATE		TOPICAL	7	%W/W
GLYCERYL MONO AND DIPALMITOSTEARATE		TOPICAL	13.5	%W/W

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
GLYCERYL MONO AND DIPALMITOSTEARATE		TOPICAL	9.5	%W/W
GLYCERYL MONO AND DIPALMITOSTEARATE	VAGINAL	CREAM	4	%W/W
GLYCERYL MONOCITRATE			0.05	%W/W
GLYCERYL MONOSTEARATE			7	%W/W
GLYCERYL MONOSTEARATE		EMULSION, SUSTAINED RELEASE	8.5	%W/W
GLYCERYL MONOSTEARATE		TOPICAL	7	%W/W
GLYCERYL MONOSTEARATE			20	%W/W
GLYCERYL MONOSTEARATE			17	%
GLYCERYL MONOSTEARATE	EMULSION, SUSTAINED RELEASE	TOPICAL	8.5	%W/W
GLYCERYL MONOSTEARATE	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	1	%W/W
GLYCERYL OLEATE		AUGMENTED	3.5	%W/W
GLYCERYL OLEATE			18.8	MG
GLYCERYL OLEATE	AUGMENTED	TOPICAL	3.5	%W/W
GLYCERYL OLEATE	TOPICAL	CREAM, AUGMENTED	3.5	%
GLYCERYL OLEATE	TRANSDERMAL	FILM, CONTROLLED RELEASE	18.8	MG
GLYCERYL OLEATE/PROPYLENE GLYCOL		AUGMENTED	3	%W/W
GLYCERYL OLEATE/PROPYLENE GLYCOL			3	%W/W
GLYCERYL OLEATE/PROPYLENE GLYCOL	AUGMENTED	TOPICAL	3	%W/W
GLYCERYL OLEATE/PROPYLENE GLYCOL	TOPICAL	CREAM, AUGMENTED	3	%
GLYCERYL OLEATE/PROPYLENE GLYCOL	TOPICAL	EMULSION, CREAM	3	%
GLYCERYL OLEATE/PROPYLENE GLYCOL	TOPICAL	OINTMENT	10	%
GLYCERYL PALMITATE	TOPICAL	EMULSION, CREAM	18	%
GLYCERYL STEARATE	RECTAL	SUPPOSITORY	32.3	MG
GLYCERYL STEARATE	TOPICAL	OINTMENT	5	%
GLYCERYL STEARATE	TOPICAL	LOTION	11.5	%
GLYCERYL STEARATE	TOPICAL	EMULSION, CREAM	20	%
GLYCERYL STEARATE	VAGINAL	EMULSION, CREAM	17	%
GLYCERYL STEARATE SE			4	%W/W
GLYCERYL STEARATE SE	TOPICAL	LOTION	0.5	%
GLYCERYL STEARATE SE	TOPICAL	EMULSION, CREAM	7	%
GLYCERYL STEARATE-LAURETH-23	TOPICAL	EMULSION, CREAM	0.7	%
GLYCERYL STEARATE/PEG STEARATE			6	%W/W
GLYCERYL STEARATE/PEG STEARATE		TOPICAL	6	%W/W
GLYCERYL STEARATE/PEG STEARATE	RECTAL	SUPPOSITORY	36.85	MG
GLYCERYL STEARATE/PEG-100 STEARATE			7.5	%W/W
GLYCERYL STEARATE/PEG-100 STEARATE		AUGMENTED	7.08	%W/W
GLYCERYL STEARATE/PEG-100 STEARATE		EMULSION, SUSTAINED RELEASE	5	%W/W
GLYCERYL STEARATE/PEG-100 STEARATE		TOPICAL	7.5	%W/W
GLYCERYL STEARATE/PEG-100 STEARATE			7.5	%W/W
GLYCERYL STEARATE/PEG-100 STEARATE	AUGMENTED	TOPICAL	7.08	%W/W
GLYCERYL STEARATE/PEG-100 STEARATE	EMULSION, SUSTAINED RELEASE	TOPICAL	5	%W/W
GLYCERYL STEARATE/PEG-100 STEARATE	TOPICAL	CREAM, AUGMENTED	7.08	%
GLYCERYL STEARATE/PEG-100 STEARATE	TOPICAL	LOTION	7.1	%
GLYCERYL STEARATE/PEG-100 STEARATE	TOPICAL	EMULSION, CREAM	7.5	%
GLYCERYL STEARATE/PEG-40 STEARATE	RECTAL	SUPPOSITORY	35	MG
GLYCOL STEARATE			1	%W/W
GLYCOL STEARATE		TOPICAL	1	%W/W
GLYCOL STEARATE			1	%W/W
GLYCOL STEARATE	TOPICAL	EMULSION, CREAM	1	%
GUM BASE, CHEWING	BUCCAL	GUM	691.2	MG

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
GUM BASE, CHEWING	BUCCAL	GUM, CHEWING	729.6	MG
HAIR CONDITIONER (18N195–1M)	TOPICAL	LOTION	78.8	%
HERBACOL	TOPICAL	SPONGE	964	MG
HEXYLENE GLYCOL			12	%W/W
HEXYLENE GLYCOL	TOPICAL	GEL	2	%
HEXYLENE GLYCOL	TOPICAL	EMULSION, CREAM	12	%
HEXYLENE GLYCOL	TOPICAL	OINTMENT	12	%
HEXYLENE GLYCOL	TOPICAL	GEL	2	%W/W
HIGH DENSITY POLYETHYLENE			54.5	%W/W
HIGH DENSITY POLYETHYLENE			85	MG
HIGH DENSITY POLYETHYLENE	TOPICAL	GEL	26	%W/W
HYALURONATE SODIUM	TOPICAL	GEL	2.5	%
HYALURONATE SODIUM	TOPICAL	GEL	2.5	%W/W
HYDROCHLORIC ACID			0.033	%W/W
HYDROCHLORIC ACID		TOPICAL	0.033	%W/W
HYDROCHLORIC ACID			0.01	%W/W
HYDROCHLORIC ACID	OPHTHALMIC	GEL		ADJPH
HYDROCHLORIC ACID	OPHTHALMIC	GEL		ADJPH
HYDROCHLORIC ACID	TOPICAL	EMULSION, CREAM	0.34	%
HYDROCHLORIC ACID	TOPICAL	GEL	0.5	%W/W
HYDROCHLORIC ACID	TOPICAL	GEL		ADJPH
HYDROCHLORIC ACID	TRANSDERMAL	GEL	0.024	%
HYDROGENATED PALM OIL	VAGINAL	GEL	1.13	%
HYDROGENATED PALM/PALM KERNEL OIL PEG-6 ESTERS			5	%W/W
HYDROGENATED PALM/PALM KERNEL OIL PEG-6 ESTERS	TOPICAL	EMULSION, CREAM	5	%
HYDROGENATED POLYBUTENE 635-690			142.99	MG
HYDROGENATED STARCH HYDROLYSATE			6.02	MG
HYDROQUINONE	VAGINAL	CREAM	0.02	%W/W
HYDROXYETHYL CELLULOSE			20	MG
HYDROXYETHYL CELLULOSE	BUCCAL	FILM	54.92	MG
HYDROXYETHYL CELLULOSE	BUCCAL	FILM	39.88	MG
HYDROXYETHYL CELLULOSE	TOPICAL	LOTION	0.8	%
HYDROXYETHYL CELLULOSE	TOPICAL	GEL	1.25	%
HYDROXYETHYL CELLULOSE	TOPICAL	SPONGE	9.09	MG
HYDROXYETHYL CELLULOSE	TOPICAL	GEL	1.75	%W/W
HYDROXYETHYL CELLULOSE	TRANSDERMAL	FILM, CONTROLLED RELEASE	20	MG
HYDROXYOCTACOSANYL HYDROXYSTEARATE		AUGMENTED	5	%W/W
HYDROXYOCTACOSANYL HYDROXYSTEARATE	AUGMENTED	TOPICAL	5	%W/W
HYDROXYOCTACOSANYL HYDROXYSTEARATE	TOPICAL	CREAM, AUGMENTED	5	%
HYDROXYPROPYL CELLULOSE	TOPICAL	LOTION	0.54	%
HYDROXYPROPYL CELLULOSE	TOPICAL	LOTION, AUGMENTED	0.54	%
HYDROXYPROPYL CELLULOSE	TOPICAL	PATCH	1.26	MG
HYDROXYPROPYL CELLULOSE	TOPICAL	GEL	4	%
HYDROXYPROPYL CELLULOSE	TRANSDERMAL	FILM, CONTROLLED RELEASE	19	MG
HYDROXYPROPYL CELLULOSE (110000 WAMW)	BUCCAL	FILM	18.92	MG
HYDROXYPROPYL CELLULOSE (1200000 WAMW)			19	MG
HYDROXYPROPYL CELLULOSE (1200000 WAMW)	BUCCAL	FILM	100.04	MG
HYDROXYPROPYL CELLULOSE (1200000 WAMW)	BUCCAL	FILM	72.91	MG
HYDROXYPROPYL CELLULOSE (1200000 WAMW)	BUCCAL	GUM	13.92	MG
HYDROXYPROPYL CELLULOSE (1200000 WAMW)	BUCCAL	GUM, CHEWING	27.92	MG
HYDROXYPROPYL CELLULOSE (1200000 WAMW)	TOPICAL	GEL	4	%W/W
HYDROXYPROPYL CELLULOSE (1200000 WAMW)	TRANSDERMAL	GEL	1.5	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	TOPICAL	GEL	2.5	%W/W
HYDROXYPROPYL CELLULOSE (1600000 WAMW)	TRANSDERMAL	GEL	2	%W/W
HYDROXYPROPYL METHYLCELLULOSE 2208	VAGINAL	EMULSION, CREAM	0.3	%
HYPROMELLOSE 2208 (4000 MPA.S)			0.3	%
HYPROMELLOSE 2208 (4000 MPA.S)	VAGINAL	CREAM	0.3	%W/W
HYPROMELLOSE 2906 (4000 MPA.S)	BUCCAL	GUM, CHEWING	14	MG
HYPROMELLOSE 2910 (15 MPA.S)			15.53	MG
HYPROMELLOSE 2910 (15 MPA.S)			2.11	MG
HYPROMELLOSE 2910 (15 MPA.S)			3.42	MG
HYPROMELLOSE 2910 (4000 MPA.S)	TOPICAL	JELLY	2.28	%W/W
HYPROMELLOSE 2910 (5 MPA.S)			2.34	MG/STRIP
HYPROMELLOSE, UNSPECIFIED			33.5	MG
HYPROMELLOSE, UNSPECIFIED			0.1	%W/W
HYPROMELLOSE, UNSPECIFIED			0.1	%W/W
HYPROMELLOSE, UNSPECIFIED	OPHTHALMIC	GEL	2.25	%
HYPROMELLOSE, UNSPECIFIED	OPHTHALMIC	GEL	2.25	%
HYPROMELLOSE, UNSPECIFIED	RECTAL	GEL	8.7	%
HYPROMELLOSE, UNSPECIFIED	TOPICAL	JELLY	2.5	%W/W
HYPROMELLOSE, UNSPECIFIED	URETHRAL	JELLY	2.3	%
HYPROMELLOSE, UNSPECIFIED	VAGINAL	GEL	3.5	%
IMIDUREA			0.3	%W/W
IMIDUREA		TOPICAL	0.3	%W/W
IMIDUREA			0.4	%W/W
IMIDUREA			0.14	%W/W
IMIDUREA	TOPICAL	EMULSION, LOTION	0.14	%
IMIDUREA	TOPICAL	LOTION	0.2	%
IMIDUREA	TOPICAL	EMULSION, CREAM	0.4	%
INK/POLYETHYLENE TEREPHTHALATE/ALUMINUM/ POLYETHYLENE/SODIUM POLYMETHACRYLATE/ ETHYLENE VINYLACETATE COPOLYMER			264	MG/PATCH
IRISH MOSS EXTRACT	TOPICAL	LOTION	0.3	%
ISOPROPYL ALCOHOL			6.5	%W/W
ISOPROPYL ALCOHOL		TOPICAL	6.5	%W/W
ISOPROPYL ALCOHOL	TOPICAL	GEL	20	%
ISOPROPYL ALCOHOL	TOPICAL	LOTION, AUGMENTED	30	%
ISOPROPYL ALCOHOL	TOPICAL	SPONGE	56.1	ML
ISOPROPYL ALCOHOL	TOPICAL	LOTION	99.57	%
ISOPROPYL ALCOHOL	TOPICAL	GEL	30	%W/W
ISOPROPYL ISOSTEARATE		EMULSION, SUSTAINED RELEASE	3	%W/W
ISOPROPYL ISOSTEARATE			3	%W/W
ISOPROPYL ISOSTEARATE	EMULSION, SUSTAINED RELEASE	TOPICAL	3	%W/W
ISOPROPYL ISOSTEARATE	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	3	%
ISOPROPYL ISOSTEARATE	TOPICAL	EMULSION, CREAM	3	%
ISOPROPYL MYRISTATE			10	%W/W
ISOPROPYL MYRISTATE		AUGMENTED	8	%W/W
ISOPROPYL MYRISTATE		EMULSION, SUSTAINED RELEASE	10	%W/W
ISOPROPYL MYRISTATE		TOPICAL	10	%W/W
ISOPROPYL MYRISTATE			7.9	%W/W
ISOPROPYL MYRISTATE			15	%W/W
ISOPROPYL MYRISTATE			1	%W/W
ISOPROPYL MYRISTATE			1	%
ISOPROPYL MYRISTATE			58.08	MG

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
ISOPROPYL MYRISTATE			20.4	MG
ISOPROPYL MYRISTATE	AUGMENTED	TOPICAL	8	%W/W
ISOPROPYL MYRISTATE	EMULSION, SUSTAINED RELEASE	TOPICAL	10	%W/W
ISOPROPYL MYRISTATE	TOPICAL	EMULSION, LOTION	1	%
ISOPROPYL MYRISTATE	TOPICAL	LOTION	2	%
ISOPROPYL MYRISTATE	TOPICAL	EMULSION, CREAM	10	%
ISOPROPYL MYRISTATE	TOPICAL	GEL	10	%
ISOPROPYL MYRISTATE	TOPICAL	OINTMENT	35	%
ISOPROPYL MYRISTATE	TOPICAL	GEL	10	%W/W
ISOPROPYL MYRISTATE	TRANSDERMAL	GEL	0.86	%
ISOPROPYL MYRISTATE	TRANSDERMAL	GEL	1	%W/W
ISOPROPYL MYRISTATE	TRANSDERMAL	GEL, METERED	1	%
ISOPROPYL MYRISTATE	VAGINAL	EMULSION, CREAM	5	%
ISOPROPYL MYRISTATE	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	1	%
ISOPROPYL PALMITATE			3.2	%W/W
ISOPROPYL PALMITATE			3.8	%W/W
ISOPROPYL PALMITATE			4.5	%W/W
ISOPROPYL PALMITATE		AUGMENTED	4	%W/W
ISOPROPYL PALMITATE		EMULSION, SUSTAINED RELEASE	1.8	%W/W
ISOPROPYL PALMITATE		TOPICAL	3.2	%W/W
ISOPROPYL PALMITATE		TOPICAL	3.8	%W/W
ISOPROPYL PALMITATE		TOPICAL	4.5	%W/W
ISOPROPYL PALMITATE			5	%W/W
ISOPROPYL PALMITATE			1.81	MG
ISOPROPYL PALMITATE			187.5	MG
ISOPROPYL PALMITATE	AUGMENTED	TOPICAL	4	%W/W
ISOPROPYL PALMITATE	EMULSION, SUSTAINED RELEASE	TOPICAL	1.8	%W/W
ISOPROPYL PALMITATE	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	1.8	%
ISOPROPYL PALMITATE	TOPICAL	LOTION	3.9	%
ISOPROPYL PALMITATE	TOPICAL	EMULSION, CREAM	5.5	%
ISOPROPYL PALMITATE	TOPICAL	GEL	0.001	%W/W
ISOPROPYL PALMITATE	TRANSDERMAL	FILM, CONTROLLED RELEASE	187.5	MG
ISOSTEARIC ACID		EMULSION, SUSTAINED RELEASE	25	%W/W
ISOSTEARIC ACID			25	%W/W
ISOSTEARIC ACID	EMULSION, SUSTAINED RELEASE	TOPICAL	25	%W/W
ISOSTEARIC ACID	TOPICAL	EMULSION, CREAM	2.5	%
ISOSTEARIC ACID	TRANSDERMAL	GEL	0.2	%
ISOSTEARYL ALCOHOL			3	%W/W
ISOSTEARYL ALCOHOL	TOPICAL	EMULSION, CREAM	3	%
ISOSTEARYL ALCOHOL	TOPICAL	LOTION	25	%
KATHON CG	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	0.05	%
KATHON CG	TOPICAL	EMULSION, CREAM	0.05	%
KATHON CG II	TOPICAL	EMULSION, CREAM	0.05	%
LACTIC ACID	TOPICAL	EMULSION, CREAM	1	%
LACTIC ACID	TOPICAL	LOTION	5.7	%
LACTIC ACID	TOPICAL	GEL	6.07	%
LACTIC ACID	VAGINAL	EMULSION, CREAM	0.81	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
LACTIC ACID, UNSPECIFIED FORM			0.005	%W/W
LACTIC ACID, UNSPECIFIED FORM			0.015	%W/W
LACTIC ACID, UNSPECIFIED FORM			0.05	%W/W
LACTIC ACID, UNSPECIFIED FORM				ADJ PH
LACTIC ACID, UNSPECIFIED FORM		TOPICAL	0.005	%W/W
LACTIC ACID, UNSPECIFIED FORM		TOPICAL	0.015	%W/W
LACTIC ACID, UNSPECIFIED FORM		TOPICAL	0.05	%W/W
LACTIC ACID, UNSPECIFIED FORM		TOPICAL		ADJ PH
LACTIC ACID, UNSPECIFIED FORM			1.05	%W/W
LACTIC ACID, UNSPECIFIED FORM			1	%W/W
LACTIC ACID, UNSPECIFIED FORM			0.81	%
LACTIC ACID, UNSPECIFIED FORM	TOPICAL	GEL	6.07	%W/W
LACTOSE	TRANSDERMAL	OINTMENT	18.9	%
LACTOSE	TRANSDERMAL	FILM, CONTROLLED RELEASE	675	MG
LACTOSE	VAGINAL	EMULSION, CREAM	3	%
LACTOSE, UNSPECIFIED FORM			3	%
LACTOSE, UNSPECIFIED FORM			675	MG
LANOLIN			2	%W/W
LANOLIN			2	%
LANOLIN	TOPICAL	EMULSION, CREAM	2	%
LANOLIN	TOPICAL	OINTMENT	2	%
LANOLIN	TOPICAL	LOTION	2.5	%
LANOLIN	VAGINAL	EMULSION, CREAM	2	%
LANOLIN ALCOHOL—MINERAL OIL			5	%W/W
LANOLIN ALCOHOL—MINERAL OIL	TOPICAL	EMULSION, CREAM	5	%
LANOLIN ALCOHOL—MINERAL OIL	TOPICAL	LOTION	11	%
LANOLIN ALCOHOLS			3.48	%W/W
LANOLIN ALCOHOLS		AUGMENTED	8	%W/W
LANOLIN ALCOHOLS		EMULSION, SUSTAINED RELEASE	3	%W/W
LANOLIN ALCOHOLS		TOPICAL	3.48	%W/W
LANOLIN ALCOHOLS			6	%W/W
LANOLIN ALCOHOLS	AUGMENTED	TOPICAL	8	%W/W
LANOLIN ALCOHOLS	EMULSION, SUSTAINED RELEASE	TOPICAL	3	%W/W
LANOLIN ALCOHOLS	TOPICAL	OINTMENT	3.01	%
LANOLIN ALCOHOLS	TOPICAL	EMULSION, CREAM	6	%
LANOLIN OIL			1	%W/W
LANOLIN OIL			2	%W/W
LANOLIN OIL		TOPICAL	1	%W/W
LANOLIN OIL		TOPICAL	2	%W/W
LANOLIN, ANHYDROUS	TOPICAL	EMULSION, CREAM	2	%
LANOLIN, ANHYDROUS	TRANSDERMAL	OINTMENT	35	%
LANOLIN, ANHYDROUS	VAGINAL	EMULSION, CREAM	0.2	%
LANOLIN, HYDROGENATED	TOPICAL	OINTMENT	10	%
LAURETH-23			0.45	%W/W
LAURETH-23			1.08	%W/W
LAURETH-4			1.1	%W/W
LAURETH-4	TOPICAL	EMULSION, CREAM	1.1	%
LAURETH-4	TOPICAL	LOTION	3	%
LAURETH-4	TOPICAL	GEL	3	%W/W
LAURIC DIETHANOLAMIDE			15	%W/W
LAURIC DIETHANOLAMIDE	TOPICAL	LOTION	1.7	%
LAURIC MYRISTIC DIETHANOLAMIDE	TOPICAL	LOTION	0.54	%
LAURYL LACTATE			12	MG

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
LAVENDER OIL	TOPICAL	GEL	0.1	%W/W
LECITHIN			1	%
LECITHIN			9.86	MG
LECITHIN	RECTAL	SUPPOSITORY	6.5	MG
LECITHIN	TOPICAL	GEL	1	%
LECITHIN	TOPICAL	GEL	1	%W/W
LECITHIN	TRANSDERMAL	FILM, CONTROLLED RELEASE	9.86	MG
LECITHIN	VAGINAL	EMULSION, CREAM	1	%
LECITHIN UNBLEACHED			0.81	%
LECITHIN, SOYBEAN			1	%
LECITHIN, SOYBEAN	VAGINAL	EMULSION, CREAM	0.33	%
LEMON OIL	TOPICAL	GEL	1	%
LEMON OIL	TOPICAL	GEL	0.05	%W/W
LEVOMENTHOL	BUCCAL	GUM	9.2	MG
LEVOMENTHOL	BUCCAL	GUM, CHEWING	4.4	MG
LIGHT MINERAL OIL			1	%W/W
LIGHT MINERAL OIL		AUGMENTED	25	%W/W
LIGHT MINERAL OIL		TOPICAL	1	%W/W
LIGHT MINERAL OIL			5	%W/W
LIGHT MINERAL OIL			6	%W/W
LIGHT MINERAL OIL			20	%W/W
LIGHT MINERAL OIL			18	%W/W
LIGHT MINERAL OIL			162	MG
LIGHT MINERAL OIL			26.4	MG
LIGHT MINERAL OIL	AUGMENTED	TOPICAL	25	%W/W
LIGHT MINERAL OIL	TOPICAL	LOTION	16	%
LIGHT MINERAL OIL	TOPICAL	EMULSION, CREAM	20	%
LIGHT MINERAL OIL	TOPICAL	OINTMENT	23	%
LIGHT MINERAL OIL	TOPICAL	CREAM, AUGMENTED	25	%
LIGHT MINERAL OIL	TRANSDERMAL	FILM, CONTROLLED RELEASE	162	MG
LIGHT MINERAL OIL	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	7	%
LIMONENE, (+)-	TOPICAL	GEL	0.5	%W/W
LIPOCOL SC-15			1	%W/W
LIPOCOL SC-15	TOPICAL	EMULSION, CREAM	1	%
MAGNESIUM ALUMINUM SILICATE		AUGMENTED	3	%W/W
MAGNESIUM ALUMINUM SILICATE			1.5	%W/W
MAGNESIUM ALUMINUM SILICATE	AUGMENTED	TOPICAL	3	%W/W
MAGNESIUM ALUMINUM SILICATE	TOPICAL	EMULSION, CREAM	1.5	%
MAGNESIUM ALUMINUM SILICATE	TOPICAL	LOTION	1.5	%
MAGNESIUM ALUMINUM SILICATE	VAGINAL	OINTMENT	5	%
MAGNESIUM ALUMINUM SILICATE HYDRATE	TOPICAL	EMULSION, CREAM	1.5	%
MAGNESIUM ALUMINUM SILICATE HYDRATE	TOPICAL	CREAM, AUGMENTED	3	%
MAGNESIUM ALUMINUM SILICATE HYDRATE	VAGINAL	OINTMENT	5.39	%
MAGNESIUM OXIDE	BUCCAL	GUM	7.2	MG
MAGNESIUM OXIDE	BUCCAL	GUM, CHEWING	7.2	MG
MAGNESIUM STEARATE			0.001	%W/W
MAGNESIUM STEARATE	TOPICAL	EMULSION, CREAM	0.0008	%
MAGNESIUM STEARATE	VAGINAL	SPONGE	0.85	MG
MALTITOL			7.33	MG
MALTITOL	BUCCAL	GUM, CHEWING	209.2	MG
MALTODEXTRIN			3.2	MG
MANNITOL	BUCCAL	GUM, CHEWING	37.11	MG
MANNITOL	OPHTHALMIC	GEL	5	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
MANNITOL	OPHTHALMIC	GEL	5	%
MAPROFIX	TOPICAL	EMULSION, CREAM	2	%
MEDICAL ADHESIVE MODIFIED S-15	TRANSDERMAL	FILM, CONTROLLED RELEASE	164	MG
MEDICAL ANTIFORM A-F EMULSION			0.1	%W/W
MEDICAL ANTIFORM A-F EMULSION	TOPICAL	EMULSION, CREAM	0.1	%
MEDIUM-CHAIN TRIGLYCERIDES			2.5	%W/W
MEDIUM-CHAIN TRIGLYCERIDES		AUGMENTED	8	%W/W
MEDIUM-CHAIN TRIGLYCERIDES		EMULSION, SUSTAINED RELEASE	1.37	%W/V
MEDIUM-CHAIN TRIGLYCERIDES		EMULSION, SUSTAINED RELEASE	10	%W/W
MEDIUM-CHAIN TRIGLYCERIDES		TOPICAL	2.5	%W/W
MEDIUM-CHAIN TRIGLYCERIDES			10.87	%W/W
MEDIUM-CHAIN TRIGLYCERIDES			10.8	%W/W
MEDIUM-CHAIN TRIGLYCERIDES	AUGMENTED	TOPICAL	8	%W/W
MEDIUM-CHAIN TRIGLYCERIDES	EMULSION, SUSTAINED RELEASE	TOPICAL	1.37	%W/V
MEDIUM-CHAIN TRIGLYCERIDES	EMULSION, SUSTAINED RELEASE	TOPICAL	10	%W/W
MEDIUM-CHAIN TRIGLYCERIDES	TOPICAL	GEL	10	%W/W
MEGLUMINE	URETERAL	SOLUTION	7.238	%
MENTHOL	TOPICAL	LOTION	0.05	%
MENTHOL, UNSPECIFIED FORM	BUCCAL	GUM, CHEWING	21	MG
METHOXY PEG-16		EMULSION, SUSTAINED RELEASE	18	%W/W
METHOXY PEG-16	EMULSION, SUSTAINED RELEASE	TOPICAL	18	%W/W
METHOXY PEG-22/DODECYL GLYCOL COPOLYMER		AUGMENTED	5	%W/W
METHOXY PEG-22/DODECYL GLYCOL COPOLYMER	AUGMENTED	TOPICAL	5	%W/W
METHOXYPOLYOXYETHYLENE GLYCOL 350	TOPICAL	GEL	20	%
METHYL ALCOHOL	TRANSDERMAL	FILM, CONTROLLED RELEASE	4015	MG
METHYL GLUCETH-10		AUGMENTED	5	%W/W
METHYL GLUCETH-10	AUGMENTED	TOPICAL	5	%W/W
METHYL GLUCETH-10	TOPICAL	CREAM, AUGMENTED	5	%
METHYL GLUCETH-20		EMULSION, SUSTAINED RELEASE	13.6	%W/W
METHYL GLUCETH-20			5	%W/W
METHYL GLUCETH-20	EMULSION, SUSTAINED RELEASE	TOPICAL	13.6	%W/W
METHYL GLUCETH-20	TOPICAL	EMULSION, CREAM	5	%
METHYL GLUCETH-20 SESQUISTEARATE	TOPICAL	EMULSION, CREAM	3.5	%
METHYL GLUCOSE SESQUISTEARATE		AUGMENTED	3.5	%W/W
METHYL GLUCOSE SESQUISTEARATE			3.5	%W/W
METHYL GLUCOSE SESQUISTEARATE	AUGMENTED	TOPICAL	3.5	%W/W
METHYL GLUCOSE SESQUISTEARATE	TOPICAL	EMULSION, CREAM	3.5	%
METHYL LAURATE			17.6	MG
METHYL LAURATE	TRANSDERMAL	FILM, CONTROLLED RELEASE	17.6	MG
METHYL LAURATE	TRANSDERMAL	GEL	0.25	%
METHYL SALICYLATE	TOPICAL	GEL	1	%
METHYL SALICYLATE	TOPICAL	GEL	0.05	%W/W
METHYL STEARATE			1	%W/W
METHYL STEARATE			1	%
METHYL STEARATE	TOPICAL	EMULSION, CREAM	1	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
METHYL STEARATE	VAGINAL	EMULSION, CREAM	1	%
METHYL STEARATE	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	1.5	%
METHYLCELLULOSE	TOPICAL	EMULSION, CREAM	1.3	%
METHYLCELLULOSE	TOPICAL	LOTION	1.5	%
METHYLCELLULOSE, UNSPECIFIED			0.11	%W/W
METHYLCELLULOSE, UNSPECIFIED			1.3	%W/W
METHYLCHLOROISOTHIAZOLINONE/ METHYLISOTHIAZOLINONE MIXTURE		EMULSION, SUSTAINED RELEASE	0.05	%W/W
METHYLCHLOROISOTHIAZOLINONE/ METHYLISOTHIAZOLINONE MIXTURE			0.05	%W/W
METHYLCHLOROISOTHIAZOLINONE/ METHYLISOTHIAZOLINONE MIXTURE	EMULSION, SUSTAINED RELEASE	TOPICAL	0.05	%W/W
METHYLPARABEN			0.15	%W/W
METHYLPARABEN			0.2	%W/W
METHYLPARABEN		AUGMENTED	0.2	%W/W
METHYLPARABEN		EMULSION, SUSTAINED RELEASE	0.2	%W/W
METHYLPARABEN		TOPICAL	0.15	%W/W
METHYLPARABEN		TOPICAL	0.2	%W/W
METHYLPARABEN			0.2	%W/W
METHYLPARABEN			0.11	%W/W
METHYLPARABEN			0.5	%W/W
METHYLPARABEN			0.17	%W/W
METHYLPARABEN			0.1	%
METHYLPARABEN			0.2	%
METHYLPARABEN			14	MG
METHYLPARABEN	AUGMENTED	TOPICAL	0.2	%W/W
METHYLPARABEN	BUCCAL	FILM	1	MG
METHYLPARABEN	BUCCAL	FILM	0.71	MG
METHYLPARABEN	EMULSION, SUSTAINED RELEASE	TOPICAL	0.2	%W/W
METHYLPARABEN	IONTOPHORESIS	SOLUTION	0.1	%
METHYLPARABEN	TOPICAL	EMULSION, LOTION	0.17	%
METHYLPARABEN	TOPICAL	CREAM, AUGMENTED	0.2	%
METHYLPARABEN	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	0.2	%
METHYLPARABEN	TOPICAL	OINTMENT	0.2	%
METHYLPARABEN	TOPICAL	GEL	0.3	%
METHYLPARABEN	TOPICAL	PATCH	0.35	MG
METHYLPARABEN	TOPICAL	LOTION	15	%
METHYLPARABEN	TOPICAL	EMULSION, CREAM	18	%
METHYLPARABEN	TOPICAL	JELLY	70	%
METHYLPARABEN	TOPICAL	GEL	0.3	%W/W
METHYLPARABEN	TOPICAL	JELLY	0.07	%W/V
METHYLPARABEN	URETHRAL	INJECTION	0.18	%
METHYLPARABEN	URETHRAL	JELLY	0.07	%
METHYLPARABEN	VAGINAL	GEL	0.08	%
METHYLPARABEN	VAGINAL	EMULSION, CREAM	0.2	%
METHYLPARABEN	VAGINAL	CREAM	0.2	%W/W
METHYLPARABEN	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	0.18	%
METHYLPARABEN	VAGINAL	GEL	0.08	%
MICROCRYSTALLINE WAX		EMULSION, SUSTAINED RELEASE	0.45	%W/W
MICROCRYSTALLINE WAX			0.45	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
MICROCRYSTALLINE WAX	EMULSION, SUSTAINED RELEASE	TOPICAL	0.45	%W/W
MICROCRYSTALLINE WAX	TOPICAL	OINTMENT	30	%
MICROCRYSTALLINE WAX	VAGINAL	EMULSION, CREAM	0.45	%
MICROCRYSTALLINE WAX	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	0.45	%W/W
MINERAL OIL			23.63	%W/W
MINERAL OIL		AUGMENTED	50.62	%W/W
MINERAL OIL		EMULSION, SUSTAINED RELEASE	50.6	%W/W
MINERAL OIL		TOPICAL	23.63	%W/W
MINERAL OIL			40	%W/W
MINERAL OIL			20	%W/W
MINERAL OIL			15	%
MINERAL OIL			11.42	MG
MINERAL OIL			34	MG
MINERAL OIL	AUGMENTED	TOPICAL	50.62	%W/W
MINERAL OIL	EMULSION, SUSTAINED RELEASE	TOPICAL	50.6	%W/W
MINERAL OIL	TOPICAL	LOTION	19.4796	%
MINERAL OIL	TOPICAL	EMULSION, LOTION	20	%
MINERAL OIL	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	23.63	%
MINERAL OIL	TOPICAL	EMULSION, CREAM	40	%
MINERAL OIL	TOPICAL	CREAM, AUGMENTED	50.618	%
MINERAL OIL	TOPICAL	OINTMENT	95	%
MINERAL OIL	TOPICAL	GEL	2.5	%W/W
MINERAL OIL	TRANSDERMAL	PATCH, CONTROLLED RELEASE	1.52	MG
MINERAL OIL	TRANSDERMAL	FILM, CONTROLLED RELEASE	11.8	MG
MINERAL OIL	VAGINAL	GEL	4.725	%
MINERAL OIL	VAGINAL	EMULSION, CREAM	15	%
MINERAL OIL	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	7	%
MINERAL OIL	VAGINAL	GEL	4.73	%
MONO AND DIGLYCERIDE			13	%W/W
MONO AND DIGLYCERIDE		AUGMENTED	1	%W/W
MONO AND DIGLYCERIDE		TOPICAL	13	%W/W
MONO AND DIGLYCERIDE			0.54	%W/W
MONO AND DIGLYCERIDE	AUGMENTED	TOPICAL	1	%W/W
MYRISTYL ALCOHOL			3	%W/W
MYRISTYL ALCOHOL	TOPICAL	LOTION	1	%
MYRISTYL ALCOHOL	TOPICAL	EMULSION, CREAM	3	%
MYRISTYL LACTATE	TOPICAL	LOTION	92.8	%
N-3-CHLOROALLYL-METHENAMINE CHLORIDE	TOPICAL	EMULSION, CREAM	0.1	%
NIACINAMIDE	TOPICAL	GEL	1.25	%
NIACINAMIDE	TOPICAL	GEL	1.25	%W/W
NITRIC ACID				ADJPH
NONOXYNOL-15	TOPICAL	SPONGE	50.5	MG
OCTADECENE-1/MALEIC ACID COPOLYMER	TOPICAL	LOTION	2	%
OCTOXYNOL-9	TOPICAL	GEL	0.012	%
OCTOXYNOL-9	TOPICAL	GEL	0.12	%W/W
OCTYL HYDROXYSTEARATE	TOPICAL	EMULSION, CREAM	12	%
OCTYLDODECANOL			12	%W/W
OCTYLDODECANOL			13.5	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
OCTYLDODECANOL			32.44	MG
OCTYLDODECANOL			253.4	MG
OCTYLDODECANOL	TOPICAL	LOTION	3.3	%
OCTYLDODECANOL	TOPICAL	GEL	10	%
OCTYLDODECANOL	TOPICAL	EMULSION, CREAM	12	%
OCTYLDODECANOL	TOPICAL	GEL	10	%W/W
OCTYLDODECANOL	TRANSDERMAL	FILM, CONTROLLED RELEASE	253.4	MG
OCTYLDODECANOL	VAGINAL	CREAM, AUGMENTED	13.5	%
OCTYLDODECANOL	VAGINAL	EMULSION, CREAM	13.5	%
OCTYLDODECANOL	VAGINAL	CREAM, AUGMENTED	13.5	%
OLEIC ACID			25	%W/W
OLEIC ACID			22	MG
OLEIC ACID	TOPICAL	GEL	2.5	%W/W
OLEIC ACID	TRANSDERMAL	PATCH, CONTROLLED RELEASE	5.51	MG
OLEIC ACID	TRANSDERMAL	FILM, CONTROLLED RELEASE	22	MG
OLEYL ALCOHOL		AUGMENTED	10	%W/W
OLEYL ALCOHOL			10	%W/W
OLEYL ALCOHOL			6.11	MG
OLEYL ALCOHOL			6.03	MG
OLEYL ALCOHOL			7.45	MG
OLEYL ALCOHOL	AUGMENTED	TOPICAL	10	%W/W
OLEYL ALCOHOL	TOPICAL	OINTMENT	5	%
OLEYL ALCOHOL	TOPICAL	EMULSION, CREAM	10	%
OLEYL ALCOHOL	TRANSDERMAL	GEL	1.5	%
OLEYL OLEATE	TOPICAL	OINTMENT	2.55	%
OLEYL POLYETHYLENE GLYCOL GLYCERIDE	NASAL	GEL	4	%
OLIVE OIL		AUGMENTED	27.75	%W/W
OLIVE OIL	AUGMENTED	TOPICAL	27.75	%W/W
PALM OIL, HYDROGENATED	VAGINAL	GEL	1.125	%
PARAFFIN			2.5	%W/W
PARAFFIN		TOPICAL	2.5	%W/W
PARAFFIN			2	%W/W
PARAFFIN	TOPICAL	EMULSION, CREAM	4.5	%
PARAFFIN	TOPICAL	OINTMENT	68.995	%
PARAFFIN, WHITE SOFT	TOPICAL	EMULSION, CREAM	15	%
PARFUM CREME 45/3	TOPICAL	GEL	0.1	%W/W
PEANUT OIL		AUGMENTED	10	%W/W
PEANUT OIL			9	%
PEANUT OIL	AUGMENTED	TOPICAL	10	%W/W
PEANUT OIL	TOPICAL	EMULSION, CREAM	3	%
PEANUT OIL	VAGINAL	EMULSION, CREAM	9	%
PEG 6-32 STEARATE/GLYCOL STEARATE			19.6	%W/W
PEG 6-32 STEARATE/GLYCOL STEARATE			19.6	%
PEG 6–32 STEARATE/GLYCOL STEARATE	TOPICAL	EMULSION, CREAM	19.6	%
PEG 6–32 STEARATE/GLYCOL STEARATE	VAGINAL	EMULSION, CREAM	19.6	%
PEG-100 STEARATE		AUGMENTED	0.5	%W/W
PEG-100 STEARATE			2.1	%W/W
PEG-100 STEARATE	AUGMENTED	TOPICAL	0.5	%W/W
PEG-120 GLYCERYL STEARATE			5	%W/W
PEG-120 GLYCERYL STEARATE			2	%
PEG-2 STEARATE			1	%W/W
PEG-20 METHYL GLUCOSE SESQUISTEARATE		AUGMENTED	3.5	%W/W
PEG-20 METHYL GLUCOSE SESQUISTEARATE			3.5	%W/W

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
PEG-20 METHYL GLUCOSE SESQUISTEARATE	AUGMENTED	TOPICAL	3.5	%W/W
PEG-22 METHYL ETHER/DODECYL GLYCOL COPOLYMER	TOPICAL	CREAM, AUGMENTED	5	%
PEG-25 PROPYLENE GLYCOL STEARATE	TOPICAL	EMULSION, CREAM	2.5	%
PEG-45/DODECYL GLYCOL COPOLYMER		AUGMENTED	3	%W/W
PEG-45/DODECYL GLYCOL COPOLYMER	AUGMENTED	TOPICAL	3	%W/W
PEG-45/DODECYL GLYCOL COPOLYMER	TOPICAL	CREAM, AUGMENTED	3	%
PEG-5 OLEATE			3.05	%W/W
PEG-5 OLEATE			3	%
PEG-50 STEARATE			2	%W/W
PEG-6 ISOSTEARATE			2	%W/W
PEG-60 HYDROGENATED CASTOR OIL			1.9	%W/W
PEG-60 HYDROGENATED CASTOR OIL	TOPICAL	GEL	1.9	%W/W
PEG-7 METHYL ETHER	TOPICAL	GEL	20	%W/W
PEG-75 LANOLIN			1.5	%W/W
PEG-8 STEARATE			2	%W/W
PEG-8 STEARATE			5	%W/W
PEG-8 STEARATE		TOPICAL	2	%W/W
PEG-8 STEARATE		TOPICAL	5	%W/W
PEG-8 STEARATE			6.66	%W/W
PEG/PPG-18/18 DIMETHICONE	TOPICAL	GEL	1	%W/W
PEGLICOL-5-OLEATE	TOPICAL	EMULSION, CREAM	3.05	%
PEGLICOL-5-OLEATE	VAGINAL	EMULSION, CREAM	3	%
PEGOXOL 7 STEARATE			20	%W/W
PEGOXOL 7 STEARATE		TOPICAL	20	%W/W
PEGOXOL 7 STEARATE			22	%W/W
PEGOXOL 7 STEARATE			20	%
PEGOXOL 7 STEARATE	TOPICAL	EMULSION, CREAM	22	%
PEGOXOL 7 STEARATE	VAGINAL	EMULSION, CREAM	20	%
PENTADECALACTONE	TRANSDERMAL	GEL	40	%
PENTADECALACTONE	TRANSDERMAL	GEL	8	%
PENTADECALACTONE	TRANSDERMAL	GEL	8	%W/W
PENTAERYTHRITOL COCOATE	TOPICAL	OINTMENT	1	%
PEPPERMINT OIL	BUCCAL	FILM	0.51	MG
PEPPERMINT OIL	BUCCAL	FILM	0.85	MG
PEPPERMINT OIL	BUCCAL	GUM, CHEWING	31	MG
PEPPERMINT OIL	ORAL	GUM, CHEWING	15	MG
PERFUME GD 5604			0.12	%W/W
PERFUME GD 5604	TOPICAL	EMULSION, CREAM	0.12	%
PERFUME TANA 90/42 SCBA	TOPICAL	LOTION	0.075	%
PETROLATUM			26.5	%W/W
PETROLATUM			45.93	%W/W
PETROLATUM		AUGMENTED	26	%W/W
PETROLATUM		EMULSION, SUSTAINED RELEASE	42	%W/W
PETROLATUM		TOPICAL	26.5	%W/W
PETROLATUM		TOPICAL	45.93	%W/W
PETROLATUM			5.3	%W/W
PETROLATUM			7.9	%W/W
PETROLATUM			58.2	%W/W
PETROLATUM			42	%W/W
PETROLATUM			2.7	%
PETROLATUM	AUGMENTED	TOPICAL	26	%W/W
PETROLATUM	EMULSION, SUSTAINED RELEASE	TOPICAL	42	%W/W
PETROLATUM	TOPICAL	LOTION	2.5	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
PETROLATUM	TOPICAL	EMULSION, CREAM	16.43	%
PETROLATUM	TOPICAL	OINTMENT	99.98	%
PETROLATUM, WHITE	TOPICAL	LOTION	15	%
PETROLATUM, WHITE	TOPICAL	CREAM, AUGMENTED	26	%
PETROLATUM, WHITE	TOPICAL	EMULSION, CREAM	58.2	%
PETROLATUM, WHITE	TOPICAL	OINTMENT, AUGMENTED	81.936	%
PETROLATUM, WHITE	TOPICAL	OINTMENT	99.98	%
PETROLATUM, WHITE	TRANSDERMAL	OINTMENT	29	%
PETROLATUM, WHITE	VAGINAL	OINTMENT	88.49	%
PETROLEUM DISTILLATES	TOPICAL	EMULSION, CREAM	6	%
PHENONIP	IONTOPHORESIS	PATCH, CONTROLLED RELEASE	0.23	MG
PHENONIP	TOPICAL	PATCH, CONTROLLED RELEASE	0.23	MG
PHENONIP	TOPICAL	GEL	0.035	%W/W
PHENOXYETHANOL		AUGMENTED	1	%W/W
PHENOXYETHANOL		EMULSION, SUSTAINED RELEASE	0.5	%W/W
PHENOXYETHANOL			1.05	%W/W
PHENOXYETHANOL			0.7	%W/W
PHENOXYETHANOL	AUGMENTED	TOPICAL	1	%W/W
PHENOXYETHANOL	EMULSION, SUSTAINED RELEASE	TOPICAL	0.5	%W/W
PHENOXYETHANOL	TOPICAL	CREAM, AUGMENTED	0.5	%
PHENOXYETHANOL	TOPICAL	EMULSION, CREAM	0.5	%
PHENOXYETHANOL	TOPICAL	GEL	0.7	%
PHENOXYETHANOL	TOPICAL	LOTION	0.7	%
PHENOXYETHANOL	TOPICAL	GEL	0.7	%W/W
PHENYLMERCURIC ACETATE			0.01	%W/W
PHENYLMERCURIC ACETATE			0.01	%
PHENYLMERCURIC ACETATE	TOPICAL	EMULSION, CREAM	0.01	%
PHENYLMERCURIC ACETATE	VAGINAL	EMULSION, CREAM	0.01	%
PHOSPHOLIPON 90G	VAGINAL	EMULSION, CREAM	1	%
PHOSPHORIC ACID		AUGMENTED	0.02	%W/W
PHOSPHORIC ACID		EMULSION, SUSTAINED RELEASE	0.002	%W/W
PHOSPHORIC ACID			0.1	%W/W
PHOSPHORIC ACID			0.8	%
PHOSPHORIC ACID	AUGMENTED	TOPICAL	0.02	%W/W
PHOSPHORIC ACID	EMULSION, SUSTAINED RELEASE	TOPICAL	0.002	%W/W
PHOSPHORIC ACID	TOPICAL	OINTMENT	0.004	%
PHOSPHORIC ACID	TOPICAL	LOTION, AUGMENTED	0.012	%
PHOSPHORIC ACID	TOPICAL	LOTION	0.1	%
PHOSPHORIC ACID	TOPICAL	EMULSION, CREAM	0.5	%
PHOSPHORIC ACID	VAGINAL	EMULSION, CREAM	0.8	%
PINE NEEDLE OIL	TOPICAL	LOTION	0.25	%
PLASTIBASE-50 W	TOPICAL	OINTMENT	99.95	%
POLACRILIN	IONTOPHORESIS	DRUG DELIVERY SYSTEM	1.1	MG
POLACRILIN	TRANSDERMAL	DRUG DELIVERY SYSTEM	1.1	MG
POLOXAMER 124	TOPICAL	GEL	0.2	%
POLOXAMER 124	TOPICAL	GEL	0.2	%W/W
POLOXAMER 182	TOPICAL	GEL	0.2	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
POLOXAMER 182	TOPICAL	GEL	0.2	%W/W
POLOXAMER 188			1	%W/W
POLOXAMER 188	PERIODONTAL	GEL	5.5	%
POLOXAMER 188	TOPICAL	EMULSION, CREAM	0.0126	%
POLOXAMER 188	TOPICAL	GEL	5.5	%
POLOXAMER 407			1	%W/W
POLOXAMER 407	PERIODONTAL	GEL	15.5	%
POLOXAMER 407	TOPICAL	EMULSION, CREAM	1	%
POLOXAMER 407	TOPICAL	GEL	15.5	%
POLOXAMER 407	TOPICAL	GEL	0.2	%W/W
POLYCARBOPHIL	BUCCAL	FILM	2.06	MG
POLYCARBOPHIL	BUCCAL	FILM	1.37	MG
POLYCARBOPHIL	OPHTHALMIC	GEL	0.38	%
POLYCARBOPHIL	OPHTHALMIC	GEL	0.38	%
POLYCARBOPHIL	TOPICAL	PATCH	3.54	MG
POLYCARBOPHIL	VAGINAL	GEL	2.25	%
POLYCARBOPHIL	VAGINAL	GEL	2.25	%
POLYESTER			24	MG
POLYESTER	TRANSDERMAL	FILM, CONTROLLED RELEASE	24	MG
POLYESTER—FLUORO CHEMICAL RELEASING AGENT	TRANSDERMAL	FILM, CONTROLLED RELEASE	393	MG
POLYESTER FLUOROCARBON DIACRYLATE	TRANSDERMAL	FILM, CONTROLLED RELEASE	566	MG
POLYESTER POLYAMINE COPOLYMER			6.67	MG
POLYESTER POLYAMINE COPOLYMER	TRANSDERMAL	FILM, CONTROLLED RELEASE	6.6668	MG
POLYETHYLENE	TOPICAL	OINTMENT	9	%
POLYETHYLENE	TOPICAL	GEL	26	%
POLYETHYLENE	TRANSDERMAL	FILM, CONTROLLED RELEASE	85	MG
POLYETHYLENE	VAGINAL	SUPPOSITORY	3321.2	MG
POLYETHYLENE GLYCOL 1000			0.5	%W/W
POLYETHYLENE GLYCOL 1000	RECTAL	SUPPOSITORY	1625000	MG
POLYETHYLENE GLYCOL 1000	TOPICAL	EMULSION, CREAM	7.2	%
POLYETHYLENE GLYCOL 1000	TRANSDERMAL	GEL	0.5	%
POLYETHYLENE GLYCOL 1450	URETHRAL	SUPPOSITORY	9.75	MG
POLYETHYLENE GLYCOL 1500			5	%
POLYETHYLENE GLYCOL 1500	TOPICAL	OINTMENT	5	%
POLYETHYLENE GLYCOL 1540	TOPICAL	OINTMENT	38	%
POLYETHYLENE GLYCOL 200	TOPICAL	OINTMENT	39	%
POLYETHYLENE GLYCOL 300	TOPICAL	OINTMENT	57	%
POLYETHYLENE GLYCOL 3350			4.6	%W/W
POLYETHYLENE GLYCOL 3350		TOPICAL	4.6	%W/W
POLYETHYLENE GLYCOL 3350	RECTAL	SUPPOSITORY	1425.96	MG
POLYETHYLENE GLYCOL 3350	TOPICAL	OINTMENT	40	%
POLYETHYLENE GLYCOL 400			1.5	%W/W
POLYETHYLENE GLYCOL 400		EMULSION, SUSTAINED RELEASE	7.5	%W/W
POLYETHYLENE GLYCOL 400		TOPICAL	1.5	%W/W
POLYETHYLENE GLYCOL 400			4.76	MG
POLYETHYLENE GLYCOL 400			7.5	%W/W
POLYETHYLENE GLYCOL 400	EMULSION, SUSTAINED RELEASE	TOPICAL	7.5	%W/W
POLYETHYLENE GLYCOL 400	TOPICAL	EMULSION, CREAM	7.5	%
POLYETHYLENE GLYCOL 400	TOPICAL	LOTION	12	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
POLYETHYLENE GLYCOL 400	TOPICAL	GEL	45	%
POLYETHYLENE GLYCOL 400	TOPICAL	OINTMENT	65	%
POLYETHYLENE GLYCOL 400	TOPICAL	GEL	45	%W/W
POLYETHYLENE GLYCOL 4000			0.5	%
POLYETHYLENE GLYCOL 4000	RECTAL	SUPPOSITORY	1269	MG
POLYETHYLENE GLYCOL 4000	TOPICAL	OINTMENT	84	%
POLYETHYLENE GLYCOL 4000	VAGINAL	EMULSION, CREAM	0.5	%
POLYETHYLENE GLYCOL 540	TOPICAL	OINTMENT	76.5	%
POLYETHYLENE GLYCOL 6000			5	%W/W
POLYETHYLENE GLYCOL 6000	RECTAL	SUPPOSITORY	128	MG
POLYETHYLENE GLYCOL 6000	TOPICAL	OINTMENT	1	%
POLYETHYLENE GLYCOL 8000			4.6	%W/W
POLYETHYLENE GLYCOL 8000		EMULSION, SUSTAINED RELEASE	4	%W/W
POLYETHYLENE GLYCOL 8000		TOPICAL	4.6	%W/W
POLYETHYLENE GLYCOL 8000			12.2	MG
POLYETHYLENE GLYCOL 8000			5	%W/W
POLYETHYLENE GLYCOL 8000	EMULSION, SUSTAINED RELEASE	TOPICAL	4	%W/W
POLYETHYLENE GLYCOL 8000	RECTAL	SUPPOSITORY	52	MG
POLYETHYLENE GLYCOL 8000	TOPICAL	EMULSION, CREAM	11	%
POLYETHYLENE GLYCOL, UNSPECIFIED			43.96	MG
POLYETHYLENE OXIDE 100000			12.04	MG
POLYETHYLENE OXIDE 200000			27.1	MG
POLYETHYLENE OXIDE 900000			4.82	MG
POLYGLYCERYL-3 OLEATE		EMULSION, SUSTAINED RELEASE	2.7	%W/W
POLYGLYCERYL-3 OLEATE		EMULSION, SUSTAINED RELEASE	2.7	%W/W
POLYGLYCERYL-3 OLEATE			2.7	%
POLYGLYCERYL-3 OLEATE	EMULSION, SUSTAINED RELEASE	TOPICAL	2.7	%W/W
POLYGLYCERYL-3 OLEATE	EMULSION, SUSTAINED RELEASE	TOPICAL	2.7	%W/W
POLYGLYCERYL-3 OLEATE	VAGINAL	EMULSION, CREAM	2.7	%
POLYGLYCERYL-4 OLEATE			2.71	%
POLYGLYCERYL-4 OLEATE	VAGINAL	EMULSION, CREAM	2.71	%
POLYISOBUTYLENE			16.83	MG
POLYISOBUTYLENE			615.4	MG
POLYISOBUTYLENE	TRANSDERMAL	PATCH, CONTROLLED RELEASE	10.5	MG
POLYISOBUTYLENE	TRANSDERMAL	FILM, CONTROLLED RELEASE	119	MG
POLYISOBUTYLENE (1100000 MW)			69	MG
POLYISOBUTYLENE (2300 MW)			121.68	MG
POLYISOBUTYLENE (35000 MW)			86	MG
POLYISOBUTYLENE (55000 MW)			238.44	MG
POLYISOBUTYLENE (800000 MW)			159	MG
POLYISOBUTYLENE 1200,000	TRANSDERMAL	FILM, CONTROLLED RELEASE	69	MG
POLYISOBUTYLENE 35,000	TRANSDERMAL	FILM, CONTROLLED RELEASE	86	MG
POLYISOBUTYLENE/POLYBUTENE ADHESIVE			221.25	MG
POLYOLS			65.82	%
POLYOXYETHYLENE ALCOHOLS			7.5	%W/W
POLYOXYETHYLENE ALCOHOLS	TOPICAL	EMULSION, CREAM	9	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
POLYOXYETHYLENE FATTY ACID ESTERS			1.9	%W/W
POLYOXYETHYLENE FATTY ACID ESTERS	TOPICAL	EMULSION, CREAM	1.9	%
POLYOXYL 100 GLYCERYL STEARATE	TOPICAL	EMULSION, CREAM	5	%
POLYOXYL 100 GLYCERYL STEARATE	VAGINAL	EMULSION, CREAM	2	%
POLYOXYL 100 STEARATE	TOPICAL	LOTION	1	%
POLYOXYL 100 STEARATE	TOPICAL	EMULSION, CREAM	2.1	%
POLYOXYL 2 STEARATE	TOPICAL	EMULSION, CREAM	1	%
POLYOXYL 20 CETOSTEARYL ETHER			2.5	%W/W
POLYOXYL 20 CETOSTEARYL ETHER		AUGMENTED	3	%W/W
POLYOXYL 20 CETOSTEARYL ETHER		EMULSION, SUSTAINED RELEASE	6	%W/W
POLYOXYL 20 CETOSTEARYL ETHER		TOPICAL	2.5	%W/W
POLYOXYL 20 CETOSTEARYL ETHER			4.74	%W/W
POLYOXYL 20 CETOSTEARYL ETHER			2	%W/W
POLYOXYL 20 CETOSTEARYL ETHER	AUGMENTED	TOPICAL	3	%W/W
POLYOXYL 20 CETOSTEARYL ETHER	EMULSION, SUSTAINED RELEASE	TOPICAL	6	%W/W
POLYOXYL 20 CETOSTEARYL ETHER	TOPICAL	EMULSION, CREAM	10	%
POLYOXYL 20 CETOSTEARYL ETHER	TOPICAL	GEL	1.3	%W/W
POLYOXYL 20 CETOSTEARYL ETHER	TOPICAL	GEL	2	%W/W
POLYOXYL 4 DILAURATE	TOPICAL	LOTION	2	%
POLYOXYL 40 HYDROGENATED CASTOR OIL			1	%W/W
POLYOXYL 40 HYDROGENATED CASTOR OIL	TOPICAL	EMULSION, CREAM	1	%
POLYOXYL 40 STEARATE			8	%W/W
POLYOXYL 40 STEARATE		EMULSION, SUSTAINED RELEASE	5.25	%W/W
POLYOXYL 40 STEARATE		TOPICAL	8	%W/W
POLYOXYL 40 STEARATE			1.08	%W/W
POLYOXYL 40 STEARATE			8.8	%W/W
POLYOXYL 40 STEARATE	EMULSION, SUSTAINED RELEASE	TOPICAL	5.25	%W/W
POLYOXYL 40 STEARATE	TOPICAL	LOTION	5.1	%
POLYOXYL 40 STEARATE	TOPICAL	EMULSION, CREAM	8.8	%
POLYOXYL 400 STEARATE	TOPICAL	EMULSION, CREAM	8	%
POLYOXYL 50 STEARATE	TOPICAL	EMULSION, CREAM	2	%
POLYOXYL 6 AND POLYOXYL 32 PALMITOSTEARATE			20	%W/W
POLYOXYL 6 AND POLYOXYL 32 PALMITOSTEARATE	TOPICAL	EMULSION, CREAM	20	%
POLYOXYL 6 ISOSTEARATE	TOPICAL	EMULSION, LOTION	2	%
POLYOXYL 60 HYDROGENATED CASTOR OIL	TOPICAL	EMULSION, CREAM	1.9	%
POLYOXYL 8 STEARATE	TOPICAL	EMULSION, CREAM	8	%
POLYOXYL GLYCERYL OLEATE			3	%W/W
POLYOXYL GLYCERYL OLEATE		TOPICAL	3	%W/W
POLYOXYL GLYCERYL STEARATE			5	%W/W
POLYOXYL GLYCERYL STEARATE	TOPICAL	LOTION	1.5	%
POLYOXYL GLYCERYL STEARATE	TOPICAL	EMULSION, CREAM	5	%
POLYOXYL PALMITATE	VAGINAL	SUPPOSITORY	276	MG
POLYOXYL STEARATE			1.4	%W/W
POLYOXYL STEARATE		TOPICAL	1.4	%W/W
POLYOXYL STEARATE			20	%W/W
POLYOXYL STEARATE	TOPICAL	LOTION	2	%
POLYOXYL STEARATE	TOPICAL	EMULSION, CREAM	20	%
POLYPROPYLENE			13.5	MG
POLYPROPYLENE	TRANSDERMAL	FILM, CONTROLLED RELEASE	13.5	MG

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
POLYSORBATE 20			2	%W/W
POLYSORBATE 20			3.7	%W/W
POLYSORBATE 20			0.8	%W/W
POLYSORBATE 20	TOPICAL	EMULSION, CREAM	0.8	%
POLYSORBATE 20	TOPICAL	LOTION	7.8	%
POLYSORBATE 20	TOPICAL	GEL	5	%W/W
POLYSORBATE 40			3	%W/W
POLYSORBATE 40	TOPICAL	GEL	0.2	%
POLYSORBATE 40	TOPICAL	LOTION	3	%
POLYSORBATE 40	TOPICAL	EMULSION, CREAM	6	%
POLYSORBATE 40	TOPICAL	GEL	0.2	%W/W
POLYSORBATE 60			2.15	%W/W
POLYSORBATE 60			6	%W/W
POLYSORBATE 60		AUGMENTED	3	%W/W
POLYSORBATE 60		EMULSION, SUSTAINED RELEASE	5	%W/W
POLYSORBATE 60		AUGMENTED	1.5	%
POLYSORBATE 60		EMULSION, SUSTAINED RELEASE	5	%
POLYSORBATE 60		TOPICAL	2.15	%W/W
POLYSORBATE 60		TOPICAL	6	%W/W
POLYSORBATE 60			0.42	%W/W
POLYSORBATE 60			6.1	%W/W
POLYSORBATE 60			5	%
POLYSORBATE 60	AUGMENTED	TOPICAL	3	%W/W
POLYSORBATE 60	AUGMENTED	TOPICAL	1.5	%
POLYSORBATE 60	BUCCAL	GUM, CHEWING	0.23	MG
POLYSORBATE 60	EMULSION, SUSTAINED RELEASE	TOPICAL	5	%W/W
POLYSORBATE 60	EMULSION, SUSTAINED RELEASE	TOPICAL	5	%
POLYSORBATE 60	TOPICAL	LOTION	5	%
POLYSORBATE 60	TOPICAL	EMULSION, CREAM	8	%
POLYSORBATE 60	VAGINAL	CREAM, AUGMENTED	1.5	%
POLYSORBATE 60	VAGINAL	EMULSION, CREAM	7.5	%
POLYSORBATE 65	TOPICAL	OINTMENT	5	%
POLYSORBATE 80		AUGMENTED	15	%W/W
POLYSORBATE 80		EMULSION, SUSTAINED RELEASE	5	%W/W
POLYSORBATE 80			0.001	%W/W
POLYSORBATE 80		TOPICAL	0.001	%W/W
POLYSORBATE 80			2.5	%W/W
POLYSORBATE 80			0.98	%W/W
POLYSORBATE 80			4.5	%W/W
POLYSORBATE 80			0.4	%
POLYSORBATE 80	AUGMENTED	TOPICAL	15	%W/W
POLYSORBATE 80	EMULSION, SUSTAINED RELEASE	TOPICAL	5	%W/W
POLYSORBATE 80	RECTAL	SUPPOSITORY	72.15	MG
POLYSORBATE 80	TOPICAL	OINTMENT	0.1	%
POLYSORBATE 80	TOPICAL	EMULSION, CREAM	5	%
POLYSORBATE 80	TOPICAL	GEL	8.5	%
POLYSORBATE 80	TOPICAL	LOTION	9.4	%
POLYSORBATE 80	TOPICAL	GEL	8.5	%W/W
POLYSORBATE 80	VAGINAL	EMULSION, CREAM	0.5	%
POLYSORBATE 80	VAGINAL	SUPPOSITORY	28	MG

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
POLYVINYL ACETATE			16	MG
POLYVINYL ACETATE	TRANSDERMAL	PATCH, CONTROLLED RELEASE	3.99	MG
POLYVINYL ACETATE	TRANSDERMAL	FILM, CONTROLLED RELEASE	16	MG
POLYVINYL ALCOHOL	IONTOPHORESIS	DRUG DELIVERY SYSTEM	119	MG
POLYVINYL ALCOHOL	TOPICAL	LOTION	2.5	%
POLYVINYL ALCOHOL	TOPICAL	PATCH	25.2	MG
POLYVINYL ALCOHOL	TRANSDERMAL	DRUG DELIVERY SYSTEM	119	MG
POLYVINYL ALCOHOL, UNSPECIFIED			0.5	%
POLYVINYL CHLORIDE-POLYVINYL ACETATE COPOLYMER			899.88	MG
POLYVINYL CHLORIDE-POLYVINYL ACETATE COPOLYMER	TRANSDERMAL	FILM, CONTROLLED RELEASE	899.88	MG
POTASSIUM CITRATE			0.17	%W/W
POTASSIUM HYDROXIDE		EMULSION, SUSTAINED RELEASE	0.045	%W/W
POTASSIUM HYDROXIDE			0.5	%W/W
POTASSIUM HYDROXIDE			0.5	%
POTASSIUM HYDROXIDE	EMULSION, SUSTAINED RELEASE	TOPICAL	0.045	%W/W
POTASSIUM HYDROXIDE	TOPICAL	EMULSION, CREAM	0.5	%
POTASSIUM HYDROXIDE	TOPICAL	GEL	0.5	%W/W
POTASSIUM HYDROXIDE	VAGINAL	EMULSION, CREAM	0.5	%
POTASSIUM HYDROXIDE	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	0.045	%
POTASSIUM SORBATE			0.09	%W/W
POTASSIUM SORBATE			0.2	%W/W
POTASSIUM SORBATE		TOPICAL	0.09	%W/W
POTASSIUM SORBATE		TOPICAL	0.2	%W/W
POTASSIUM SORBATE			0.2	%W/W
POTASSIUM SORBATE			0.25	%W/W
POTASSIUM SORBATE	TOPICAL	LOTION	0.2	%
POTASSIUM SORBATE	TOPICAL	EMULSION, CREAM	2.7	%
POVIDONE HYDROGEL	IONTOPHORESIS	PATCH, CONTROLLED RELEASE	506.5	MG
POVIDONE HYDROGEL	TOPICAL	PATCH, CONTROLLED RELEASE	506.5	MG
POVIDONE K29–32	TRANSDERMAL	FILM, CONTROLLED RELEASE	7.266	MG
POVIDONE K30			2.3	MG
POVIDONE K30			2.3	MG
POVIDONE K30			1.9	%W/W
POVIDONE K30			5.11	MG
POVIDONE K30			7.27	MG
POVIDONE, UNSPECIFIED			9.69	MG
POVIDONE/EICOSENE COPOLYMER			1	%W/W
POVIDONE/EICOSENE COPOLYMER	TOPICAL	LOTION	1	%
PPG-12/SMDI COPOLYMER			1	%W/W
PPG-12/SMDI COPOLYMER	TOPICAL	EMULSION, CREAM	10	%
PPG-12/SMDI COPOLYMER	TOPICAL	GEL	10	%
PPG-15 STEARYL ETHER	TOPICAL	GEL	2	%
PPG-15 STEARYL ETHER	TOPICAL	OINTMENT	15	%
PPG-15 STEARYL ETHER	TOPICAL	GEL	2	%W/W

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
PPG-20 METHYL GLUCOSE ETHER DISTEARATE	TOPICAL	GEL	4.75	%
PPG-20 METHYL GLUCOSE ETHER DISTEARATE	TOPICAL	GEL	4.75	%W/W
PPG-26 OLEATE			4	%W/W
PPG-26 OLEATE	TOPICAL	EMULSION, CREAM	4	%
PROMALGEN TYPE G	TOPICAL	LOTION	1.5	%
PROMULGEN D			4	%W/W
PROMULGEN D	TOPICAL	LOTION	3.5	%
PROMULGEN G			7	%W/W
PROMULGEN G	TOPICAL	LOTION	2.16	%
PROPYL GALLATE	TOPICAL	OINTMENT	0.015	%
PROPYL GALLATE	TOPICAL	GEL	0.05	%
PROPYL GALLATE	TOPICAL	GEL	0.05	%W/W
PROPYLENE CARBONATE	TOPICAL	OINTMENT	5	%
PROPYLENE GLYCOL			71.08	%W/W
PROPYLENE GLYCOL			11.5	%W/W
PROPYLENE GLYCOL			50	%W/W
PROPYLENE GLYCOL		AUGMENTED	30	%W/W
PROPYLENE GLYCOL		TOPICAL	71.08	%W/W
PROPYLENE GLYCOL		TOPICAL	11.5	%W/W
PROPYLENE GLYCOL		TOPICAL	50	%W/W
PROPYLENE GLYCOL			8	%W/W
PROPYLENE GLYCOL			21.05	%W/W
PROPYLENE GLYCOL			71.08	%W/W
PROPYLENE GLYCOL			47.5	%W/W
PROPYLENE GLYCOL			6.4	%
PROPYLENE GLYCOL			20	%
PROPYLENE GLYCOL			700	MG
PROPYLENE GLYCOL			58.13	MG
PROPYLENE GLYCOL	AUGMENTED	TOPICAL	30	%W/W
PROPYLENE GLYCOL	BUCCAL	FILM	1.48	MG
PROPYLENE GLYCOL	BUCCAL	FILM	1.02	MG
PROPYLENE GLYCOL	OPHTHALMIC	GEL	0.44	%
PROPYLENE GLYCOL	OPHTHALMIC	GEL	0.44	%
PROPYLENE GLYCOL	RECTAL	GEL	82.88	%
PROPYLENE GLYCOL	TOPICAL	PATCH	0.44	MG
PROPYLENE GLYCOL	TOPICAL	CREAM, AUGMENTED	8	%
PROPYLENE GLYCOL	TOPICAL	LOTION, AUGMENTED	30	%
PROPYLENE GLYCOL	TOPICAL	OINTMENT	38	%
PROPYLENE GLYCOL	TOPICAL	EMULSION, LOTION	47.5	%
PROPYLENE GLYCOL	TOPICAL	LOTION	50.9	%
PROPYLENE GLYCOL	TOPICAL	OINTMENT, AUGMENTED	65	%
PROPYLENE GLYCOL	TOPICAL	EMULSION, CREAM	71.08	%
PROPYLENE GLYCOL	TOPICAL	GEL	98.09	%
PROPYLENE GLYCOL	TOPICAL	GEL	4	%W/W
PROPYLENE GLYCOL	TOPICAL	GEL	98.09	%W/W
PROPYLENE GLYCOL	TRANSDERMAL	GEL	25	%
PROPYLENE GLYCOL	TRANSDERMAL	FILM, CONTROLLED RELEASE	58.13	MG
PROPYLENE GLYCOL	TRANSDERMAL	GEL	20	%
PROPYLENE GLYCOL	TRANSDERMAL	GEL	5	%W/W
PROPYLENE GLYCOL	VAGINAL	GEL	3	%
PROPYLENE GLYCOL	VAGINAL	EMULSION, CREAM	20	%
PROPYLENE GLYCOL	VAGINAL	SUPPOSITORY	252	MG
PROPYLENE GLYCOL	VAGINAL	CREAM	10	%
PROPYLENE GLYCOL	VAGINAL	CREAM	10	%W/W

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
PROPYLENE GLYCOL	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	20	%
PROPYLENE GLYCOL	VAGINAL	GEL	3	%
PROPYLENE GLYCOL DIACETATE			10	%W/W
PROPYLENE GLYCOL DIACETATE	TOPICAL	EMULSION, CREAM	10	%
PROPYLENE GLYCOL DICAPRYLATE			10	%W/W
PROPYLENE GLYCOL DICAPRYLATE			10	%W/W
PROPYLENE GLYCOL DICAPRYLATE	TOPICAL	EMULSION, CREAM	10	%
PROPYLENE GLYCOL MONOPALMITOSTEARATE			9.3	%W/W
PROPYLENE GLYCOL MONOPALMITOSTEARATE			7	%
PROPYLENE GLYCOL MONOPALMITOSTEARATE	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	7	%
PROPYLENE GLYCOL MONOSTEARATE			8	%W/W
PROPYLENE GLYCOL MONOSTEARATE	TOPICAL	OINTMENT, AUGMENTED	2	%
PROPYLENE GLYCOL MONOSTEARATE	TOPICAL	LOTION	4.69	%
PROPYLENE GLYCOL MONOSTEARATE	TOPICAL	OINTMENT	8	%
PROPYLENE GLYCOL MONOSTEARATE	TOPICAL	EMULSION, CREAM	9.3	%
PROPYLENE GLYCOL MONOSTEARATE	VAGINAL	EMULSION, CREAM	7	%
PROPYLENE GLYCOL PALMITOSTEARATE	TOPICAL	OINTMENT	5	%
PROPYLPARABEN			0.15	%W/W
PROPYLPARABEN			0.4	%W/W
PROPYLPARABEN		AUGMENTED	0.1	%W/W
PROPYLPARABEN		EMULSION, SUSTAINED RELEASE	0.1	%W/W
PROPYLPARABEN		TOPICAL	0.15	%W/W
PROPYLPARABEN		TOPICAL	0.4	%W/W
PROPYLPARABEN			0.06	%W/W
PROPYLPARABEN			0.011	%W/W
PROPYLPARABEN			5.25	%W/W
PROPYLPARABEN			0.1	%W/W
PROPYLPARABEN			0.06	%W/W
PROPYLPARABEN			0.1	%
PROPYLPARABEN	AUGMENTED	TOPICAL	0.1	%W/W
PROPYLPARABEN	BUCCAL	FILM	0.22	MG
PROPYLPARABEN	BUCCAL	FILM	0.18	MG
PROPYLPARABEN	EMULSION, SUSTAINED RELEASE	TOPICAL	0.1	%W/W
PROPYLPARABEN	TOPICAL	PATCH	0.02	MG
PROPYLPARABEN	TOPICAL	CREAM, AUGMENTED	0.032	%
PROPYLPARABEN	TOPICAL	EMULSION, LOTION	0.06	%
PROPYLPARABEN	TOPICAL	GEL	0.08	%
PROPYLPARABEN	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	0.1	%
PROPYLPARABEN	TOPICAL	OINTMENT	0.2	%
PROPYLPARABEN	TOPICAL	EMULSION, CREAM	1	%
PROPYLPARABEN	TOPICAL	LOTION	10	%
PROPYLPARABEN	TOPICAL	JELLY	30	%
PROPYLPARABEN	TOPICAL	GEL	0.05	%W/W
PROPYLPARABEN	TOPICAL	JELLY	0.03	%W/V
PROPYLPARABEN	URETHRAL	INJECTION	0.02	%
PROPYLPARABEN	URETHRAL	JELLY	0.03	%
PROPYLPARABEN	VAGINAL	GEL	0.02	%
PROPYLPARABEN	VAGINAL	EMULSION, CREAM	0.1	%
PROPYLPARABEN	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	0.05	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
PROPYLPARABEN	VAGINAL	GEL	0.02	%
PROTEIN HYDROLYSATE	TOPICAL	LOTION	0.39	%
QUATERNIUM-15		AUGMENTED	0.1	%W/W
QUATERNIUM-15			0.02	%W/W
QUATERNIUM-15	AUGMENTED	TOPICAL	0.1	%W/W
QUATERNIUM-15	TOPICAL	EMULSION, CREAM	0.02	%
QUATERNIUM-15	TOPICAL	CREAM, AUGMENTED	0.1	%
QUATERNIUM-15	TOPICAL	LOTION	0.2	%
QUATERNIUM-15 CIS-FORM			0.1	%W/W
RA-2397			142.2	MG
RA-2397	TRANSDERMAL	FILM, CONTROLLED RELEASE	142.2	MG
RA-3011			142.2	MG
RA-3011	TRANSDERMAL	FILM, CONTROLLED RELEASE	142.2	MG
RHODAMINE B			0.001	%W/W
SACCHARIN	TOPICAL	OINTMENT	0.5	%
SACCHARIN SODIUM			0.3	%
SACCHARIN SODIUM	BUCCAL	FILM	2.99	MG
SACCHARIN SODIUM	BUCCAL	FILM	0.57	MG
SAFFLOWER OIL	TOPICAL	LOTION	3	%
SCOTCHPAK 1022			904.92	MG
SCOTCHPAK 1109	TRANSDERMAL	FILM, CONTROLLED RELEASE	115.71	MG
SCOTCHPAK 9739 BACKING FILM PET/EVA	TRANSDERMAL	PATCH	211.8	MG
SD ALCOHOL 40			46	%W/W
SD ALCOHOL 40-2	TOPICAL	GEL	97.5	%W/W
SD ALCOHOL 40–2	TOPICAL	GEL	97.5	%
SD ALCOHOL 40B			56.09	%W/W
SEPINEO P 600	TOPICAL	GEL	4	%W/W
SHEA BUTTER		AUGMENTED	2	%W/W
SHEA BUTTER	AUGMENTED	TOPICAL	2	%W/W
SILICON			0.4	%W/W
SILICON	TOPICAL	EMULSION, CREAM	0.4	%
SILICON	TOPICAL	LOTION	92.5	%
SILICON DIOXIDE			0.6	MG
SILICON DIOXIDE			19	%
SILICON DIOXIDE			1.01	%
SILICON DIOXIDE			49	MG
SILICON DIOXIDE	ENDOCERVICAL	GEL	8	%
SILICON DIOXIDE	NASAL	GEL	4	%
SILICON DIOXIDE	TOPICAL	GEL	0.25	%
SILICON DIOXIDE	TOPICAL	GEL	0.25	%W/W
SILICON DIOXIDE	VAGINAL	EMULSION, CREAM	1	%
SILICON DIOXIDE	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	0.75	%W/W
SILICON DIOXIDE, COLLOIDAL	RECTAL	SUPPOSITORY	14	MG
SILICON DIOXIDE, COLLOIDAL	TRANSDERMAL	FILM, CONTROLLED RELEASE	49	MG
SILICON DIOXIDE, COLLOIDAL	VAGINAL	EMULSION, CREAM	1.01	%
SILICONE			353.51	MG
SILICONE	TRANSDERMAL	FILM, CONTROLLED RELEASE	353.51	MG
SILICONE	VAGINAL	DRUG DELIVERY SYSTEM	8.7	MG

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
SILICONE ADHESIVE 4102	PERCUTANEOUS	PATCH, CONTROLLED RELEASE	165	CMS
SILICONE ADHESIVE 4102	TRANSDERMAL	FILM, CONTROLLED RELEASE	228.23	MG
SILICONE EMULSION	TOPICAL	LOTION	0.5	%
SILICONE/POLYESTER FILM STRIP			873	MG
SILICONE/POLYESTER FILM STRIP	TRANSDERMAL	PATCH	485.2	MG
SILICONE/POLYESTER FILM STRIP	TRANSDERMAL	FILM, CONTROLLED RELEASE	873	MG
SIMETHICONE			0.2	%W/W
SIMETHICONE	TOPICAL	LOTION	0.5	%
SIMETHICONE	TOPICAL	EMULSION, CREAM	1	%
SIMETHICONE EMULSION			0.2	%W/W
SIMETHICONE EMULSION			0.2	%W/W
SIMETHICONE EMULSION		TOPICAL	0.2	%W/W
SIMETHICONE EMULSION		TOPICAL	0.2	%W/W
SIMETHICONE EMULSION			0.2	%W/W
SIMETHICONE EMULSION	TOPICAL	EMULSION, CREAM	0.2	%
SIPON LS 20NP			38	%W/W
SODIUM ACETATE, ANHYDROUS	TOPICAL	EMULSION, CREAM	0.02	%
SODIUM BENZOATE			0.08	%
SODIUM BENZOATE			0.2	%W/W
SODIUM BENZOATE			0.2	%W/W
SODIUM BENZOATE	BUCCAL	FILM	0.96	MG
SODIUM BENZOATE	BUCCAL	FILM	0.69	MG
SODIUM BENZOATE	RECTAL	GEL	2.54	%
SODIUM BENZOATE	TOPICAL	EMULSION, CREAM	0.2	%
SODIUM BENZOATE	TOPICAL	PATCH	0.44	MG
SODIUM BENZOATE	TOPICAL	GEL	0.24	%W/W
SODIUM BICARBONATE			0.6	MG
SODIUM BICARBONATE	BUCCAL	GUM	7.2	MG
SODIUM BICARBONATE	BUCCAL	GUM, CHEWING	25	MG
SODIUM BICARBONATE	ORAL	GUM, CHEWING	15	MG
SODIUM BISULFITE			0.3	%W/W
SODIUM BISULFITE	IONTOPHORESIS	SOLUTION	0.055	%
SODIUM BISULFITE	TOPICAL	LOTION	0.22	%
SODIUM BISULFITE	TOPICAL	EMULSION, CREAM	0.3	%
SODIUM CARBONATE	BUCCAL	GUM	14.4	MG
SODIUM CARBONATE	BUCCAL	GUM, CHEWING	30	MG
SODIUM CARBONATE	ORAL	GUM, CHEWING	10	MG
SODIUM CETEARYL SULFATE	TOPICAL	EMULSION, CREAM	1	%
SODIUM CETOSTEARYL SULFATE			1	%W/W
SODIUM CHLORIDE	IONTOPHORESIS	DRUG DELIVERY SYSTEM	0.6	MG
SODIUM CHLORIDE	IONTOPHORESIS	SOLUTION	0.6	%
SODIUM CHLORIDE	IONTOPHORESIS	PATCH, CONTROLLED RELEASE	3.1	MG
SODIUM CHLORIDE	OPHTHALMIC	GEL	0.9	%
SODIUM CHLORIDE	OPHTHALMIC	GEL	0.9	%
SODIUM CHLORIDE	RECTAL	SUPPOSITORY	52.5	MG
SODIUM CHLORIDE	TOPICAL	LOTION	0.27	%
SODIUM CHLORIDE	TOPICAL	EMULSION, CREAM	0.5	%
SODIUM CHLORIDE	TOPICAL	PATCH, CONTROLLED RELEASE	3.1	MG
SODIUM CHLORIDE	TOPICAL	GEL	0.18	%W/W

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
SODIUM CHLORIDE	TRANSDERMAL	DRUG DELIVERY SYSTEM	0.6	MG
SODIUM CITRATE	IONTOPHORESIS	DRUG DELIVERY SYSTEM	2.2	MG
SODIUM CITRATE	TOPICAL	EMULSION, LOTION	0.08	%
SODIUM CITRATE	TOPICAL	EMULSION, CREAM	0.319	%
SODIUM CITRATE	TRANSDERMAL	DRUG DELIVERY SYSTEM	2.2	MG
SODIUM CITRATE	VAGINAL	SPONGE	7.6	MG
SODIUM CITRATE, ANHYDROUS	TOPICAL	EMULSION, CREAM	0.28	%
SODIUM CITRATE, UNSPECIFIED FORM			0.12	%W/W
SODIUM CITRATE, UNSPECIFIED FORM			0.12	%W/W
SODIUM CITRATE, UNSPECIFIED FORM		TOPICAL	0.12	%W/W
SODIUM CITRATE, UNSPECIFIED FORM		TOPICAL	0.12	%W/W
SODIUM CITRATE, UNSPECIFIED FORM			0.25	%W/W
SODIUM CITRATE, UNSPECIFIED FORM			0.12	%W/W
SODIUM CITRATE, UNSPECIFIED FORM			0.08	%W/W
SODIUM HYDROXIDE			0.55	%W/W
SODIUM HYDROXIDE		AUGMENTED	2.72	%W/V
SODIUM HYDROXIDE		EMULSION, SUSTAINED RELEASE	2.72	%W/V
SODIUM HYDROXIDE		TOPICAL	0.55	%W/W
SODIUM HYDROXIDE			1.84	MG
SODIUM HYDROXIDE			0.2	%W/W
SODIUM HYDROXIDE				ADJPH
SODIUM HYDROXIDE			0.52	%W/W
SODIUM HYDROXIDE				ADJ PH
SODIUM HYDROXIDE			0.022	%W/W
SODIUM HYDROXIDE			0.19	%
SODIUM HYDROXIDE			0.85	MG
SODIUM HYDROXIDE	AUGMENTED	TOPICAL	2.72	%W/V
SODIUM HYDROXIDE	BUCCAL	FILM	0.09	MG
SODIUM HYDROXIDE	BUCCAL	FILM	1.18	MG
SODIUM HYDROXIDE	EMULSION, SUSTAINED RELEASE	TOPICAL	2.72	%W/V
SODIUM HYDROXIDE	IONTOPHORESIS	DRUG DELIVERY SYSTEM	4.2	MG
SODIUM HYDROXIDE	OPHTHALMIC	GEL	1.69	%
SODIUM HYDROXIDE	OPHTHALMIC	GEL	1.69	%
SODIUM HYDROXIDE	TOPICAL	JELLY	0.0134	%
SODIUM HYDROXIDE	TOPICAL	EMULSION, LOTION	0.022	%
SODIUM HYDROXIDE	TOPICAL	OINTMENT, AUGMENTED	0.106	%
SODIUM HYDROXIDE	TOPICAL	EMULSION, CREAM	0.52	%
SODIUM HYDROXIDE	TOPICAL	LOTION	2.6	%
SODIUM HYDROXIDE	TOPICAL	CREAM, AUGMENTED	2.72	%
SODIUM HYDROXIDE	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	2.72	%
SODIUM HYDROXIDE	TOPICAL	GEL	10	%
SODIUM HYDROXIDE	TOPICAL	GEL	3.2	%W/W
SODIUM HYDROXIDE	TOPICAL	GEL	0.0684	ADJ PH
SODIUM HYDROXIDE	TRANSDERMAL	FILM, CONTROLLED RELEASE	0.85	MG
SODIUM HYDROXIDE	TRANSDERMAL	DRUG DELIVERY SYSTEM	4.2	MG
SODIUM HYDROXIDE	TRANSDERMAL	GEL	4.72	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
SODIUM HYDROXIDE	TRANSDERMAL	GEL	4.72	%
SODIUM HYDROXIDE	TRANSDERMAL	GEL		ADJ PH
SODIUM HYDROXIDE	TRANSDERMAL	GEL, METERED	7	%
SODIUM HYDROXIDE	VAGINAL	EMULSION, CREAM	0.1881	%
SODIUM HYDROXIDE	VAGINAL	GEL	0.25	%
SODIUM HYDROXIDE	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	0.025	%
SODIUM HYDROXIDE	VAGINAL	GEL	0.25	%
SODIUM LACTATE	TOPICAL	GEL	0.77	%
SODIUM LACTATE	TOPICAL	GEL	0.77	%W/W
SODIUM LAURETH-5 SULFATE	TOPICAL	EMULSION, CREAM	1	%
SODIUM LAUROYL SARCOSINATE	TOPICAL	LOTION	7.5	%
SODIUM LAURYL SULFATE			0.75	%W/W
SODIUM LAURYL SULFATE		TOPICAL	0.75	%W/W
SODIUM LAURYL SULFATE			1.47	%
SODIUM LAURYL SULFATE			2.5	%W/W
SODIUM LAURYL SULFATE			0.33	%W/W
SODIUM LAURYL SULFATE	TOPICAL	LOTION	0.5	%
SODIUM LAURYL SULFATE	TOPICAL	OINTMENT	1	%
SODIUM LAURYL SULFATE	TOPICAL	EMULSION, CREAM	2.5	%
SODIUM LAURYL SULFATE	TOPICAL	GEL	0.05	%W/W
SODIUM LAURYL SULFATE	VAGINAL	EMULSION, CREAM	0.333	%
SODIUM LAURYL SULFATE	VAGINAL	CREAM	0.3	%W/W
SODIUM LAURYL SULFATE	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	0.3	%W/W
SODIUM METABISULFITE		AUGMENTED	0.2	%W/W
SODIUM METABISULFITE	AUGMENTED	TOPICAL	0.2	%W/W
SODIUM METABISULFITE	IONTOPHORESIS	SOLUTION	0.05	%
SODIUM METABISULFITE	IONTOPHORESIS	PATCH, CONTROLLED RELEASE	0.5	MG
SODIUM METABISULFITE	TOPICAL	EMULSION, CREAM	0.03	%
SODIUM METABISULFITE	TOPICAL	CREAM, AUGMENTED	0.2	%
SODIUM METABISULFITE	TOPICAL	PATCH, CONTROLLED RELEASE	0.5	MG
SODIUM METABISULFITE	VAGINAL	SPONGE	1.5	MG
SODIUM PHOSPHATE	TOPICAL	OINTMENT	0.15	%
SODIUM PHOSPHATE, DIBASIC	TOPICAL	EMULSION, CREAM	0.2	%
SODIUM PHOSPHATE, DIBASIC, ANHYDROUS			0.054	MG
SODIUM PHOSPHATE, DIBASIC, ANHYDROUS			4.066	MG
SODIUM PHOSPHATE, DIBASIC, ANHYDROUS			0.09	%W/W
SODIUM PHOSPHATE, DIBASIC, ANHYDROUS			0.36	%W/W
SODIUM PHOSPHATE, DIBASIC, ANHYDROUS	BUCCAL	FILM	0.35	MG
SODIUM PHOSPHATE, DIBASIC, ANHYDROUS	TOPICAL	OINTMENT	0.026	%
SODIUM PHOSPHATE, DIBASIC, ANHYDROUS	TOPICAL	LOTION	0.1	%
SODIUM PHOSPHATE, DIBASIC, ANHYDROUS	TOPICAL	EMULSION, CREAM	0.36	%
SODIUM PHOSPHATE, DIBASIC, ANHYDROUS	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	0.09	%
SODIUM PHOSPHATE, DIBASIC, DIHYDRATE			0.25	%W/W
SODIUM PHOSPHATE, DIBASIC, DIHYDRATE	TOPICAL	EMULSION, CREAM	0.25	%
SODIUM PHOSPHATE, DIBASIC, DIHYDRATE	TOPICAL	GEL	0.003	%W/W
SODIUM PHOSPHATE, DIBASIC, HEPTAHYDRATE		EMULSION, SUSTAINED RELEASE	0.2	%W/W
SODIUM PHOSPHATE, DIBASIC, HEPTAHYDRATE			0.34	%W/W
SODIUM PHOSPHATE, DIBASIC, HEPTAHYDRATE	EMULSION, SUSTAINED RELEASE	TOPICAL	0.2	%W/W
SODIUM PHOSPHATE, DIBASIC, HEPTAHYDRATE	TOPICAL	OINTMENT	0.15	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
SODIUM PHOSPHATE, DIBASIC, HEPTAHYDRATE	TOPICAL	EMULSION, CREAM	0.39	%
SODIUM PHOSPHATE, DIBASIC, HEPTAHYDRATE	TOPICAL	LOTION	1.59	%
SODIUM PHOSPHATE, DIBASIC, HEPTAHYDRATE	URETHRAL	INJECTION	2	%
SODIUM PHOSPHATE, DIBASIC, UNSPECIFIED FORM			0.1	%W/W
SODIUM PHOSPHATE, MONOBASIC	IONTOPHORESIS	PATCH, CONTROLLED RELEASE	14.2	MG
SODIUM PHOSPHATE, MONOBASIC	TOPICAL	LOTION, AUGMENTED	0.2	%
SODIUM PHOSPHATE, MONOBASIC	TOPICAL	EMULSION, CREAM	0.265	%
SODIUM PHOSPHATE, MONOBASIC	TOPICAL	LOTION	0.3	%
SODIUM PHOSPHATE, MONOBASIC	TOPICAL	PATCH, CONTROLLED RELEASE	14.2	MG
SODIUM PHOSPHATE, MONOBASIC, ANHYDROUS			0.3	%W/W
SODIUM PHOSPHATE, MONOBASIC, ANHYDROUS				ADJPH
SODIUM PHOSPHATE, MONOBASIC, ANHYDROUS	BUCCAL	FILM	1.09	MG
SODIUM PHOSPHATE, MONOBASIC, ANHYDROUS	TOPICAL	EMULSION, CREAM	0.5	%
SODIUM PHOSPHATE, MONOBASIC, ANHYDROUS	TOPICAL	LOTION	0.6	%
SODIUM PHOSPHATE, MONOBASIC, ANHYDROUS	TOPICAL	GEL	0.3	%W/W
SODIUM PHOSPHATE, MONOBASIC, DIHYDRATE	TOPICAL	GEL	0.022	%W/W
SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE			0.3	%W/W
SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE	TOPICAL	LOTION, AUGMENTED	0.15	%
SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE	TOPICAL	LOTION	0.2	%
SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE	TOPICAL	EMULSION, CREAM	0.3	%
SODIUM PHOSPHATE, MONOBASIC, UNSPECIFIED FORM		AUGMENTED	0.2	%W/W
SODIUM PHOSPHATE, MONOBASIC, UNSPECIFIED FORM		EMULSION, SUSTAINED RELEASE	0.27	%W/W
SODIUM PHOSPHATE, MONOBASIC, UNSPECIFIED FORM			0.27	%W/W
SODIUM PHOSPHATE, MONOBASIC, UNSPECIFIED FORM	AUGMENTED	TOPICAL	0.2	%W/W
SODIUM PHOSPHATE, MONOBASIC, UNSPECIFIED FORM	BUCCAL	FILM	0.47	MG
SODIUM PHOSPHATE, MONOBASIC, UNSPECIFIED FORM	BUCCAL	FILM	0.76	MG
SODIUM PHOSPHATE, MONOBASIC, UNSPECIFIED FORM	EMULSION, SUSTAINED RELEASE	TOPICAL	0.27	%W/W
SODIUM PHOSPHATE, TRIBASIC	BUCCAL	FILM	0.76	MG
SODIUM POLYACRYLATE (2500000 MW)			700	MG
SODIUM PYRROLIDONE CARBOXYLATE	TOPICAL	LOTION	5.2	%
SODIUM SULFITE			0.2	%W/W
SODIUM SULFITE	TOPICAL	EMULSION, CREAM	0.2	%
SODIUM SULFOSUCCINATED UNDECYCLENIC MONOALKYLOLAMIDE	TOPICAL	LOTION	0.1	%
SODIUM THIOSULFATE			0.1	%W/W
SODIUM THIOSULFATE		AUGMENTED	0.1	%W/V
SODIUM THIOSULFATE		EMULSION, SUSTAINED RELEASE	0.1	%W/V
SODIUM THIOSULFATE		TOPICAL	0.1	%W/W
SODIUM THIOSULFATE	AUGMENTED	TOPICAL	0.1	%W/V
SODIUM THIOSULFATE	EMULSION, SUSTAINED RELEASE	TOPICAL	0.1	%W/V
SODIUM THIOSULFATE	TOPICAL	CREAM, AUGMENTED	0.1	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
SODIUM THIOSULFATE	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	0.1	%
SORBIC ACID			0.07	%W/W
SORBIC ACID			0.1	%W/W
SORBIC ACID		EMULSION, SUSTAINED RELEASE	0.2	%W/W
SORBIC ACID		TOPICAL	0.07	%W/W
SORBIC ACID		TOPICAL	0.1	%W/W
SORBIC ACID			0.15	%W/W
SORBIC ACID			0.75	%W/W
SORBIC ACID	EMULSION, SUSTAINED RELEASE	TOPICAL	0.2	%W/W
SORBIC ACID	TOPICAL	OINTMENT	0.1	%
SORBIC ACID	TOPICAL	GEL	0.175	%
SORBIC ACID	TOPICAL	LOTION	0.2	%
SORBIC ACID	TOPICAL	EMULSION, CREAM	2.7	%
SORBIC ACID	TOPICAL	GEL	0.18	%W/W
SORBIC ACID	VAGINAL	GEL	0.09	%
SORBIC ACID	VAGINAL	SPONGE	6	MG
SORBIC ACID	VAGINAL	GEL	0.09	%
SORBITAN MONOLAURATE			4.74	%W/W
SORBITAN MONOLAURATE	TOPICAL	GEL	1	%W/W
SORBITAN MONOOLEATE			0.4	%W/W
SORBITAN MONOOLEATE		AUGMENTED	0.2	%W/V
SORBITAN MONOOLEATE		EMULSION, SUSTAINED RELEASE	3.5	%W/W
SORBITAN MONOOLEATE		TOPICAL	0.4	%W/W
SORBITAN MONOOLEATE			2.5	%W/W
SORBITAN MONOOLEATE			3.5	%W/W
SORBITAN MONOOLEATE	AUGMENTED	TOPICAL	0.2	%W/V
SORBITAN MONOOLEATE	EMULSION, SUSTAINED RELEASE	TOPICAL	3.5	%W/W
SORBITAN MONOOLEATE	RECTAL	SUPPOSITORY	22	MG
SORBITAN MONOOLEATE	TOPICAL	CREAM, AUGMENTED	0.2	%
SORBITAN MONOOLEATE	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	0.2	%
SORBITAN MONOOLEATE	TOPICAL	EMULSION, CREAM	3.5	%
SORBITAN MONOOLEATE	TOPICAL	LOTION	7	%
SORBITAN MONOOLEATE	TOPICAL	GEL	0.2	%W/W
SORBITAN MONOPALMITATE			2	%W/W
SORBITAN MONOPALMITATE	TOPICAL	LOTION	1	%
SORBITAN MONOPALMITATE	TOPICAL	EMULSION, CREAM	2	%
SORBITAN MONOPALMITATE	TOPICAL	PATCH	10.5	MG
SORBITAN MONOSTEARATE			1.95	%W/W
SORBITAN MONOSTEARATE			8	%W/W
SORBITAN MONOSTEARATE		AUGMENTED	2	%W/W
SORBITAN MONOSTEARATE		EMULSION, SUSTAINED RELEASE	5	%W/W
SORBITAN MONOSTEARATE		TOPICAL	1.95	%W/W
SORBITAN MONOSTEARATE		TOPICAL	8	%W/W
SORBITAN MONOSTEARATE			6	%W/W
SORBITAN MONOSTEARATE			5	%
SORBITAN MONOSTEARATE	AUGMENTED	TOPICAL	2	%W/W
SORBITAN MONOSTEARATE	EMULSION, SUSTAINED RELEASE	TOPICAL	5	%W/W
SORBITAN MONOSTEARATE	TOPICAL	LOTION	2.5	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
SORBITAN MONOSTEARATE	TOPICAL	EMULSION, CREAM	8	%
SORBITAN MONOSTEARATE	VAGINAL	CREAM, AUGMENTED	2	%
SORBITAN MONOSTEARATE	VAGINAL	EMULSION, CREAM	5	%
SORBITAN MONOSTEARATE	VAGINAL	CREAM, AUGMENTED	2	%
SORBITAN SESQUIOLEATE	TOPICAL	OINTMENT	2	%
SORBITAN TRISTEARATE		AUGMENTED	0.5	%W/W
SORBITAN TRISTEARATE	AUGMENTED	TOPICAL	0.5	%W/W
SORBITOL			10	%W/W
SORBITOL		TOPICAL	10	%W/W
SORBITOL			7	%W/W
SORBITOL			5	%W/W
SORBITOL	BUCCAL	GUM, CHEWING	257	MG
SORBITOL	ORAL	GUM, CHEWING	257	MG
SORBITOL	TOPICAL	EMULSION, CREAM	67.52	%
SORBITOL SOLUTION			3.25	%W/W
SORBITOL SOLUTION			13.5	%W/W
SORBITOL SOLUTION			17.5	MG/1G
SORBITOL SOLUTION		AUGMENTED	15	%W/W
SORBITOL SOLUTION		EMULSION, SUSTAINED RELEASE	36.8	%W/W
SORBITOL SOLUTION		TOPICAL	3.25	%W/W
SORBITOL SOLUTION		TOPICAL	13.5	%W/W
SORBITOL SOLUTION		TOPICAL	17.5	MG/1G
SORBITOL SOLUTION			25	%W/W
SORBITOL SOLUTION			36.8	%
SORBITOL SOLUTION			2800	MG
SORBITOL SOLUTION	AUGMENTED	TOPICAL	15	%W/W
SORBITOL SOLUTION	BUCCAL	GUM, CHEWING	45	MG
SORBITOL SOLUTION	EMULSION, SUSTAINED RELEASE	TOPICAL	36.8	%W/W
SORBITOL SOLUTION	ORAL	GUM, CHEWING	45	MG
SORBITOL SOLUTION	TOPICAL	OINTMENT	1.5	%
SORBITOL SOLUTION	TOPICAL	LOTION	5	%
SORBITOL SOLUTION	TOPICAL	CREAM, AUGMENTED	15	%
SORBITOL SOLUTION	TOPICAL	EMULSION, CREAM	25	%
SORBITOL SOLUTION	VAGINAL	EMULSION, CREAM	36.8	%
SORBITOL SOLUTION	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	36.8	%W/W
SOYBEAN			3	%W/W
SOYBEAN OIL	TOPICAL	LOTION	50.2	%
SPERMACETI			11	%W/W
SPERMACETI			3	%
SPERMACETI	TOPICAL	EMULSION, CREAM	11	%
SPERMACETI	VAGINAL	EMULSION, CREAM	3	%
SQUALANE		AUGMENTED	6	%W/W
SQUALANE			6	%W/W
SQUALANE	AUGMENTED	TOPICAL	6	%W/W
SQUALANE	TOPICAL	EMULSION, CREAM	6	%
STEARALKONIUM CHLORIDE	TOPICAL	LOTION	3.15	%
STEARAMIDOETHYL DIETHYLAMINE			2.5	%
STEARAMIDOETHYL DIETHYLAMINE	TOPICAL	EMULSION, CREAM	0.6	%
STEARAMIDOETHYL DIETHYLAMINE	VAGINAL	EMULSION, CREAM	2.5	%
STEARETH-100			0.35	%W/W
STEARETH-100	TOPICAL	EMULSION, CREAM	0.35	%
STEARETH-100	TOPICAL	OINTMENT	0.6	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
STEARETH-2		EMULSION, SUSTAINED RELEASE	0.85	%W/W
STEARETH-2			4.5	%W/W
STEARETH-2	EMULSION, SUSTAINED RELEASE	TOPICAL	0.85	%W/W
STEARETH-2	TOPICAL	LOTION	0.4	%
STEARETH-2	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	0.85	%
STEARETH-2	TOPICAL	EMULSION, CREAM	4.5	%
STEARETH-2	TOPICAL	OINTMENT	5	%
STEARETH-20		EMULSION, SUSTAINED RELEASE	4.15	%W/W
STEARETH-20	EMULSION, SUSTAINED RELEASE	TOPICAL	4.15	%W/W
STEARETH-20	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	4.15	%
STEARETH-21		EMULSION, SUSTAINED RELEASE	2.5	%W/W
STEARETH-21			3	%W/W
STEARETH-21	EMULSION, SUSTAINED RELEASE	TOPICAL	2.5	%W/W
STEARETH-21	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	2.5	%
STEARETH-21	TOPICAL	EMULSION, CREAM	3	%
STEARETH-21	TOPICAL	LOTION	3	%
STEARETH-40			0.92	%W/W
STEARETH-40			12	%W/W
STEARIC ACID		AUGMENTED	3	%W/W
STEARIC ACID		EMULSION, SUSTAINED RELEASE	16	%W/W
STEARIC ACID			8	%W/W
STEARIC ACID			22.5	%W/W
STEARIC ACID			5	%W/W
STEARIC ACID			4	%
STEARIC ACID			14	%
STEARIC ACID	AUGMENTED	TOPICAL	3	%W/W
STEARIC ACID	EMULSION, SUSTAINED RELEASE	TOPICAL	16	%W/W
STEARIC ACID	TOPICAL	CREAM, AUGMENTED	3	%
STEARIC ACID	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	4	%
STEARIC ACID	TOPICAL	OINTMENT	15	%
STEARIC ACID	TOPICAL	LOTION	20	%
STEARIC ACID	TOPICAL	EMULSION, CREAM	22.6	%
STEARIC ACID	VAGINAL	EMULSION, CREAM	14	%
STEAROXYTRIMETHYLSILANE		AUGMENTED	1	%W/W
STEAROXYTRIMETHYLSILANE	AUGMENTED	TOPICAL	1	%W/W
STEAROXYTRIMETHYLSILANE	TOPICAL	CREAM, AUGMENTED	1	%
STEAROYL POLYOXYLGLYCERIDES			7.5	%W/W
STEAROYL POLYOXYLGLYCERIDES		TOPICAL	7.5	%W/W
STEARTRIMONIUM HYDROLYZED ANIMAL COLLAGEN	TOPICAL	LOTION	0.5	%
STEARYL ALCOHOL			3.8	%W/W
STEARYL ALCOHOL			13	%W/W
STEARYL ALCOHOL		AUGMENTED	4	%W/W

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
STEARYL ALCOHOL		EMULSION, SUSTAINED RELEASE	15	%W/W
STEARYL ALCOHOL		TOPICAL	3.8	%W/W
STEARYL ALCOHOL		TOPICAL	13	%W/W
STEARYL ALCOHOL			1	%W/W
STEARYL ALCOHOL			30	%W/W
STEARYL ALCOHOL			42.5	%W/W
STEARYL ALCOHOL	AUGMENTED	TOPICAL	4	%W/W
STEARYL ALCOHOL	EMULSION, SUSTAINED RELEASE	TOPICAL	15	%W/W
STEARYL ALCOHOL	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	3	%
STEARYL ALCOHOL	TOPICAL	CREAM, AUGMENTED	4	%
STEARYL ALCOHOL	TOPICAL	OINTMENT	8	%
STEARYL ALCOHOL	TOPICAL	LOTION	12	%
STEARYL ALCOHOL	TOPICAL	EMULSION, CREAM	30	%
STEARYL ALCOHOL	VAGINAL	EMULSION, CREAM	42.5	%
STEARYL ALCOHOL	VAGINAL	CREAM	7	%W/W
STEARYL ALCOHOL	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	8.4	%W/W
STEARYL CITRATE	TOPICAL	OINTMENT	0.75	%
SUCRALOSE			5.5	MG
SUCRALOSE	BUCCAL	GUM, CHEWING	3.5	MG
SUCROSE	TOPICAL	OINTMENT	20	%
SUCROSE DISTEARATE			5	%W/W
SUCROSE DISTEARATE	TOPICAL	EMULSION, CREAM	5	%
SULFACETAMIDE SODIUM			3.01	%W/W
T-BUTYLHYDROQUINONE	VAGINAL	EMULSION, CREAM	0.02	%
TALC	TOPICAL	LOTION	7.28	%
TALC	TOPICAL	OINTMENT	8.27	%
TALLOW GLYCERIDES			2.55	%W/W
TALLOW GLYCERIDES			2.78	%W/W
TALLOW GLYCERIDES	TOPICAL	EMULSION, CREAM	2.78	%
TARTARIC ACID				ADJPH
TEGACID			16	%W/W
TENOX			0.025	%W/W
TENOX	TOPICAL	EMULSION, CREAM	0.025	%
TENOX	TOPICAL	OINTMENT	0.025	%
TENOX-2	TOPICAL	OINTMENT	0.025	%
TERT-BUTYL ALCOHOL	TOPICAL	GEL	0.12	%W/W
TERT-BUTYLHYDROQUINONE			0.02	%
TERT-BUTYLHYDROQUINONE	VAGINAL	CREAM	0.02	%W/W
THIMEROSAL	TOPICAL	EMULSION, CREAM	0.005	%
THIMEROSAL	TOPICAL	OINTMENT	0.04	%
TITANIUM DIOXIDE			0.25	%W/W
TITANIUM DIOXIDE			1	%W/W
TITANIUM DIOXIDE			1.66	MG
TITANIUM DIOXIDE			2.78	MG
TITANIUM DIOXIDE		TOPICAL	0.25	%W/W
TITANIUM DIOXIDE		TOPICAL	1	%W/W
TITANIUM DIOXIDE			0.6	MG
TITANIUM DIOXIDE			2	%W/W
TITANIUM DIOXIDE	BUCCAL	GUM	7.58	MG
TITANIUM DIOXIDE	BUCCAL	GUM, CHEWING	7.58	MG
TITANIUM DIOXIDE	TOPICAL	EMULSION, CREAM	2	%
TITANIUM DIOXIDE	TOPICAL	OINTMENT	5	%

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
TITANIUM DIOXIDE	TOPICAL	GEL	0.063	%W/W
TOCOPHEROL	TOPICAL	OINTMENT	0.002	%
TRIACETIN	TRANSDERMAL	PATCH	22.1	MG
TRIETHANOLAMINE LAURYL SULFATE			10.78	%W/W
TRIETHANOLAMINE LAURYL SULFATE			0.13	%W/W
TRIGLYCERIDES, MEDIUM CHAIN	TOPICAL	GEL	1	%
TRIGLYCERIDES, MEDIUM CHAIN	TOPICAL	CREAM, AUGMENTED	1.37	%
TRIGLYCERIDES, MEDIUM CHAIN	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	1.37	%
TRIGLYCERIDES, MEDIUM CHAIN	TOPICAL	EMULSION, CREAM	15	%
TRIHYDROXYSTEARIN	TOPICAL	OINTMENT	3	%
TRILANETH-4 PHOSPHATE	TOPICAL	OINTMENT	1.9	%
TRILAURETH-4 PHOSPHATE	TOPICAL	OINTMENT	4.7	%
TRIMETHYLSILYL TREATED DIMETHICONOL/ TRIMETHYLSILOXYSILICATE CROSSPOLYMER (35/65 W/W; 50000000 PA.S)			171.17	MG
TRIMETHYLSILYL TREATED DIMETHICONOL/ TRIMETHYLSILOXYSILICATE CROSSPOLYMER (40/60 W/W; 5000000 PA.S)			228.23	MG
TRISODIUM CITRATE DIHYDRATE			0.08	%W/W
TRISODIUM CITRATE DIHYDRATE		TOPICAL	0.08	%W/W
TRISODIUM CITRATE DIHYDRATE			3.62	MG
TRISODIUM CITRATE DIHYDRATE			0.1	%W/W
TRISODIUM CITRATE DIHYDRATE	TOPICAL	LOTION	0.32	%
TRISODIUM CITRATE DIHYDRATE	TOPICAL	GEL	0.14	%W/W
TROLAMINE		AUGMENTED	1	%W/W
TROLAMINE		EMULSION, SUSTAINED RELEASE	0.4	%W/W
TROLAMINE			0.5	%W/W
TROLAMINE			2.6	%W/W
TROLAMINE			1	%W/W
TROLAMINE			0.75	%
TROLAMINE	AUGMENTED	TOPICAL	1	%W/W
TROLAMINE	EMULSION, SUSTAINED RELEASE	TOPICAL	0.4	%W/W
TROLAMINE	TOPICAL	EMULSION, CREAM	1	%
TROLAMINE	TOPICAL	GEL	1	%
TROLAMINE	TOPICAL	LOTION	31.7	%
TROLAMINE	TOPICAL	GEL	1	%W/W
TROLAMINE	TRANSDERMAL	GEL	0.35	%
TROLAMINE	TRANSDERMAL	GEL	0.35	%
TROLAMINE	VAGINAL	EMULSION, CREAM	0.75	%
TROLAMINE LAURYL SULFATE	TOPICAL	EMULSION, CREAM	0.13	%
TROMETHAMINE	TOPICAL	GEL	0.8	%
TROMETHAMINE	TOPICAL	GEL	0.8	%W/W
TROMETHAMINE	TRANSDERMAL	GEL	0.5	%
TROMETHAMINE	TRANSDERMAL	GEL	0.1	%W/W
TROMETHAMINE	URETHRAL	SOLUTION	0.121	%
TYLOXAPOL	OPHTHALMIC	GEL	0.05	%
TYLOXAPOL	OPHTHALMIC	GEL	0.05	%
UNION 76 AMSCO-RES 6038			5.7	MG
UNION 76 AMSCO-RES 6038	TRANSDERMAL	FILM, CONTROLLED RELEASE	5.7	MG
UREA			0.64	%
UREA	VAGINAL	EMULSION, CREAM	0.64	%
VEGETABLE OIL			3.5	%W/W

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
VEGETABLE OIL	BUCCAL	GUM, CHEWING	14.4	MG
VEGETABLE OIL	TOPICAL	EMULSION, CREAM	3.5	%
VEGETABLE OIL GLYCERIDE, HYDROGENATED	RECTAL	SUPPOSITORY	870	MG
VEGETABLE OIL, HYDROGENATED	RECTAL	SUPPOSITORY	2026.5	MG
VEGETABLE OIL, HYDROGENATED	TOPICAL	EMULSION, CREAM	72	%
VEGETABLE OIL, HYDROGENATED	VAGINAL	EMULSION, CREAM	72	%
VEGETABLE OIL, HYDROGENATED	VAGINAL	SUPPOSITORY	2400	MG
VISCARIN	TOPICAL	LOTION	1	%
VISCOSE/COTTON			84	MG
VISCOSE/COTTON	TRANSDERMAL	FILM, CONTROLLED RELEASE	84	MG
WAX, DEHYDAG	TOPICAL	EMULSION, CREAM	8.5	%
WAX, EMULSIFYING	TOPICAL	OINTMENT	1.5	%
WAX, EMULSIFYING	TOPICAL	LOTION	4	%
WAX, EMULSIFYING	TOPICAL	EMULSION, CREAM	24.8	%
WAX, WHITE	RECTAL	SUPPOSITORY	265	MG
WAX, WHITE	TOPICAL	EMULSION, CREAM	6	%
WAX, WHITE	TOPICAL	OINTMENT, AUGMENTED	6.75	%
WAX, WHITE	TOPICAL	OINTMENT	7.3	%
WAX, WHITE	TOPICAL	CREAM, AUGMENTED	10	%
WAX, WHITE	VAGINAL	EMULSION, CREAM	2	%
WECOBEE FS			67.2	%W/W
WECOBEE FS			1495	MG
WECOBEE FS	VAGINAL	SUPPOSITORY	1700	MG
WHITE CERESIN WAX	VAGINAL	EMULSION, CREAM	7	%
WHITE WAX			1	%W/W
WHITE WAX			1.5	%W/W
WHITE WAX			1.25	%W/W
WHITE WAX		AUGMENTED	10	%W/W
WHITE WAX		TOPICAL	1	%W/W
WHITE WAX		TOPICAL	1.5	%W/W
WHITE WAX		TOPICAL	1.25	%W/W
WHITE WAX			6	%W/W
WHITE WAX			2	%
WHITE WAX	AUGMENTED	TOPICAL	10	%W/W
XANTHAN GUM		AUGMENTED	0.22	%W/W
XANTHAN GUM		EMULSION, SUSTAINED RELEASE	0.75	%W/W
XANTHAN GUM			0.3	MG
XANTHAN GUM			0.27	%W/W
XANTHAN GUM			0.75	%W/W
XANTHAN GUM	AUGMENTED	TOPICAL	0.22	%W/W
XANTHAN GUM	EMULSION, SUSTAINED RELEASE	TOPICAL	0.75	%W/W
XANTHAN GUM	TOPICAL	LOTION	0.18	%
XANTHAN GUM	TOPICAL	CREAM, AUGMENTED	0.215	%
XANTHAN GUM	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	0.3	%
XANTHAN GUM	TOPICAL	EMULSION, CREAM	0.75	%
XANTHAN GUM	TOPICAL	GEL	2.85	%W/W
XYLITOL			4.76	MG
XYLITOL	BUCCAL	GUM	492.01	MG

(*Continued*)

Ingredient	Route	Dosage FoRM	Quantity	Unit
XYLITOL	BUCCAL	GUM, CHEWING	506.13	MG
YELLOW WAX			5	%W/W
YELLOW WAX	VAGINAL	CREAM, EMULSION, SUSTAINED RELEASE	10	MG/GM
ZINC ACETATE	TOPICAL	LOTION	1.2	%
ZINC OXIDE	RECTAL	SUPPOSITORY	375	MG
ZINC STEARATE			6	%W/W

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Part II

Manufacturing Formulations

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Semisolid Formulations

ACECLOFENAC GEL CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg Tablets (g)
1.5	1	Aceclofenac	1.5
9.9	2	Miglyol® 812 (Dynamit-Nobel)	9.9
4.9	3	Lutrol E 400	4.9
64.0	4	Deionized water	64.0
19.7	5	Lutrol F 127	19.7

Manufacturing Directions

1. Mix item 1 with water and cool to approximately 5°C.
2. Add slowly Lutrol F 127 and continue stirring until it is dissolved.
3. Maintain cool until the air bubbles escape. A milky, firm gel is obtained.

ACETAMINOPHEN SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
80.00	1	Acetaminophen (micronized)	80.00
836.80	2	Hard fat (Suppocire AM®)	836.80
3.20	3	Sorbitan monostearate (Crill-3)	3.20

Manufacturing Directions

1. Fill weight is 920 mg/suppository. Stir the molten suppository mass throughout the storage period and during manufacturing and filling to avoid sedimentation of the active drug.
2. Load items 2 and 3 into the fat-melting vessel and heat to 50°C ± 3°C.
3. Transfer the molten mass to a mixer through filter sieves.
4. Set the temperature at 45°C ± 2°C.
5. Load item 1 into the mixer containing molten item 2.
6. Carefully mix the powder with molten item 2 for 20 minutes at 10 rpm, at a temperature of 45°C ± 2°C, and at a vacuum of 0.4 to 0.5 bar, then homogenize for 10 minutes at low speed.
7. Continue mixing at 10 rpm.
8. Heat the storage vessel and set the temperature at 45°C ± 2°C.
9. Transfer the molten mass from the mixer to the storage vessel.
10. Hold the mass at 45°C ± 2°C, with continuous mixing at low speed.

ACETAMINOPHEN SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
125.00	1	Acetaminophen micronized, 5% excess	131.25
785.54	2	Suppocire AM	785.54
3.21	3	Crill-3	3.21

Manufacturing Directions

1. Load item 2 in the fat-melting vessel and heat to 60°C.
2. Transfer about one-third of step 1 to a Becomix vessel through filter sieves. Set the temperature to 60°C.
3. Add item 3 to step 2. Mix at 10 rpm and homogenize at speed I for 15 minutes at 60°C under vacuum of 0.4 to 0.6 bar to dissolve.
4. Cool down to 50°C to 55°C.
5. Load item 1 in step 4 and mix at 10 rpm and homogenize at speed I for 10 minutes maintaining the temperature of 50°C to 55°C under vacuum as above to make a smooth slurry.
6. Transfer balance quantity of item 2 from step 1 into step 5 through filter sieve, set the temperature at 50°C and speed at 10 rpm, homogenize at speed II and under vacuum for 10 minutes.
7. Transfer into storage vessel and set temperature at 45°C.
8. Fill 920 mg in a suppository mold.

ACETAMINOPHEN SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
150.00	1	Acetaminophen (fine powder), excess	150.00
20.00	2	Aerosil® 200	20.00
1290.00	3	Lutrol E 1500	1290.00
554.00	4	Lutrol E 4000	554.00

Manufacturing Directions

1. Melt the mixture of items 1 and 2 in a mixture of items 3 and 4.
2. Fill the molten mass in suppository molds.
3. Average weight is 2 g.

ACETAMINOPHEN SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
500.00	1	Acetaminophen (fine powder)	500.00
100.00	2	Lutrol E 400	100.00
600.00	3	Lutrol E 1500	600.00
800.00	4	Lutrol E 4000	800.00

Manufacturing Directions

1. Fill weight is 2.09 g. Melt items 2 through 4 and add and dispense item 1.
2. Fill the molten mass in suppository molds.

ACETAMINOPHEN SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
250.00	1	Acetaminophen micronized, 5% excess	252.50
1137.50	2	Suppocire AM	1137.50

Manufacturing directions

1. Load item 2 in the fat-melting vessel and heat to 60°C.
2. Transfer step 1 to a Becomix vessel through filter sieves; set the temperature to 60°C.
3. Cool down to 50°C to 55°C and apply vacuum 0.4 to 0.6 bar.
4. Load item 1 and mix at 10 rpm and homogenize at speed I for 10 minutes, maintaining the temperature of 50°C to 55°C under vacuum as above to make a smooth slurry.
5. Transfer into storage vessel and set temperature at 45°C.
6. Fill 1390 mg in a suppository mold.

ACETAMINOPHEN SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
500.00	1	Acetaminophen micronized, 5% excess	525.00
1137.50	2	Suppocire AM	1137.50

Manufacturing Directions

1. Load item 2 in the fat-melting vessel and heat to 60°C.
2. Transfer step 1 to a Becomix vessel through filter sieves. Set the temperature to 60°C.
3. Cool down to 50°C to 55°C and apply vacuum 0.4 to 0.66 bar.
4. Load item 1 and mix at 10 rpm and homogenize at speed I for 10 minutes maintaining the temperature of 50°C to 55° C under vacuum as above to make a smooth slurry.
5. Transfer into storage vessel and set temperature at 45°C.
6. Fill 1390 mg in a suppository mold.

ACETYLSALICYLIC ACID SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
100.00	1	Acetylsalicylic acid	100.00
400.00	2	Suppocire AM	400.00

Manufacturing Directions

1. Heat item 2 to 50°C.
2. Allow to cool to 40°C and add item 1 while stirring with a turbine mixer.
3. Continue mixing and cooling and pour into molds at 35°C that were previously chilled to 0° to 5°C. Remove suppositories from molds after 7 minutes.
4. Fill to appropriate weight for strength desired.

ACNE COVER CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
37.00	1	Glyceryl stearate S/E	37.00
46.00	2	Mineral oil/lanolin alcohol (liquid base CB3939)	46.00
9.00	3	Polawax GP2000	9.00
18.00	4	Stearic acid	18.00
QS	5	Deionized water	QS
36.00	6	Propylene glycol	36.00
2.00	7	Carboxymethylcellulose (CMC-7HF)	2.00
9.00	8	Magnesium aluminum silicate (regular) Veegum®	9.00
9.00	9	Triethanolamine (99%)	9.00
120.00	10	Titanium dioxide	120.00
QS	11	Iron oxides	QS
50.00	12	Actives	50.00
QS	13	Perfume, preservative	QS

Manufacturing Directions

1. Disperse CMC in propylene glycol and triethanolamine and add warm water (60–65° C) while stirring, until the gum is hydrated.
2. Add Veegum and stir until hydrated.
3. Heat oil phase to 60°C to 65°C.
4. Add water phase to oil phase while stirring.
5. Add pigments and stir to cool, adding the actives at 30°C.
6. Homogenize using suitable equipment.
7. Fill. (*Note*: Active ingredients may be added as required to this base formula.)

ACNE TREATMENT CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Polychol 10 (Laneth-10)	20.00
5.00	2	Lanolin alcohols (Super Hartolan)	5.00
55.00	3	Cetyl alcohol C90	55.00
60.00	4	Polawax, NF	60.00
14.00	5	Sulfur	14.00
QS	6	Deionized water	QS
40.00	7	Veegum (regular)	40.00
20.00	8	Propylene glycol	20.00
20.00	9	Resorcinol	20.00
QS	10	Perfume, preservative	QS

Manufacturing Directions

1. Hydrate Veegum in water.
2. Add rest of the water-phase ingredients and heat to 70°C.
3. Heat oil phase to 70°C.
4. Disperse sulfur in the oil phase.
5. Add oil phase to water phase while stirring.
6. Stir to cool. Fill.

ACYCLOVIR CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Acyclovir: Use acyclovir micronized	52.00
5.20	2	Acyclovir: Use acyclovir micronized	52.00
1.63	3	Polyoxyl 20 cetostearyl ether (cetomacrogol 1000)	16.35
20.40	4	Propylene glycol	204.00
17.00	5	Propylene glycol	170.00
9.65	6	Petrolatum (white soft paraffin)	96.50
6.50	7	Cetostearyl alcohol	65.00
3.50	8	Mineral oil (liquid paraffin)	35.00
36.50	9	Purified water	365.00

Manufacturing Directions

1. Oil phase
   a. Load items 5 to 7 in fat-melting vessel and melt at 70°C. Maintain temperature at 70°C ± 2°C.
2. Aqueous phase
   a. Heat item 8 in mixer at 90°C. Cool down to 70°C. Add item 2 in item 8 at 70°C and stir to dissolve.
   b. Add item 4 to mixer (step 2b) and mix. Maintain temperature at 70°C ± 2°C.
3. Cream phase
   a. Add oil phase through stainless-steel filter to aqueous phase in mixer while mixing at 10 to 12 rpm, manual mode, and temperature 70°C ± 2°C.
   b. Homogenize at low speed with mixing 10 to 12 rpm, vacuum 0.4 to 0.6 bar, temperature 70°C ± 2°C for 10 minutes.
   c. Cool down to 50°C with mixing.
4. Drug phase
   a. Heat 169 g of item 3 at 50°C in water bath.
   b. Disperse item 1 in item 3 (step 4a) with the help of homogenizer. Homogenize two times with homogenizer (gap setting 1) to make smooth dispersion. Dispersion should be smooth with no gritty particles.

c. Add the drug phase from step 4b to cream base at step 3.3 in mixer.
d. Rinse the homogenizer and the container with 35 g of item 3 (50°C) and add the rinsing to cream base in mixer.

5. Final mixing
   a. Homogenize at high speed for 15 minutes at a temperature of 45°C with continuous mixing at 10 to 12 rpm.
   b. Cool down to 25°C to 30°C with continuous mixing.
   c. Unload in stainless-steel drum lined with polythene bag.

ACYCLOVIR OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.000	1	Acyclovir micronized (4% excess)	52.00
28.000	2	Polyethylene glycol 3350	280.00
41.800	3	Polyethylene glycol 400	418.00
25.000	4	Propylene glycol	250.00

Manufacturing Directions

1. Oil phase
   a. Heat items 2 and 3 to 70°C ± 2°C in mixer to melt. Cool down to 45°C with mixing.
2. Drug dispersion
   a. Disperse item 1 in 200 g of item 4 at 50°C in a water bath with the help of homogenizer. The drug dispersion should be smooth with no gritty particles.
   b. Add the drug dispersion to mixer at step 1.
   c. Rinse the container with 50 g of item 4 at 50°C and add the rinsing to mixer.
3. Final mixing
   a. Homogenize at high speed with mixing under vacuum 0.4 to 0.6 bar at 45°C ± 2°C for 30 minutes.
   b. Cool down to 25° to 30°C with continuous mixing.
   c. Unload in stainless-steel drum lined with polythene bag.

ADAPALENE CREAM

Adapalene cream, 0.1%, contains adapalene, 0.1%, in an aqueous cream emulsion consisting of carbomer 934P, cyclomethicone, edetate disodium, glycerin, methyl glucose sesquistearate, methyl paraben, PEG-20 methyl glucose sesquistearate, phenoxyethanol, propyl paraben, purified water, squalane, and trolamine.

ALCLOMETASONE DIPROPIONATE CREAM AND OINTMENT

Each gram of cream contains 0.5 mg of alclometasone dipropionate in a hydrophilic, emollient cream base of propylene glycol, white petrolatum, cetearyl alcohol, glyceryl stearate, PEG-100 stearate, ceteth-20, monobasic sodium phosphate, chlorocresol, phosphoric acid, and purified water. Each gram of ointment contains 0.5 mg of alclometasone dipropionate in an ointment base of hexylene glycol, white wax, propylene glycol stearate, and white petrolatum.

ALOE VERA GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
4.0	1	Aloe vera extract 200X	4.0
50.0	2	Propylene glycol	50.0
QS	3	Preservative	QS
736.0	4	Water	736.0
11.0	5	Cremophor RH 40	11.0
QS	6	Perfume	QS
200.0	7	Lutrol F 127	200.0

Manufacturing Directions

1. Prepare solutions items 1 to 4 and items 5 and 6 separately and add second to first mixture.
2. Cool this mixture to < 10°C (or heat to 70–80°C) and dissolve item 7. Maintain the temperature until the air bubbles escape and the appearance is clear. Viscosity should be approximately 60 Pa, pH approximately 5.5 (20–25°C) in the storage vessel.
3. Mix for 2 minutes. Store in a clean storage vessel.

ALUM CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
4.00	1	Cetostearyl alcohol	40.00
5.00	2	Octyldodecanol	50.00
4.00	3	Lanolin alcohol	40.00
2.00	4	Ethoxylated castor oil	20.00
2.00	5	White petrolatum	20.00
6.50	6	Alum (aluminum potassium sulfate, 12 H_20)	65.00
2.50	7	Cetylpyridinium ammonium chloride	25.00
95.00	8	Water purified	740.00

Manufacturing Directions

1. Heat cetostearyl alcohol, ethoxylated castor oil, lanolin alcohol, octyldodecanol, and white petrolatum that are weighed and mixed in the ratio defined above to 60°C.
2. Dissolve alum and item 7 in water at room temperature and then the solution is heated to 62°C.
3. Combine both phases in an ointment mixer and homogenize by stirring.
4. While stirring, cool the cream to approximately 30°C and supplement its weight with purified water.
5. Homogenize the cream again by stirring and then fill into an electrolyte-resistant storage bottle

6-AMINONICOTINAMIDE OINTMENT

Manufacturing Directions

1. Dissolve 0.1 g 6-Aminonicotinamide in 3.6 mL of 0.22 N HCl and 6.3 mL water.
2. Admix the solution thus obtained with commercially available USP grade hydrophilic ointment (90 g) to a uniform consistency.
3. Store the ointment thus prepared preferably in opaque jars at room temperature.

6-AMINONICOTINIC ACID METHYL ESTER OINTMENT

Manufacturing Directions

1. Dissolve 1 g 6-Aminonicotinic acid methyl ester in anhydrous ethanol (9 mL) and admix the solution with white petrolatum USP grade (54 g) and liquid petrolatum USP grade (36 g) to a uniform consistency.
2. This ointment also may be stored in opaque jars at room temperature.

6-AMINONICOTINIC ACID OINTMENT

Manufacturing Directions

1. Dissolve 1 g 6-Aminonicotinic acid in 7 mL of 1 N HCl and 2mL of water.
2. Admix the solution with USP grade hydrophilic ointment (90 g) to a uniform consistency.
3. The ointment thus prepared may also be stored in opaque jars at room temperature.

AMINACRINE HYDROCHLORIDE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.10	1	Aminacrine hydrochloride	1.00
5.00 mg	2	Thymol	50.00 mg
9.50	3	Glyceryl monostearate	95.00
3.20	4	Cetostearyl alcohol	32.00
1.90	5	Polyoxyl 40 stearate	19.00
10.00	6	Liquid paraffin	100.00
0.45	7	Cetrimide	4.50
QS	8	Isopropyl alcohol	1.30 L
QS	9	Perfume	QS
QS	10	Water purified	QS to 1 kg

Manufacturing Directions

1. Load items 3 to 5 and half of item 6 into a suitable mixing vessel. Heat to 60°C and mix well.
2. Prepare slurry of item 1 in the balance of item 6 and add to step 1 slowly at 60°C under constant stirring.
3. Heat item 10 to 60° C and add to step 2 with stirring to form an emulsion.
4. Cool down to 45°C and add perfume. Continue to mix to cool down to room temperature.
5. Fill in appropriate containers.

AMOXICILLIN LOTION

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
7.00	1	Ethoxylated cetyl stearyl alcohol	70.00
0.75	2	Cetyl alcohol	7.50
5.00	3	Isopropyl myristate	50.00
0.10	4	Butylated hydroxyanisole	1.00
0.25	5	Polyoxyl 40 stearate	2.50
71.80	6	Water purified	718.00
3.00	7	Propylene glycol	30.00
10.00	8	Acetone	100.00
0.10	9	Dioctyl sodium sulfosuccinate	1.00
2.00	10	Amoxicillin	20.00

AMPICILLIN LOTION

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
7.00	1	Ethoxylated cetyl stearyl alcohol	70.00
0.75	2	Cetyl alcohol	7.50
5.00	3	Isopropyl myristate	50.00
0.10	4	Butylated hydroxyanisole	1.00
0.25	5	Polyoxyl 40 stearate	2.50
71.80	6	Water purified	718.00
3.00	7	Propylene glycol	30.00
10.00	8	Acetone	100.00
0.10	9	Dioctyl sodium sulfosuccinate	1.00
2.00	10	Ampicillin	20.00

ANALGESIC CLEAR GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
25.00	1	Hydroxypropyl cellulose	25.00
QS	2	Deionized water	QS to 1 kg
400.00	3	Ethanol DEB 100	400.00
100.00	4	Menthol	100.00
150.00	5	Methyl salicylate	150.00
25.00	6	DEA-oleath-3-phosphate	25.00

Manufacturing Directions

1. Hydrate hydroxypropyl cellulose in water at 60°C to 65° C.
2. Stir to cool.
3. Add ethanol.
4. Add remaining ingredients and stir until homogeneous.

ANALGESIC CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
130.00	1	Methyl salicylate	130.00
60.00	2	Menthol	60.00
20.00	3	Eucalyptus oil	20.00
5.00	4	Lanolin	5.00
1.00	5	Chloroxylenol	1.00
150.00	6	Glyceryl stearate and PEG-100 stearate	150.00
73.00	7	Cetearyl alcohol	73.00
70.00	8	Glyceryl stearate	70.00
QS	9	Deionized water	QS to 1 kg
QS	10	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring. Stir to cool.
3. Fill at 30°C.

ANALGESIC LOTION

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Methyl salicylate	150.00
70.00	2	Menthol	70.00
10.00	3	Lanolin oil	10.00
30.00	4	PEG-40 stearate	30.00
20.00	5	Glyceryl stearate	20.00
QS	6	Deionized water	QS
1.50	7	Carbopol® 980	1.50
10.00	8	Potassium hydroxide (10% aqueous solution)	10.00
QS	9	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases (except potassium hydroxide) separately to 65°C to 70°C.
2. Add water phase to oil phase while stirring.
3. Add potassium hydroxide solution to neutralize.
4. Stir to cool.
5. Fill at 30°C.

ANTHRALIN CREAM

Anthralin cream, 1% USP, is a smooth, yellow cream acid, sodium hydroxide, and purified water. For topical containing 1% anthralin USP in an aqueous cream base dermatological use only.

ANTIACNE GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
422.00	1	Witch hazel (distilled, 14% alcohol)	422.00
5.00	2	Salicylic acid	5.00
5.00	3	Aloe vera gel	5.00
10.00	4	Sorbitol	10.00
500.00	5	Polyglycerylmethacrylate	500.00
10.00	6	Propylene glycol	10.00
0.80	7	Methyl paraben	0.80
0.20	8	Propyl paraben	0.20

Manufacturing Directions

1. Premix items 1 to 4.
2. Add item 5 with low-shear mixing until homogeneous.
3. Mix together items 6 to 8 and add them to the formulation.

ANTIFUNGAL FOOT POWDER

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Dichlorobenzyl alcohol (Myacide SF)	5.00
5.00	2	Allantoin	5.00
200.00	3	Cornstarch	200.00
790.00	4	Talc	790.00

Manufacturing Directions

1. Mix all ingredients using geometric dilution technique.

ANTIFUNGAL TOPICAL CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
39.00	1	Urea[a]	390.00
0.15	2	Carbopol 940	1.50
5.94	3	Petrolatum	59.40
12.06	4	Mineral oil	120.60
1.875	5	Glyceryl stearate	187.50
0.626	6	Cetyl alcohol	6.26
3.00	7	Propylene glycol	30.00
0.05	8	Xanthan gum	0.50
0.15	9	Trolamine	1.50
1.00–5.00	10	Antifungal compound[a]	10.00–50.00

[a] Adjust quantity of urea for the quantity of antifungal compound; this formula is for 1% level of antifungal added.

ANTISEPTIC CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Polawax GP200	50.00
10.00	2	Lanolin	10.00
150.00	3	Mineral oil (70 cS)	150.00
70.00	4	Cetearyl alcohol	70.00
30.00	5	Dimethicone	30.00
QS	6	Deionized water	QS to 1 kg
5.00	7	Cetrimonium bromide	5.00
0.50	8	Chlorhexidine gluconate	0.50
QS	9	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases to 65°C.
2. Add water phase to oil phase while stirring.
3. Stir to cool.
4. Fill.

ANTISEPTIC LOTION

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
30.00	1	Cetearyl alcohol and ceteareth-20	30.00
50.00	2	Mineral oil (70 cS)	50.00
2.00	3	Lanolin alcohol	2.00
QS	4	Deionized water	QS to 1 kg
5.00	5	Cetrimonium bromide (as 40% cetrimide solution BP)	5.00
20.00	6	Glycerin	20.00
QS	7	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring.
3. Stir to cool.
4. Fill at 30°C.

ANTISEPTIC LOTION

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
30.00	1	Cetearyl alcohol and ceteareth-20	30.00
45.00	2	Mineral oil (70 cS)	45.00
25.00	3	Stearyl alcohol	25.00
10.00	4	Lanolin	10.00
5.00	5	Polysorbate 60	5.00
15.00	6	Laneth-15	15.00
QS	7	Deionized water	QS to 1 kg
5.00	8	Cetrimonium bromide (as 40% cetrimide solution BP)	5.00
20.00	9	Glycerin	20.00
QS	10	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring.
3. Stir to cool.
4. Fill at 30°C.

ARGININE AND OLEORESIN CAPSICUM CREAM

Active ingredients: L-arginine and oleoresin capsicum. Other ingredients: Water, choline chloride, sodium chloride,magnesium chloride, white oil, glyceryl stearate SE, squalane, cetyl alcohol, propylene glycol stearate SE, wheat germ oil, glyceryl stearate, isopropyl myristate, stearyl stearate, polysorbate-60, propylene glycol, oleic acid, tocopheryl acetate, collagen, sorbitan stearate, vitamins A and D, triethanolamine, aloe vera extract, imidazolidinyl urea, oleoresin capsicum,methyl paraben, propyl paraben, BHA.

ARGININE CREAM

Active ingredient: L-arginine. Other ingredients: Water, choline chloride, sodium chloride, magnesium chloride, white oil, glyceryl stearate SE, squalane, cetyl alcohol, propylene glycol stearate SE, wheat germ oil, glyceryl stearate, isopropyl myristate, stearyl stearate, polysorbate-60, propylene glycol, oleic acid, tocopheryl acetate, collagen, sorbitan stearate, vitamins A and D, triethanolamine, aloe vera extract, imidazolidinyl urea, methyl paraben, propyl paraben, BHA.

ARGININE–ASPARTATE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
3.50	1	Cetostearyl alcohol	35.00
40.00	2	Squalane	400.00
3.00	3	Beeswax	30.00
5.00	4	Reduced lanolin	50.00
0.30	5	Ethyl p-oxybenzoate	3.00
2.00	6	Polyoxyethylene (20 mol) sorbitan monopalmitate	20.00
2.00	7	Monoglyceride stearate	20.00
0.50	8	Sodium N-stearoyl glutamate	5.00
1.00	9	2-Hydroxy-4-methoxy benzophenone	10.00
2.00	10	Retinol acetate	20.00
0.05	11	Evening primrose oil	0.50
0.03	12	Perfume	0.30
0.01	13	L-Arginine-L-aspartate	0.10
5.00	14	1,3-Butylene glycol	50.00
5.00	15	Polyethylene glycol 1500	50.00
QS	16	Water purified	QS to 1 kg

Manufacturing Directions

1. Place items 1 to 12 in a heating vessel and dissolve and mix.
2. In another vessel, prepare a solution of items 13 to 16 heated to 75°C with stirring.
3. Add step 2 into step 1 and homogenize to reduce the size of emulsified particles.
4. Cool rapidly to produce a cream.

ATROPINE OPTHALMIC OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Atropine sulfate	10.00
5.00	2	Liquid paraffin	50.00
5.00	3	Cetostearyl alcohol	50.00
5.00	4	Hard paraffin	50.00
84.00	5	Soft paraffin	840.00

Manufacturing Directions

1. Load items 2 to 5 in a melting vessel. Heat to 145°C and keep it at this temperature for 45 minutes.
2. Allow to cool to room temperature.
3. In a separate vessel, dissolve item 1 in 200 mL of water for injection and add to step 1 under aseptic conditions.
4. Fill and sterilize in tubes (gamma radiation).

AZELAIC ACID CREAM AND GEL

Azelaic acid cream, 20%, contains azelaic acid, a naturally occurring saturated dicarboxylic acid. Each gram contains azelaic acid (0.2 g, 20% w/w). Inactive ingredients: Cetearyl octanoate, glycerin, glyceryl stearate, cetearyl alcohol, cetyl palmitate, cocoglycerides, PEG-5 glyceryl stearate, propylene glycol, and purified water. Benzoic acid is present as a preservative. Azelaic acid in a gel form is manufactured by the following method: Benzoic acid and EDTA are dissolved in usual concentrations in 60 to 70 parts of water. Then a mixture of 1 part midchain triglycerides and 1.5 parts polysorbate 80 is added and homogenized while being stirred (preemulsion). One part lecithin is introduced into twelve parts propylene glycol. The solution that is produced is stirred into the preemulsion and homogenized. After 1 part polyacrylic acid is added, 15 parts azelaic acid are added. Sodium hydroxide is used to neutralize the carbomer to form the gel.

BABY CREAM, BENZALKONIUM CHLORIDE, AND ZINC OXIDE

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.002 mL	1	Benzalkonium chloride solution	2.30 mL
85.00 mg	2	Zinc oxide (powder)	85.00
100.00 mg	3	Polawax (emulsifying, nonionic wax)	100.00
16.00 mg	4	Alcohol cetostearyl	16.00
4.00 mg	5	Lanolin (acetylated/ anhydrous, regular)	4.00
80.00 mg	6	Glycerin (96%)	80.00
10.00 mg	7	Oil (neutral, vegetable triglycerides mixture; Miglyol)	10.00
0.50 mg	8	Propyl paraben (Aseptoform(tm) P)	0.50
1.00 mg	9	Methyl paraben (Aseptoform(tm) M)	1.00
0.80 mL	10	Purified water	QS to 800.00 mL
0.24 mg	11	Perfume (Diabolo 110.388/B)	0.24

Manufacturing Directions

Avoid mixing air into emulsion. Emulsify under vacuum to minimize air entrapment. Use jacketed tank with vacuum with high-speed agitator (adjustable, slow-speed, anchor type with Teflon sweep blades).

1. If necessary, mill zinc oxide in a Fitz mill or similar device (impact forward, maximum speed), fitted with a 250 µm screen.
2. Repeat 3 times.
3. Heat 800 mL of water to 75°C in a steam-jacketed mixing tank and dissolve methyl paraben.
4. Maintain temperature at 75°C.
5. Disperse milled zinc oxide in solution of previous step.
6. Maintain temperature at 75°C.
7. Dissolve benzalkonium chloride and glycerin in solution and maintain temperature at 75°C.
8. In a separate steam-jacketed tank, add Polawax, cetostearyl alcohol, acetylated lanolin, oil, and propyl paraben. Carefully melt at 70°C.
9. Adjust the turbomixer of the steam-jacketed tank containing the aqueous phase to maximum speed, keeping the temperature at 75°C.
10. Slowly add the oil phase to the aqueous phase.
11. Generate as much vacuum as possible and maintain it for the rest of the process.
12. Circulate cold water to allow for a very slow temperature decrease (down to 60°C).
13. Stop the turbomixer and set the anchor-type agitator at minimum speed until 40°C to 45°C is reached.
14. The temperature decrease must be very slow.
15. Break the vacuum and add perfume to cream with anchortype agitator set at slow speed.
16. Continue to mix until the perfume is completely dispersed.

BABY LOTION

Bill of Materials

Scale (mg/mL)	Item	Material Name	Qty/L
50.00	1	Alcohol (ethanol; natural cosmetic grade)	50.00 g
50.00	2	Propylene glycol	50.00 g
0.80	3	Ethoxylated nonyl phenol	0.80 g
0.005	4	FD&C Red Dye No. 40	5.70 mg
0.41	5	FD&C blue dye No. 1	0.41 g
0.70	6	FD&C yellow dye No. 5	0.70 g
0.40	7	Perfume essence (Nelandia)	0.40 g
QS	8	Hydrochloric acid (reagent-grade bottles)	~0.01 g
QS	9	Purified water	QS to 1.00 L

Manufacturing Directions

Use 316 or more resistant-grade stainless-steel tank.

1. Place approximately 800 mL of purified water in main mixing tank.
2. Add alcohol and propylene glycol and mix for 5 minutes.
3. Separately dissolve each dye in sufficient water to obtain 0.5% dye solutions.

4. Add color solutions to main tank and mix.
5. Rinse containers with small portions of purified water and add rinsings.
6. Dissolve perfume essence in ethoxylated nonyl phenol.
7. Add solution from previous step to main tank and mix for 5 minutes.
8. Determine pH of solution and adjust if necessary with 5% hydrochloric acid solution.
9. Mix well. ph should be 5.7 to 5.9.
10. QS to 1 L with purified water.

BABY LOTION

Bill of Materials

Scale (mg/mL)	Item	Material Name	Qty/L (g)
50.00	1	Alcohol	50.0
50.00	2	Propylene glycol	50.0
0.80	3	Ethoxylated nonyl phenol	0.80
0.57	4	Dye red FD&C No. 40	0.57
0.41	5	Dye blue FD&C No. 1	0.41
0.70	6	Dye yellow FD&C No. 5	0.70
0.40	7	Perfume essence nelandia	0.40
QS	8	Acid hydrochloric reagent grade bottles	~0.012
QS	9	Water purified	QS to 1 L

Manufacturing Directions

1. Use 316 or more resistant grade stainless-steel tank.
2. Place approximately 800 mL of purified water in main mixing tank.
3. Add alcohol and propylene glycol and mix for 5 minutes. Separately dissolve each dye in sufficient water to obtain 0.5% dye solutions.
4. Add color solutions to main tank and mix. Rinse containers with small portions of purified water and add rinsings.
5. Dissolve perfume essence nelandia in ethoxylated nonyl phenol.
6. Add solution from step above to main tank and mix for 5 minutes.
7. Determine pH of solution and adjust if necessary with 5% hydrochloric acid solution.
8. Mix well (pH 5.7–5.9). QS to 1 L with purified water.

BABY SHAMPOO

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg
250.00	1	Sodium alkyl ether sulfate/ sulfonate	250.00 g
30.00	2	Monateric CAB surfactant	30.00 g
30.00	3	Cocamide DEA surfactant (Synotol CN 90)	30.00 g
1.00	4	Methyl paraben	1.00 g
0.52	5	Anhydrous citric acid	0.52 g
0.003	6	FD&C yellow dye No. 6	3.50 mg
0.01	7	FD&C yellow dye No. 5	15.00 mg
4.00	8	Ethoxylated nonyl phenol	4.00 g
3.00	9	Perfume I	3.00 g
1.00	10	Perfume II	1.00 g
8.50	11	Sodium chloride	8.50 g
QS	12	Purified water	QS to 1.00 kg

Manufacturing Directions

Use 315 or more resistant-grade stainless-steel tank.

1. Add approximately 270 g of purified water to the main mixing tank.
2. With slow agitation add cocamide DEA surfactant.
3. Add and dissolve methyl paraben and mix for approximately 10 minutes.
4. Add the following ingredients to tank: Sodium alkyl sulfate/sodium alkyl ether sulfate/sulfonate, monateric CAB surfactant, and approximately 280 g of purified water.
5. Mix for 15 minutes until complete solution is obtained.
6. With constant stirring, slowly add citric acid (10% solution) until a pH of 6.9 to 7.1 is maintained constantly for 5 minutes after the last addition of the citric acid solution.
7. Separately dissolve FD&C yellow dyes No. 6 and 5 (if used) in sufficient purified water.
8. Add dye solution from step above to main tank and mix.
9. Rinse containers with a small portion of purified water and add rinsings.
10. Separately mix ethoxylated nonyl phenol with perfumes (perfume available from Firmenich; Plainsboro, NJ) and add to main mixing tank.
11. Rinse container with purified water and add rinsing.
12. Mix until completely dissolved.
13. Slowly add in small portions sodium chloride to adjust the viscosity to between 1500 and 3500 cps.
14. Mix for 15 minutes.
15. If necessary, QS to 1 kg with purified water.

BACITRACIN ZINC AND POLYMYXIN B SULFATE OPTHALMIC OINTMENT

The bacitracin zinc and polymyxin B sulfate ophthalmic ointment USP is a sterile antimicrobial ointment formulated for ophthalmic use. Bacitracin zinc is the zinc salt of bacitracin, a mixture of related cyclic polypeptides (mainly bacitracin A) produced by the growth of an organism of the licheniformis group of *Bacillus subtilis* var. Tracy. It has a potency of not less than 40 bacitracin units per milligram. Polymyxin B sulfate is the sulfate salt of polymyxin B1 and B2, which are produced by the growth of *Bacillus polymyxa* (Prazmowski) Migula (family Bacillaceae). It has a potency of not less than 6000 polymyxin B units per milligram, calculated on an anhydrous basis. Each gram contains the following actives: Bacitracin zinc equal to 500 bacitracin units and polymyxin B sulfate equal to 10,000 polymyxin B units. Inactives: White petrolatum and mineral oil.

BASE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
7.0	1	Cetyl stearyl alcohol	70.00
1.5	2	Cremophor A 6	15.00
1.5	3	Cremophor A 25	15.00
12.0	4	Liquid paraffin	120.00
0.2	5	Paraben(s)	2.00
67.8–69.7	6	Water	678–697
8.0	7	Propylene glycol	80.00
0.1–2.0	8	Active ingredient	1–2.00

Manufacturing Directions

1. Heat a mixture of items 1 to 5 and the water separately to approximately 80°C.
2. With rigorous stirring, add the water to the obtained solution.
3. Heat items 7 and 8 until the active ingredient is dissolved, mix with aqueous solution, and continue to stir during cooling to room temperature.
4. This white basic cream can be readily used for active ingredients soluble in 1, 2-propylene glycol.

BASE OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
2.50	1	Propylene glycol	25.00
2.50	2	Triacetin	25.00
57.00	3	Mineral oil	570.00
35.00	4	Microcrystalline wax	350.00
3.00	5	Propylene glycol stearate	30.00
0.05	6	Citric acid	0.50

Manufacturing Directions

1. The mineral oil, microcrystalline wax, and propylene glycol stearate are melted together by heating to 75°C to 85°C and mixed, thus creating the oleaginous phase.
2. The citric acid, if used, is dissolved in the triacetin by stirring and using heat is necessary.
3. If used optionally, add the propylene glycol to the triacetin and mix.
4. After cooling the oleaginous phase to approximately 55°C, add the triacetin solution to the oleaginous phase while mixing. Mixing should be of sufficient intensity to disperse the triacetin finely and uniformly.
5. Continue mixing while cooling the ointment to 30°C or lower.

BASE OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
10.00	1	Triacetin	100.00
30.00	2	Lanolin alcohol and petrolatum (Americhol CAB)	300.00
1.00	3	Cholesterol	10.00
59.00	4	White petrolatum	590.00

Manufacturing Directions

1. Melt together Amerchol CAB, white petrolatum, and cholesterol by heating to 75°C to 85°C and mix to form the oleaginous phase.
2. After cooling the oleaginous phase to approximately 45°C, add the triacetin to the oleaginous phase while mixing. Mixing should be of sufficient intensity to disperse the triacetin finely and uniformly.
3. Continue mixing while cooling the ointment to 30°C or lower.

BASE OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Triacetin	50.00
25.00	2	Dimethicone (1000 cS)	250.00
61.50	3	White petrolatum	615.00
5.00	4	Microcrystalline wax	50.00
1.00	5	Cholesterol	10.00
2.50	6	Sucrose distearate	25.00

Manufacturing Directions

1. To make the oleaginous phase, melt white petrolatum, sucrose distearate, cholesterol, and microcrystalline wax at 75°C to 85°C.
2. Add dimethicone and mix. After cooling the oleaginous phase to approximately 55° C, add the triacetin to the oleaginous phase while mixing. Mixing should be of sufficient intensity to disperse the triacetin finely and uniformly.
3. Continue mixing while cooling the ointment to 30° C or lower.

BASE OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Liquid paraffin	50.00
10.00	2	White paraffin	100.00
30.00	3	Glycerin	300.00
8.00	4	Cetostearyl alcohol	80.00
0.30	5	Methyl paraben	3.00
3.60	6	Polyoxyethylene sorbitan monostearate	36.00
2.00	7	Glyceryl monostearate	20.00
QS	8	Water purified	QS to 1 kg

Manufacturing Directions

1. Preparation of water phase
   a. Add purified water, polysorbate 60, and glycerin with agitation to a melting kettle.
   b. Heat the contents to 61°C to 65°C.
   c. Add methyl paraben and mix the composition to dissolve while maintaining temperature.
2. Preparation of oil phase
   a. In a suitable vessel, place liquid paraffin, cetostearyl alcohol, white petrolatum, glycerol monostearate, and white beeswax and mix continuously while heating to 71°C to 75°C.
3. Mixing of phases
   a. The mixture of step 2 is transferred to step 1 kettle with the water phase maintained less than 300 mbar vacuum.
   b. With mixing and keeping the temperature at 61°C to 65°C, draw the oil phase into the water phase.
   c. Mix for 15 minutes with agitation and vacuum at 300 mbar and 61°C to 65°C.
   d. While mixing and under vacuum, allow the mixture to cool gradually to room temperature.
4. Fill in appropriate container.

BECAPLERMIN GEL (0.01%)

The gel contains becaplermin, a recombinant human platelet-derived growth factor for topical administration. Becaplermin is produced by recombinant DNA technology by insertion of the gene for the B chain of platelet-derived growth factor into the yeast *Saccharomyces cerevisiae*. Becaplermin has a molecular weight of approximately 25 kDa and is a homodimer composed of two identical polypeptide chains that are bound together by disulfide bonds. The gel is a nonsterile, low-bioburden, preserved, sodium carboxymethylcellulose-based topical gel containing the active ingredient becaplermin and the following inactive ingredients: Sodium chloride, sodium acetate trihydrate, glacial acetic acid, water for injection, and methyl paraben, propyl paraben, and M-cresol as preservatives, and L-lysine hydrochloride as a stabilizer. Each gram of gel contains 100 g of becaplermin.

BENZALKONIUM CHLORIDE AND ZINC OXIDE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.0023 mL	1	Benzalkonium chloride solution	2.3 mL
85.0	2	Zinc oxide USP powder	85.0
100.0	3	Wax emulsifying nonionic (Polawax®)	100.0
16.0	4	Alcohol cetostearyl	16.0
4.0	5	Lanolin acetylated/ anhydrous USP regular	4.0
80.0	6	Glycerin USP (96%)	80.0
10.0	7	Oil-neutral vegetable triglycerides mixture Miglyol	10.0
0.5	8	Propyl paraben NF (Aseptoform P)	0.5
1.0	9	Methyl paraben NF (Aseptoform M)	1.0
0.80 mL	10	Purified water	QS to 800.0 mL
0.24	11	Perfume diabolo 110.388/B	0.24 g

Manufacturing Directions

1. Avoid mixing air into emulsion. Emulsify under vacuum to minimize air entrapment. Use jacketed tank with vacuum with high-speed agitator and an adjustable slow-speed anchor type with Teflon sweep blades.
2. If necessary, mill zinc oxide in a Fitz mill or similar impactforward, maximum-speed mill, fitted with a 250 μm aperture screen. Repeat three times. Heat 800 mL of water to 75°C in a steam-jacketed mixing tank and dissolve methyl paraben.
3. Maintain temperature at 75°C. Disperse milled zinc oxide in solution of step above. Maintain temperature at 75°C.
4. Dissolve benzalkonium chloride and glycerin in solution. Maintain temperature at 75°C.
5. In a separate steam-jacketed tank, add Polawax, cetostearyl alcohol, acetylated lanolin, oil-neutral vegetable triglycerides mixture, and propyl paraben and carefully melt at 70°C.
6. Adjust the turbomixer of the steam-jacketed tank containing the aqueous phase to maximum speed, keeping the temperature at 75°C. Slowly add the oil phase into the aqueous phase. Generate as much vacuum as possible and maintain it for the rest of the process.
7. Circulate cold water to allow for a very slow temperature decrease (down to 60°C). Stop turbomixer and put the anchor-type agitator at minimum speed until 40°C to 45°C is reached. The temperature decrease must be very slow.
8. Break the vacuum and add perfume to cream with anchortype agitator at slow speed.
9. Continue to mix until the perfume is completely dispersed.

BENZALKONIUM CHLORIDE CONTRACEPTIVE GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	PEG-6, PEG-32, and glycol stearate (Tefose® 63)	50.00
30.00	2	Apricot kernel oil PEG-6 esters (Labrafil® M 1944 CS)	30.00
816.00	3	Deionized water	816.00
80.00	4	Hydroxyethyl cellulose	80.00
24.00	5	Benzalkonium chloride (50 wt% in water)	24.00

Manufacturing Directions

1. Mix items 3 and 4 at room temperature.
2. Heat to 75°C and add items 1 and 2 while stirring.
3. Cool with gentle stirring to 30°C, then add item 5 and stir.

BENZOCAINE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
180.00	1	Trilaneth-4 phosphate and glyceryl stearate and PEG-2 stearate	180.00
20.00	2	Hydrogenated palm/kernel oil PEG-6 esters	20.00
80.00	3	Mineral oil	80.00
0.30	4	Sodium methyl paraben	0.30
0.70	5	Sorbic acid	0.70
646.70	6	Deionized water	646.70
10.00	7	Benzocaine	10.00
10.00	8	Butamben	10.00
2.00	9	Menthol	2.00
0.30	10	Resorcinol	0.30
50.00	11	Ethoxydiglycol	50.00

Manufacturing Directions

1. Dissolve items 7 to 10 in item 11.
2. Mix and heat items 1 to 6 to 75°C. Allow to cool slowly with constant stirring. At 35°C, add this to mixture above.
3. Homogenize if necessary.

BENZOYL PEROXIDE AND ALPHA-BISABOLOL GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
2.00	1	Alpha-bisabolol, natural (BASF)	2.00
60.00	2	Propylene glycol	60.00
100.00	3	Triethanolamine	100.00
30.00	4	Cremophor RH 40	30.00
30.00	5	Kollidon 30	30.00
408.00	6	Water	408.00
10.00	7	Carbopol 940	10.00
400.00	8	Water	400.00
50.00	9	Benzoyl peroxide	50.00

Manufacturing Directions

1. Prepare suspension of items 7 and 8, then let swell for 1 hour.
2. Add this suspension to the well-stirred solution of items 1 to 5.
3. Add item 9 to create a colorless transparent gel.

BENZOYL PEROXIDE ANTIACNE MICROEMULSION

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
470.00	1	Ethoxydiglycol (Transcutol®)	470.00
250.00	2	PEG-8 caprylic/Capric glycerides (Labrasol®)	250.00
150.00	3	Dipelargonate propylene glycol (DPPG)	150.00
80.00	4	Benzoyl peroxide	80.00
50.00	5	Propylene glycol laurate (Lauroglycol®)	50.00

Manufacturing Directions

1. Mix items 1 to 3.
2. Dissolve item 4 in this mixture with mixing for 1.5 to 2.0 hours.
3. Add item 5 to mixture and mix until uniform emulsion is obtained.

BENZOYL PEROXIDE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/1000 Tablets (g)
460.50	1	Deionized water	460.50
5.00	2	Carbomer 940	5.00
10.00	3	Hydroxypropylmethylcellulose, medium viscosity	10.00
137.50	4	Deionized water	137.50
70.00	5	Purified bentonite (Polargel NF)	70.00
2.00	6	Methyl paraben	2.00
1.00	7	Propyl paraben	1.00
20.00	8	Glyceryl stearate	20.00
60.00	9	Propylene glycol	60.00
20.00	10	Polyethylene glycol 600	20.00
20.00	11	Myristyl propionate	20.00
50.00	12	Dimethicone	50.00
70.00	13	Purified bentonite (Polargel NF)	70.00
10.00	14	Titanium dioxide	10.00
100.00	15	Benzoyl peroxide 70%	100.00

Manufacturing Directions

1. Sift carbomer 940 into vortex in water; when completely dispersed, sift in item 3.
2. Add parabens with stirring and heat (to 80°C at least) until dissolved.
3. Add glyceryl stearate.
4. Blend items 10 to 13 in propylene glycol in order and mix well. With the addition of Polargel, allow 15 minutes of mixing to complete hydration.
5. Blend propylene glycol portion into the first part. Finally, add benzoyl peroxide and titanium dioxide to the mixture and mill.

BENZOYL PEROXIDE GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
2.50	1	Acrylates/C10–30 alkyl acrylate crosspolymer	2.50
4.00	2	Carbopol 980	4.00
QS	3	Deionized water	QS to 1 kg
40.00	4	Isopropyl myristate	40.00
10.00	5	Cetyl alcohol	10.00
20.00	6	Glyceryl stearate	20.00
50.00	7	Sodium hydroxide 0.5 *M*	50.00
15.00	8	Deionized water	15.00
50.00	9	Benzoyl peroxide	50.00
50.00	10	PEG-600	50.00
QS	11	Perfume, preservative	QS

Manufacturing Directions

1. Hydrate Carbopol and pemulen in warm water, 60°C. When fully hydrated, heat to 70°C.
2. Heat oil phase to 70°C. Add water phase to oil phase while stirring.
3. Add sodium hydroxide and continue stirring. Combine benzoyl peroxide, PEG-600, and water (item 8) and add to the emulsion.
4. At 35°C, homogenize with caution, using suitable equipment.

BENZOYL PEROXIDE LOTION

The cleansing lotions contain benzoyl peroxide, 4% and 8% respectively, in a lathering vehicle containing purified water, cetyl alcohol, citric acid, dimethyl isosorbide, docusate sodium, hydroxypropylmethylcellulose, laureth-12, magnesium aluminum silicate, propylene glycol, sodium hydroxide, sodium lauryl sulfoacetate, and sodium octoxynol-2 ethane sulfonate.

BENZOYL PEROXIDE LOTION

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
40.00	1	Purified bentonite (Polargel NF)	40.00
10.00	2	Hydroxypropylmethylcellulose	10.00
522.20	3	Water	522.20
190.00	4	Water	190.00
2.00	5	Methyl paraben	2.00
2.00	6	Propyl paraben	2.00
20.00	7	Glyceryl stearate	20.00
60.00	8	Propylene glycol	60.00
20.00	9	Myristyl propionate	20.00
5.00	10	Dimethicone	5.00
QS	11	Iron oxides	QS
10.00	12	Titanium dioxide	10.00
100.00	13	Benzoyl peroxide 77%	100.00

Manufacturing Directions

1. Sift the Polargel NF into water with rapid mixing. Allow to hydrate for 15 minutes.
2. Pass through coarse sieve, add item 2, and mix until all lumps are removed.
3. Add parabens to the water with stirring and heat to 90°C to dissolve parabens.
4. Add items 4 to 10 and mix well and then add these to the item 2 part. Mix well again. Finally, add items 11 to 13 and mix.
5. Mill it and fill.

BETAMETHASONE AND CINCHOCAINE SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
1.00	1	Betamethasone valerate	1.00
1.00	2	Cinchocaine hydrochloride	1.00
1798.00	3	Witepsol W 45®	1798.00

Manufacturing Directions

1. Charge item 3 in the fat-melting vessel and heat to 55°C; transfer molten mass to Becomix through stainless-steel sieve. Set the temperature at 50°C.
2. Add items 1 and 2, mix well at 50°C, and mix for 20 minutes.
3. Homogenize at 0.6 bar vacuum and 50°C.
4. Transfer to storage at 40°C.
5. Fill suppository mold.

BETAMETHASONE AND NEOMYCIN GEL CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
1.30	1	Betamethasone valerate	0.13
6.50	2	Neomycin sulfate	0.65
150.00	3	Lutrol E 400	15.00
100.00	4	Miglyol 812	10.00
200.00	5	Lutrol F 127	20.00
QS	6	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve betamethasone valerate in a mixture of Lutrol E 400 and Miglyol 812.
2. Dissolve Lutrol F127 and neomycin sulfate in water at 5°C to 10°C.
3. Mix both solutions.
4. Maintain cool temperature until the air bubbles disappear. A milky-white soft gel cream is obtained.

BETAMETHASONE AND SALICYLIC ACID LOTION

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.10	1	Betamethasone dipropionate micronized, 5% excess[a]	1.05
1.90	2	Salicylic acid	19.00
0.032	3	Disodium edetate	0.32
0.55	4	Hydroxypropylmethylcellulose	5.50
0.55	5	Sodium hydroxide	5.50
40.00	6	Isopropyl alcohol	400.00
QS	7	Water purified	QS to 1 kg

[a] Adjust quantity on the basis of assay.

Manufacturing Directions

1. Charge about half of item 7 into a suitable vessel and slowly add item 4 with vigorous mixing.
2. Use item 7 to rinse the container for item 4 and add rinsings to the mixing vessel.
3. In 10% of the amount of item 6, add and dissolve item 1 in a separate vessel and then add an additional 20% of item 6 and mix well until completely dissolved.
4. Add 10% of item 7 in a separate vessel and add and dissolve item 5 into it.
5. Add 10% of item 7 in a separate vessel and add and dissolve item 3 into it.
6. Add 20% of item 7 in a separate vessel and add and dissolve item 2 into it.

7. Add 50% of item 6 to step 4 and mix slowly for 15 minutes. Add to this vessel step 3 and step 5 and mix vigorously.
8. Use item 7 to rinse all vessels and add rinsings.
9. Check pH to 4.8 to 5.3 and adjust if necessary.
10. Add step 1 to this and mix.
11. Fill in appropriate containers.

BETAMETHASONE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
70.00	1	Cetyl stearyl alcohol	70.00
15.00	2	Cremophor A 6	15.00
15.00	3	Cremophor A 25	15.00
12.00	4	Liquid paraffin	12.00
2.00	5	Paraben(s)	2.00
697.00	6	Water	697.00
80.00	7	Propylene glycol	80.00
1.00	8	Betamethasone	1.00

Manufacturing Directions

1. Heat the mixture of items 1 to 5 and item 6 separately to approximately 80°C.
2. Add together with rigorous stirring.
3. Heat items 7 and 8 until the active ingredient is dissolved.
4. Mix with above mixture and continue to stir to cool to room temperature to produce white cream.

BETAMETHASONE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
70.00	1	Cetyl stearyl alcohol	70.00
15.00	2	Cremophor A 6	15.00
15.00	3	Cremophor A 25	15.00
12.00	4	Liquid paraffin	120.00
2.00	5	Paraben(s)	2.00
697.00	6	Water	697.00
80.00	7	Propylene glycol	80.00
1.00	8	Betamethasone	1.00

Manufacturing Directions

1. Heat a mixture of items 1 to 5 and item 6 separately to approximately 80°C.
2. Add together with rigorous stirring.
3. Heat items 7 and 8 until the active ingredient is dissolved, mix with above mixture, and continue to stir to cool to room temperature. This creates a white cream.

BETAMETHASONE DIPROPIONATE CREAM, LOTION, AND OINTMENT

Each gram of cream, 0.05%, contains 0.643 mg betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone) in a hydrophilic emollient cream consisting of purified water USP, mineral oil USP, white petrolatum USP, ceteareth-30, cetearyl alcohol 70/30 (7.2%), sodium phosphate monobasic monohydrate R, and phosphoric acid NF, with chlorocresol and propylene glycol USP as preservatives. It may also contain sodium hydroxide R to adjust pH to approximately 5. Each gram of lotion, 0.05%, w/w contains 0.643 mg betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone) in a lotion base of isopropyl alcohol USP (39.25%) and purified water USP and is slightly thickened with carbomer 974P; the pH is adjusted to approximately 4.7 with sodium hydroxide R. Each gram of lotion, 0.05%, contains 0.643 mg betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone) in a lotion base of purified water USP, isopropyl alcohol USP (30%), hydroxypropyl cellulose NF, propylene glycol USP, and sodium phosphate monobasic monohydrate R, with phosphoric acid NF used to adjust the pH to 4.5. Each gram of ointment, 0.05%, contains 0.643 mg betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone) in an ointment base of mineral oil USP and white petrolatum USP.

BETAMETHASONE DIPROPIONATE OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.064	1	Betamethasone dipropionate	0.64
2.50	2	Propylene glycol stearate	25.00
3.50	3	Triacetin	35.00
0.05	4	Citric acid	0.50
35.00	5	Microcrystalline wax	350.00
58.88	6	Mineral oil	588.80

Manufacturing Directions

1. Dissolve betamethasone dipropionate and citric acid in the triacetin with mixing and heat to 35°C if needed.
2. Melt microcrystalline wax, propylene glycol stearate, and mineral oil together by heating to 75°C to 85°C while stirring to make the oleaginous phase.
3. After cooling the oleaginous phase to approximately 55°C, add the triacetin solution while mixing to make a homogenous dispersion. Mixing should be of sufficient intensity to disperse the triacetin solution finely and uniformly.
4. Continue mixing while cooling at room temperature.

BETAMETHASONE GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
1.00	1	Betamethasone valerate	1.00
100.00	2	Ethanol (96%)	100.00
200.00	3	Propylene glycol	200.00
220.00	4	Lutrol F 127	220.00
QS	5	Water QS	470.00

Manufacturing Directions

1. Prepare a solution of items 1 to 3 at room temperature and a solution of items 4 and 5 at approximately 6°C (or at >70°C).
2. Mix both solutions.
3. Maintain the temperature until the air bubbles disappear.
4. A certain amount of propylene glycol could be substituted by water. The obtained gel is clear and colorless.

BETAMETHASONE OPTHALMIC OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Betamethasone sulfate	10.00
5.00	2	Liquid paraffin	50.00
5.00	3	Cetostearyl alcohol	50.00
5.00	4	Hard paraffin	50.00
84.00	5	Soft paraffin	840.00

Manufacturing Directions

1. Load items 2 to 5 in a melting vessel. Heat to 145°C and keep it at this temperature for 45 minutes.
2. Allow to cool to room temperature.
3. In a separate vessel, dissolve item 1 in 200 mL of water for injection and add to step 1 under aseptic condition.
4. Fill and sterilize in tubes.

BETAMETHASONE VALERATE AND CINCHOCAINE OINTMENT

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Cinchocaine hydrochloride	5.00
1.00	2	Betamethasone valerate	1.00
75.00	3	Hydrogenated castor oil	75.00
400.00	4	Eutenol G (2-octyldodecanol)	400.00
75.00	5	PEG-400 monoricinoleate	75.00
0.08	6	Lavender oil	0.08
443.00	7	Castor oil	443.00

Manufacturing Directions

1. Charge items 3, 4, 5, and 7 in a melting vessel and heat to 85°C. Melt to a clear solution and cool down to 65°C. Transfer to Becomix.
2. Mix in Becomix at 65°C under vacuum. Cool down to 50°C.
3. Add items 1 and 2 in a small portion of the melt from step 2 in a separate vessel and homogenize and then add to step 3.
4. Add item 6 at 30°C and mix for 10 minutes.
5. Transfer to storage vessel and fill.

BETAMETHASONE VALERATE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.10	1	Betamethasone valerate (34% excess)	1.34
2.00	2	Polyoxyl 20 cetosteaiyl ether (Cetomacrogol 1000)	20.00
8.00	3	Cetosteaiyl alcohol	80.00
0.10	4	Methyl paraben	1.00
0.034	5	Propyl paraben	0.34
0.10	6	Chlorocresol	1.00
6.00	7	Mineral oil (liquid paraffin)	60.00
0.29	8	Monobasic sodium phosphate	2.90
17.80	9	Petrolatum (soft white paraffin)	178.00
66.00	10	Purified water	660.00

Manufacturing Directions

1. Heat item 10 to 90°C in a mixer.
2. Dissolve items 4 and 5 (parabens) to a clear solution by stirring.

3. Dissolve 3 g of item 2 in the parabens solution while stirring.
4. Dissolve items 6 and 8 in the parabens solution while stirring.
5. Set the mixer at a temperature of 65°C to 70°C and speed at 8 rpm. Use manual mode.
6. Load 17 g of items 2, 3, and 9 and 45 g of item 7 in a fat-melting vessel.
7. Heat to 70°C to 75°C while stirring. Maintain temperature at 65°C to 75°C.
8. Mix item 1 in 10 g of item 7 in a stainless-steel container.
9. Homogenize for 10 minutes to make a smooth slurry.
10. Check the temperature of the aqueous phase in the mixer (should be 65–70°C).
11. Check the temperature of the fatty phase in the fat-melting vessel (should be 65–70°C).
12. Set the mixer speed 8 rpm and vacuum at 0.4 to 0.6 bar.
13. Transfer the fatty phase to the aqueous phase in mixer vessel through filter under vacuum, while mixing.
14. Start the homogenizer at high speed. Homogenize for 10 minutes.
15. Check and record the pH of cream (limit: 4.5–5.2 at 30°C).
16. Cool the temperature to 50°C while mixing. Release the vacuum.
17. Take out 400 g of the cream into the stainless-steel vessel and set aside.
18. Add slurry from earlier step to the remaining cream base in mixer.
19. Rinse the container of slurry using 5 g of item 7 and transfer the rinsing to the mixer.
20. Homogenize for 10 minutes at high speed (mixer speed 8 rpm).
21. Load 400 g cream from step above to the mixer.
22. Set the mixer in manual mode at 8 rpm and a vacuum of 0.4 to 0.6 bar.
23. Homogenize at high speed with recirculation, temperature 25°C. Homogenize for 10 minutes with recirculation, stop the homogenizer, and continue mixing to produce a white, homogeneous cream of pH 4.5 to 5.2 at 30°C.

BETAMETHASONE VALERATE FOAM

Each gram of foam contains 1.2 mg betamethasone valerate USP in a hydroalcoholic, thermolabile foam. The foam also contains cetyl alcohol, citric acid, ethanol (60.4%), polysorbate 60, potassium citrate, propylene glycol, purified water, and stearyl alcohol and is dispensed from an aluminum can pressurized with a hydrocarbon propellant (propane/butane).

BETAMETHASONE VALERATE OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.100	1	Betamethasone, USE: Betamethasone valerate	1.300
84.870	2	Petrolatum (white soft paraffin)	848.700
15.000	3	Mineral oil (liquid paraffin)	150.000

Manufacturing Directions

1. Melt item 2 in a fat-melting vessel at 75°C. While mixing, do not overheat.
2. Maintain temperature of the molten mass in the melting vessel at 60°C to 65°C.
3. Start the steam on the mixer vessel and set the temperature at 60°C.
4. Transfer 160 g of the molten mass at 60°C to the mixer vessel. Retain the rest of the quantity in the fat-melting vessel.
5. Start mixing in the mixer vessel at medium speed with vacuum between 0.4 and 0.6 bar until obtaining an actual temperature of 40°C to 45°C.
6. Maintain the temperature of mixer vessel at 40°C to 45°C. Add item 1 to 80 g of item 3 and homogenize for 3 minutes, using homogenizer. Keep the slurry aside.
7. Rinse the homogenizer and container with 70 g of item 3. Transfer item 1 slurry from step above and the rinsing from previous step to the mixer vessel. Start mixing under vacuum 0.4 to 0.6 bar for 15 minutes. Temperature should be maintained at 40°C to 45°C.
8. Transfer the rest of the quantity of molten mass (temperature 60°C) into mixer vessel slowly, continuing to mix for 5 minutes after each addition. At the end of addition, mix a further 10 minutes under vacuum 0.4 to 0.6 bar.
9. Homogenize for 5 minutes at high speed under vacuum 0.4 to 0.6 bar.
10. Cool the ointment to 30°C to 35°C while stirring under a vacuum of 0.4 to 0.6 bar.

BETAMETHASONE VALERATE OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.100	1	Betamethasone USE betamethasone valerate with 10% excess	1.34
0.020	2	Vitamin E oily	0.20
79.34	3	White soft paraffin	793.40
3.00	4	Cetostearyl alcohol	20.00
2.50	5	Cetmacrogol 1000	25.00
15.00	6	Liquid paraffin	150.00

Manufacturing Directions

1. Melt item 3 in a fat-melting vessel at 60°C, add items 4 and 5, and mix until clear.
2. Transfer to Becomix at 60°C. Mix at 9 rpm under vacuum of 0.4 to 0.6 bar. Cool to 40°C to 45°C.
3. Add items 1, 2, and 6 to a stainless-steel container and homogenize for 3 minutes. Transfer slurry to step 2.
4. Mix under vacuum at 40°C to 45°C.
5. Transfer to storage vessel and fill.

BIFONAZOLE CREAM (1%)

Formulation

I. Cetyl stearyl alcohol, 7.0 g, Cremophor A 6 (1), 1.5 g, Cremophor A 25 (1), 1.5 g, liquid paraffin, 12.0 g, paraben(s), 0.2 g
II. Water, 68.8 g
III. Propylene glycol (1), 8 g, bifonazole, 1 g

Manufacturing Directions

Heat the mixture I and the water II separately to approximately 80°C. Add the water II to the obtained solution I with rigorous stirring. Heat III until the active ingredient is dissolved, mix with I/II, and continue to stir during cooling to room temperature.

This formulation could be used for other active ingredients too.

BISACODYL SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
5.000	1	Bisacodyl (micronized)[a] 2% excess	5.10
447.500	2	Hard fat (Witepsol E 76®)	447.50
447.500	3	Hard fat (Witepsol W 45)	447.50

[a] 100% particles should be less than 70 m. Fill weight: 1800 mg/ suppository

Manufacturing Directions

1. The molten suppository mass must be kept stirred throughout the storage period during manufacturing and during filling to avoid the sedimentation of active drug. The active ingredient causes skin irritation, which vanishes after sometime without having after effects. Avoid dust formation during processing. In particular, protect eyes and mucous membranes.
2. Load items 2 and 3 in the fat-melting vessel and heat to 50°C ± 3°C.
3. Transfer the molten mass to mixer through filter sieves. Set the temperature at 40°C ± 2°C. Load item 1 to the mixer containing the molten mass. Carefully mix the powder with the molten mass.
4. Set the mixer at temperature 40°C ± 2°C, speed 10 rpm (manual mode), and mix for 20 minutes. Set the mixer at temperature 40°C ± 2°C, speed 10 rpm (manual mode), vacuum 0.6 bar.
5. Homogenize at low speed while mixing for 10 minutes. Homogenize at high speed while mixing for 3 minutes.
6. Continue mixing of the mass under vacuum in mixer.
7. Heat the storage vessel, set the temperature at 40°C ± 2°C.
8. Transfer the molten mass from mixer to the storage vessel. Hold the mass at 40°C ± 2°C while mixing continuously at low speed.
9. Fill weight is 900 mg/suppository, but use a fill weight of 1.8 g for 10 mg suppositories.

BISACODYL SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
10.00	1	Bisacodyl (micronized) 2% excess	10.02
895.00	2	Witepsol E 76	895.00
895.00	3	Witepsol W 45	895.00

Manufacturing Directions

1. Charge items 2 and 3 to a melting vessel, heat to 50°C, transfer to Becomix through filter sieve. Set temperature to 40°C.
2. Charge item 1 and mix carefully. Set temperature to 40°C, speed 10 rpm for 20 minutes.
3. Homogenize for 3 minutes. Continue mixing under vacuum.
4. Transfer to storage vessel and fill.

BISCARBOXYCHROMONYLOXY PROPANOL OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
4.00	1	Disodium 1,3-bis(2-carboxychromonyloxy) propan-2-ol (micronized)	40.00
76.80	2	Yellow soft paraffin	768.00
9.60	3	Liquid paraffin	96.00
9.60	4	Lanolin acetylated (Modulan R)	96.00

Manufacturing Directions

1. Slowly add the disodium salt of 1,3-bis(2-carboxy-chromon-5-yloxy) propan-2-ol in small portions, with vigorous mixing, to a small portion of the pre-heated and sterilized components of the ointment base at 90°C.
2. When the addition is complete, continue mixing for a further 15 minutes and then sterilize the concentrated dispersion by heating at 150°C for 1 hour.
3. Then add the concentrated dispersion to a homogenizer heated at 80°C to 100°C and slowly add the remaining components of the ointment basis with continuous blending.
4. When this addition is complete, blend the molten ointment for a further 15 minutes and then cool to a temperature of 58°C to 62°C.
5. Then fill the ointment in presterilized eye ointment tubes, which are crimped and allowed to cool to room temperature.

BLEACHING AND ANTIMICROBIAL DENTIFRICE

Manufacturing Directions

Weight percentage: Hydrogen peroxide (50%), 10.00; carbamide peroxide, 14.00; sodium fluoride, 0.38; Pecogel S-2120 (VP/Dimethicolylacrylate is an inclusion complex polymer to retard the solubility of emulsified bleaching actives. It is obtained from Phoenix Chemical, Inc.), 0.50; hydroxyethyl cellulose, 0.50; triethanolamine, 0.30; water purified, 10.00; glycerin, 10.75; tetrafluoroethylene (Teflon), 50.58; sodium lauryl sulfate, 1.25; sodium saccharine, 0.18; sodium citrate, 0.20; citric acid, 0.20; triclosan, 0.06; flavor, 1.10.

BREAST CARE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Polysorbate 60	20.00
70.00	2	Cetyl alcohol	70.00
60.00	3	Mineral oil 70cS	60.00
40.00	4	Glyceryl stearate	40.00
QS	5	Deionized water	QS
QS	6	Preservative	QS

Manufacturing Directions

1. Heat oil and water phases separately at 65°C to 70°C.
2. Add water phase to oil phase while stirring. Stir to cool.
3. Fill at 20°C. Only food-grade materials should be used in this preparation. Do not use unapproved preservatives.

BUDESONIDE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.25	1	Budesonide	0.25
30.00	2	Polyoxy 40 stearate	30.00
80.00	3	Stearyl alcohol	80.00
150.00	4	Liquid paraffin	150.00
30.00	5	White soft paraffin	30.00
0.10	6	Ethylene diamine tetraacetate	0.10
3.00	7	Carbopol 934	3.00
0.67	8	Sodium hydroxide	0.67
0.70	9	Sodium methyl paraben	0.70
0.30	10	Sodium propyl paraben	0.30
QS	11	Water purified	685.00

Manufacturing Directions

1. Melt white soft paraffin, stearyl alcohol, and polyoxyl 40 stearate in the fat-melting vessel at 70°C to 75°C.
2. Heat the purified water in the manufacturing vessel to a temperature of 80°C to 90°C. Disperse Carbopol 934 in the heated water. Homogenize the dispersion to obtain clear gel.

3. Dissolve item 6, sodium methyl paraben, sodium propyl paraben, and sodium hydroxide in purified water. Transfer this solution to the clear gel from step 2 in the manufacturing vessel and homogenize well.
4. Transfer the fat phase (70–75°C) into the manufacturing vessel containing aqueous phase (70–75°C) while mixing. Homogenize under vacuum for few minutes.
5. Disperse budesonide with liquid paraffin in a stainless-steel container at 40°C to 45°C and transfer this dispersion to the manufacturing vessel from step 4 at temperature 40°C to 45°C; mix and homogenize under vacuum to obtain a smooth, homogeneous cream and the stated amount of budesonide per 100 g.
6. Cool the cream to 25°C to 30°C while stirring continuously.

BUDESONIDE OINTMENT

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.25	1	Budesonide	0.25
369.75	2	Liquid paraffin	369.75
450.00	3	Hard paraffin	450.00
150.00	4	White wax	150.00
30.00	5	Hydrogenated castor oil	30.00

Manufacturing Directions

1. Melt hard paraffin, white wax, and hydrogenated castor oil in the fat-melting vessel at 100°C and maintain this temperature for 20 minutes. Then transfer this melted mass to the manufacturing vessel preheated to 85°C through 0.150 mm. Cool to 33°C while stirring.
2. Disperse budesonide with liquid paraffin at 33°C; use homogenizer to get homogeneous suspension.
3. Transfer the dispersion from step 2 to the ointment base from step 1 in the manufacturing vessel while stirring. Homogenize well to obtain a homogeneous ointment containing the stated amount of budesonide per 100 g ointment.
4. Filling in the tube is performed in an aseptic area at 33°C.

BUPRENORPHINE HYDROCHLORIDE SUPPOSITORY

Manufacturing Directions

1. Propylene glycol, 10 g; polyethylene glycol 400, 10 g; polyethylene glycol 1000, 30 g; polyethylene glycol 6000, 50 g; buprenorphine hydrochloride, 43.2 mg.
2. After mixing propylene glycol and polyethylene glycol 400, blend and dissolve buprenorphine hydrochloride, and blend the mixture with the separately heated and dissolved polyethylene glycol 1000 and 6000.
3. Place the combined mixture into a container for suppository. Cool and let solidify to obtain a suppository of buprenorphine hydrochloride (suppository weight 1.5 g/piece, each containing 0.6 mg of buprenorphine).

BURN CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
120.00	1	Glyceryl stearate SE (monthybase)	120.00
80.00	2	Octyldodecyl myristate (MOD)	80.00
20.00	3	Apricot kernel oil PEG-6 esters (Labrafil M 1944 CS)	20.00
0.50	4	Sodium methyl paraben	0.50
0.50	5	Sodium propyl paraben	0.50
0.50	6	Sorbic acid	0.50
767.50	7	Deionized water	767.50
10.00	8	Avocado oil	10.00
1.00	9	Fragrance	1.00

Manufacturing Directions

1. Mix and heat items 1 to 7 to 75°C. Cool slowly with stirring.
2. At 30°C, add item 8 and then item 9.

BURN CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
15.00	1	Magnesium aluminum silicate (Veegum)	15.00
568.00	2	Deionized water	568.00
30.00	3	Propylene glycol	30.00
2.00	4	Dimethicone emulsion	2.00
100.00	5	Mineral oil, light	100.00
170.00	6	Acetylated lanolin alcohol	170.00
50.00	7	Benzocaine USP	50.00
30.00	8	C-18-C36 acid	30.00
120.00	9	Glyceryl stearate and PEG-100 stearate	120.00
5.00	10	Polysorbate 60	5.00
QS	11	Preservatives	QS

Manufacturing Directions

1. Add item 1 to water slowly, agitating with extensive shear force until smooth.
2. Add items 3 and 4 to the mixture and heat to 75°C to 80°C. Mix and heat items 5 to 11, keeping item 7 suspended to 75°C to 80°C. Mix the two parts while cooling. Pour and fill at 40°C.

BUTENAFINE HYDROCHLORIDE CREAM

Butenafine cream, 1%, contains the synthetic antifungal agent butenafine hydrochloride. Each gram of cream, 1%, contains 10 mg of butenafine hydrochloride in a white cream base of purified water USP, propylene glycol dicaprylate, glycerin USP, cetyl alcohol NF, glyceryl monostearate SE, white petrolatum USP, stearic acid NF, polyoxyethylene cetyl ether, benzyl alcohol NF, diethanolamine NF, and sodium benzoate NF.

BUTESIN PICRATE AND METAPHEN OINTMENT

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
6.48	1	Lanolin anhydrous	6.48
0.219	2	Metaphen chloride powder	0.219
QS	3	Acetone	0.96
8.80	4	Sodium borate	8.80
2.48	5	Potassium chloride	2.48
QS	6	Water purified	253.70
115.00	7	Beeswax white	115.00
80.00	8	Wax ceresin white	80.00
510.00	9	Mineral oil	510.00
10.00	10	Butyl aminobenzoate (Butesin) picrate powder	10.00
13.31	11	2-Ethoxyethanol (Cellosolve)	13.31

Manufacturing Directions

1. Melt lanolin in vacuum flask and heat to 45°C to 60°C. Use sufficient acetone to completely dissolve metaphen chloride. Add metaphen solution to melted lanolin and mix thoroughly. Use vacuum to remove all acetone.
2. Dissolve borax and potassium chloride in the purified water at 85°C to 90°C.
3. Melt beeswax, ceresin wax, and mineral oil and strain into ointment mixing tub at 95°C.
4. Add prepared base (step 1) to melted oil–wax mixture (step 4).
5. Add borax–potassium chloride solution (step 2) to oil–wax mixture with constant stirring.
6. Mix for 1 hour.
7. Dissolve Butesin picrate in warm (50°C) Cellosolve and filter. Hold solution at 50°C for use in following step.
8. Adjust temperature of mass from step 5 to 50°C (this temperature is important).
9. Add Butesin picrate solution (at 50°C) to mass (at 50°C), with constant stirring.
10. Mix for several hours. Circulate cold water in jacket overnight.
11. Mill to smooth ointment and fill suitable containers.

BUTESIN PICRATE OINTMENT

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
249.40	1	Water purified	249.40
8.85	2	Sodium borate powder	8.85
2.47	3	Potassium chloride	2.47
1.00	4	Methyl paraben	1.00
1.00	5	Propyl paraben	1.00
6.65	6	Lanolin anhydrous	6.65
114.60	7	Beeswax white	114.60
79.82	8	Wax ceresin white	79.82
405.30	9	Oil mineral light	405.30
119.90	10	Oil-neutral vegetable triglycerides mixture: Miglyol 812; Neobee M-5	119.90
10.00	11	Butyl aminobenzoate picrate (butesin picrate), 11% excess	11.10

Manufacturing Directions

1. Place purified water into a suitable steam tank and begin heating to 85°C to 90°C.
2. Add borax and potassium chloride and mix until dissolved (at 85–90°C).
3. Add parabens to above solution and mix for at least 15 minutes (at 85–90°C) or until dissolution.
4. Melt lanolin, beeswax, ceresin wax, and mineral oil into a suitable equipment. Heat mixture to 90°C to 95°C. Mix until uniform.
5. Filter the melted waxes from step 4 through a 74 µm aperture SS screen into a suitable mixing tank.
6. Heat waxes to 90°C to 95°C while mixing slowly.
7. Filter approximately 6.3 mL of borax-potassium-paraben solution (at 85–90°C) from step 2 slowly through a 74 µm aperture SS screen into the wax-oil mixture from step 5. *Caution*: Slow the addition of water solution if the product shows tendency to bubble over the side of the equipment.
8. While mixing, slowly pass the remaining borax-potassium-paraben solution (at 85–90°C) from step 2 through a 74 µm aperture SS screen into the wax-oil mixture from step 5. See caution above.
9. If necessary, adjust batch temperature to 85°C to 90°C and maintain temperature of batch at 85°C to 90°C while mixing for 60 minutes (range 60–75 minutes).

10. Add Neobee M-5 oil to a clean suitable SS container and start heating to 72°C (70–74°C). Add and dissolve the butyl aminobenzoate picrate while mixing and maintaining temperature at 72°C (70–74°C).
11. Reduce main batch temperature to 70°C (68–72°C) while continuing mixing slowly.
12. Filter Neobee M-5 oil-butyl picrate solution at 72°C (70–74°C) through a 74 µm aperture SS screen into the main batch, mixing and maintaining temperature at 70°C (68–72°C).
13. Continue mixing and maintain main batch temperature at 70°C (68–72°C) for 15 to 30 minutes.
14. While mixing slowly cool the main batch to 40°C to 45°C. Maintain 40°C to 45°C temperature and continue mixing for at least 10 minutes. *Note*: Use 35°C (30–40°C) water for cooling. Do not force cool with cold water.
15. Set cooling water to 20°C (range 18–25°C) and continue cooling batch to 25°C to 30°C while mixing. When batch reaches 25°C to 30°C, stop mixing. The product is ready for milling. *Note*: The cooling water temperature must not drop below 18°C.
16. Pump product to roller mill and mill at high speed to a smooth uniform consistency.
17. Collect product in suitable bulk containers.
18. Fill in suitable containers. Theoretical tube fill weight: 30 g, minimum 28.35 g. If product does not flow freely, heat the water in hopper jacket to a maximum of 40°C.

BUTOCONAZOLE NITRATE VAGINAL CREAM

The butoconazole nitrate vaginal cream, 2%, contains butoconazole nitrate, 2%, in a cream of edetate disodium, glyceryl monoisostearate, methyl paraben, mineral oil, polyglyceryl-3 oleate, propylene glycol, propyl paraben, colloidal silicon dioxide, sorbitol solution, purified water, and microcrystalline wax. Another formulation contains inactive ingredients cetyl alcohol, glyceryl stearate and PEG-100 stearate, methyl paraben and propyl paraben (preservatives), mineral oil, polysorbate 60, propylene glycol, sorbitan monostearate, stearyl alcohol, and water (purified).

CALAMINE AND DIPHENHYDRAMINE HYDROCHLORIDE LOTION

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
8.00	1	Calamine	80.00
1.00	2	Diphenhydramine hydrochloride	10.00
0.10	3	Camphor	1.00
2.40	4	Alcohol	24.00
70.00	5	Water purified	700.00
2.70	6	Carboxymethylcellulose	27.00
7.00	7	Zinc oxide	70.00
2.00	8	Water purified	20.00
0.06	9	Ferric oxide yellow	0.60
1.00	10	Zinc oxide	10.00
1.00	11	Glycerin	10.00
1.50	12	Glycerin	15.00
0.12	13	Ferric oxide red	1.20
QS	14	Perfume	QS
QS	15	Water purified	QS to 1 kg

Manufacturing Directions

1. Hydrate item 6 in item 5 and disperse item 7 in the suspension.
2. Mix the ferric oxides in items 10 and 11, homogenize, and add to step 1.
3. Dissolve item 2 in item 15 at 75°C, dissolve camphor and perfume in alcohol, and add to step 2.
4. Add item 12 and blend well.
5. QS to volume with item 15.

CALAMINE AND PRAMOXINE HYDROCHLORIDE LOTION

Active ingredients are calamine, 8%, and pramoxine hydrochloride, 1%. Inactive ingredients include caladryl lotion, alcohol USP, camphor, diazolidinyl urea, fragrance, hydroxypropylmethylcellulose, methyl paraben, oil of lavender, oil of rosemary, polysorbate 80, propylene glycol, propyl paraben, purified water, and xanthan gum.

CALAMINE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
80.00	1	Polawax GP200	80.00
10.00	2	Polysorbate 60	10.00
50.00	3	Caprylic/Capric triglyceride	50.00
QS	4	Deionized water	QS to 1 kg
100.00	5	Witch hazel distillate	100.00
50.00	6	Glycerin	50.00
20.00	7	Zinc oxide	20.00
20.00	8	Calamine	20.00
QS	9	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 65°C to 70°C.
2. Add water phase to oil phase while stirring.
3. Add zinc oxide and calamine under high shear. Stir to cool.

CALAMINE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Microcrystalline cellulose (Avicel RC-591)	20.00
100.00	2	Glycerin	100.00
1.80	3	Methyl paraben	1.80
0.20	4	Propyl paraben	0.20
100.00	5	Glyceryl stearate and PEG-100 stearate	100.00
25.00	6	Cetyl alcohol	25.00
50.00	7	Zinc oxide	50.00
50.00	8	Calamine	50.00
653.00	9	Distilled water	653.00

Manufacturing Directions

1. Mix item 2 with item 9 and heat to 75°C.
2. Add items 3 and 4. Mix until dissolved using a shearing mixer.
3. Maintain temperature at 75°C and gradually add item 1. Continue mixing at 75°C for 15 minutes or until item 1 is homogenously dispersed. Mix well.
4. When temperature drops to 60°C to 65°C, gradually add items 7 and 8. Mix well until powders are homogenously dispersed.
5. Pass through homogenizer if necessary. Adjust theoretical weight with warm distilled water and continue mixing until the cream congeals.

CALAMINE LOTION

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/1000 Tablets (g)
78.30	1	Calamine	78.30
78.30	2	Zinc oxide	78.30
19.60	3	Glycerin	19.60
230.80	4	Deionized water	230.80
558.00	5	Calcium hydroxide solution	558.00
34.40	6	Purified bentonite (Polargel NF)	34.40
0.60	7	Carboxymethylcellulose	0.60

Manufacturing Directions

1. Prepare a saturated item 5 solution using 3 g of item 5 in 1000 mL purified water, mixing vigorously for 1 hour.
2. Decant the clear supernatant liquid for use in the formula.
3. Add the balance of water. Add item 6 and item 7 to the above solution with rapid mixing for 15 minutes.
4. In a separate vessel, blend items 1 and 2.
5. Add item 3 and mix until uniform. Begin adding the aqueous solution with mixing until it is blended into a lotion.

CALCIPOTRIENE CREAM

Calcipotriene cream, 0.005%, contains calcipotriene monohydrate, a synthetic vitamin D3 derivative, for topical dermatological use. The cream contains calcipotriene monohydrate equivalent to 50 g/g anhydrous calcipotriene in a cream base of cetearyl alcohol, ceteth-20, diazolidinyl urea, dichlorobenzyl alcohol, dibasic sodium phosphate, edetate disodium, glycerin, mineral oil, petrolatum, and water.

CALCIPOTRIENE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00 mg	1	Calcipotriene	10.00 mg
1.00	2	Almond oil	10.00
40.00	3	Mineral oil	400.00
20.00	4	Self-emulsifying beeswax	200.00
QS	5	Water purified	QS to 1 kg

Manufacturing Directions

1. Add and dissolve item 1 in item 2.
2. Add to this solution item 3 and item 4.

3. Heat the mixture to liquefy at 70°C.
4. In a separate vessel, heat item 5 to 80°C and add to step 3.
5. Mix well and then homogenize.
6. Cool and fill.

CALCIUM CARBONATE OINTMENT

Formulation

Calcium carbonate, 250 mg; magnesium hydroxide, 200 mg; aluminum hydroxide, 225 mg; dibucaine (1% in petrolatum), 100 mg; anhydrous lanolin, 28.35 g; hydrophilic ointment, 28.35 g; petrolatum, 10 g; water, 5 mL.

1. Calcium carbonate, magnesium hydroxide, and the aluminum hydroxide are substantially insoluble in water. To assist in the dispersion of these components in the base carrier material, form a paste therefrom by adding a little water at a time to form a relatively homogeneous dispersion thereof.
2. Then add dibucaine (1%), which is provided in a petrolatum base, with mixing to obtain a smooth homogeneous mixture.
3. Then mix nhydrous lanolin and hydrophilic ointment to provide a homogeneous composition; then blend with the dispersion of calcium carbonate, magnesium hydroxide, aluminum hydroxide, and dibucaine.
4. Mix the entire composition thoroughly to ensure a homogeneous dispersion of all of the ingredients.
5. Calcium carbonate and magnesium hydroxide provide a relatively rapid neutralization of the area under treatment. Aluminum hydroxide, however, provides a slower, longer-lasting neutralization in addition to a mild astringent effect. The 1% dibucaine hydrochloride dispersed in petrolatum is used for its analgesic or anesthetic effect and the amount may be varied to increase or decrease the anesthetic effect depending on the condition being treated. Anhydrous lanolin and hydrophilic ointment are utilized to provide a base for the composition, which facilitates its application and retention in the area of treatment.

CAMPHOR, EUCALYPTUS OIL, AND MENTHOL OINTMENT

Camphor, eucalyptus oil, and menthol ointment contains camphor, 5.2%, eucalyptus oil, 1.2%, and menthol, 2.8%. Inactive ingredients are carbomer 954, cedar leaf oil, cetyl alcohol, cetyl palmitate, cyclomethicone copolyol, dimethicone copolyol, dimethicone, ethylene diamine tetraacetate, glycerin, imidazolidinyl urea, isopropyl palmitate, methyl paraben, nutmeg oil, PEG-100 stearate, propyl paraben, purified water, sodium hydroxide, stearic acid, stearyl alcohol, thymol, titanium dioxide, turpentine oil.

CARBAMAZEPINE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Carbamazepine	10.00
50.00	2	Propylene glycol	500.00
5.00	3	Cetostearyl alcohol	50.00
1.00	4	Sodium lauryl sulfate	10.00
43.00	5	Water purified	430.00

Manufacturing Directions

1. Prepare an oil-in-water emulsion to form an elegant cream. Dissolve carbamazepine in pure powder form in propylene glycol (e.g., up to approximately 95%). Alternatives for the aqueous phase include alcohol, such as ethanol or isopropanol, with a thickener added, for example, carbomer 934 or 940.
2. The oil phase preferably includes mineral oil, petrolatum, cetyl alcohol, or stearyl alcohol. Emulsifiers such as polysorbate 80, sorbitan monostearate, or others known in the art may be used. Buffering agents, antioxidants, and chelating agents may be added to improve the characteristics of the formulation.

CARBAMAZEPINE GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Carbamazepine	50.00
93.00	2	Propylene glycol	930.00
2.00	3	Carbopol 934	20.00
QS	4	Sodium hydroxide (to neutralize item 3)	QS

CARBAMAZEPINE OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
3.00	1	Carbamazepine	30.00
5.00	2	Mineral oil	50.00
92.00	3	Petrolatum	920.00

Manufacturing Directions

1. Micronize carbamazepine to provide particles with a size distribution primarily below 10 μm.
2. Add item 1 to mineral oil to form a finely dispersed suspension. Homogenize.
3. Add and mix item 3 and homogenize again.

CARBAMIDE PEROXIDE CHEWING GUM

Formulation

Gum base, 26.25 g; calcium carbonate, 3.75 g; sorbitol, 28.05 g; mannitol, 7.50 g; maltitol, 21.62 g; glycerin, 1.00 g; flavorant, 3.15 g; gum arabic, 1.16 g; titanium dioxide, 0.17 g; wax candellia, 0.03 g; sodium stearate/sodium palmitate 50%, each 3.00 g; tripolyphosphate sweetener, 0.82 g; Imwitor 370, 1.00 g; carbamide peroxide, 3.00 g.

Manufacturing Directions

1. Heat the gum base to sufficiently soften the base without adversely affecting the physical and chemical makeup of the base.
2. Then add the molten gum base and the filler to a mixing kettle.
3. Add the sugar alcohols, glycerin, flavor, high-intensity sweetener, and stain-removing agent carbamide peroxide last with mixing to obtain a homogenous mixture.
4. Then discharge the mixture from the mixing kettle and roll and scor into a desired piece size by conventional techniques.

2-CARBAMOYLPYRAZINAMIDE OINTMENT

Manufacturing Directions

1. Dissolve 2-Carbamoylpyrazinamide, also known as 2, 3-pyrazinedicarboxamide, 1 g, in 5 L of water and 4 mL of acetone.
2. Admix the solution with USP grade hydrophilic ointment (90 g) to a uniform consistency.
3. Store the ointment thus prepared in opaque jars at room temperature.

CASTOR OIL OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
68.80	1	Castor oil	688.00
10.00	2	Hydrogenated castor oil	100.00
8.70	3	Balsam Peru oil	87.00
0.018	4	Trypsin	0.180
QS	5	Safflower oil	QS to 1 kg

Manufacturing Directions

This is an enzymatic wound debrider.

1. Disperse the aluminum/magnesium hydroxide stearate in the castor oil.
2. Add the hydrogenated castor oil while mixing with a high-shear mixer.
3. Continue mixing until a semisolid forms.
4. Then blend the remaining ingredients with the semisolid until homogeneous mixing appears.

CEFACLOR AND BENZOYL PEROXIDE GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
3.00	1	Cefaclor	30.00
5.00	2	Benzoyl peroxide	50.00
92.00	3	Gel carrier or vehicle	920.00
QS	4	Alcohol 70%	QS
QS	5	Citric acid for pH adjustment	QS

Manufacturing Directions

1. To a first container, add the benzoyl peroxide and the gel carrier or vehicle ingredients (approximately 5 g of benzoyl peroxide and approximately 89 g of gel carrier or vehicle).
2. To a second container, add powdered cefaclor (approximately 3 g of cefaclor) and dissolve in item 4 and add to step 1.
3. Adjust pH using citric acid.

CEFACLOR AND BENZOYL PEROXIDE LOTION

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
7.00	1	Ethoxylated cetyl stearyl alcohol	70.00
0.75	2	Cetyl alcohol	7.50
5.00	3	Isostearyl neopentanoate	50.00
0.10	4	Butylated hydroxyanisole	1.00
0.25	5	Polyoxyl 40 stearate	2.50
66.80	6	Water purified	668.00
3.00	7	Propylene glycol	30.00
5.00	8	Benzoyl peroxide micronized	50.00
10.00	9	Acetone	100.00
0.10	10	Dioctyl sodium sulfosuccinate	1.00
2.00	11	Cefaclor	20.00

CETRIMIDE ANTISEPTIC CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Cetearyl alcohol and cetrimonium bromide	50.00
75.00	2	White petroleum jelly	75.00
60.00	3	Mineral oil 70 cS	60.00
QS	4	Deionized water	QS to 1 kg
QS	5	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 60°C to 65°C.
2. Add the water phase to the oil phase while stirring.
3. Stir to cool.

CETRIMONIUM BROMIDE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Cetearyl alcohol and cetrimonium bromide	50.00
75.00	2	White petroleum jelly	75.00
60.00	3	Mineral oil (70 cS)	60.00
QS	4	Deionized water	QS to 1 kg
QS	5	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 60°C to 65°C.
2. Add water phase to oil phase while stirring. Stir to cool.

CHLORAMPHENICOL OPTHALMIC OINTMENT

Each gram of ophthalmic ointment, 1%, contains 10 mg chloramphenicol in a special base of liquid petrolatum and polyethylene. It contains no preservatives. Another formulation contains active ingredient chloramphenicol, 11%.

CHLORHEXIDINE AND CETRIMONIUM BROMIDE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Polawax GP200	50.00
10.00	2	Lanolin	10.00
150.00	3	Mineral oil 70 cS	150.00
70.00	4	Cetearyl alcohol	70.00
30.00	5	Dimethicone	30.00
QS	6	Deionized water	QS to 1 kg
5.00	7	Cetrimonium bromide	5.00
0.50	8	Chlorhexidine gluconate	0.50
QS	9	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil (items 1–5) and water (items 6–9) phases to 65°C.
2. Add water phase to oil phase while stirring.
3. Stir to cool. Fill.

CHLORHEXIDINE GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Chlorhexidine diacetate	20.00
300.00	2	1,2-Propylene glycol pharma	300.00
220.00	3	Lutrol F 127	220.00
460.00	4	Water	460.00

Manufacturing Directions

1. Dissolve chlorhexidine diacetate in propylene glycol at >70°C, stir well, and slowly add Lutrol F 127 and water.
2. Maintain the temperature until the air bubbles escape. A clear, colorless gel is obtained.

CHLORPROMAZINE SUPPOSITORIES

Each suppository contains chlorpromazine (25 or 100 mg), glycerin, glyceryl monopalmitate, glyceryl monostearate (10 mg/g), and preservative chlorobutanol (chloral derivative), 0.5% (5 mg/g), and inactives white petrolatum, mineral oil, polyoxyl 40 stearate, polyethylene glycol 300 and petrolatum and lanolin alcohol, hydrogenated coconut oil fatty acids, and hydrogenated palm kernel oil fatty acids.

CICLOPIROX CREAM, LOTION, AND GEL

Cream, 0.77%, and lotion, 0.77%, are for topical use. Each gram of cream contains 7.70 mg ciclopirox (as ciclopirox olamine) in a water-miscible vanishing cream base consisting of purified water USP, cetyl alcohol NF, mineral oil USP, octyl-dodecanol NF, stearyl alcohol NF, cocamide DEA, polysorbate 60 NF, myristyl alcohol NF, sorbitan monostearate NF, lactic acid USP, and benzyl alcohol NF (1%) as preservative. Each gram of lotion contains 7.70 mg ciclopirox (as ciclopirox olamine) in a water-miscible lotion base consisting of purified water USP, cocamide DEA, octyldodecanol NF, mineral oil USP, stearyl alcohol.

CICLOPIROX NAIL VARNISH

NF, cetyl alcohol NF, polysorbate 60 NF, myristyl alcohol NF, sorbitan monostearate NF, lactic acid USP, and benzyl alcohol NF (1%) as preservative. Cream and lotion contain a synthetic, broad-spectrum antifungal agent ciclopirox (as ciclopirox olamine). Each gram of gel contains 7.70 mg ciclopirox in a gel consisting of purified water USP, isopropyl alcohol USP, octyldodecanol NF, dimethicone copolyol 190, carbomer 980, sodium hydroxide NF, and docusate sodium USP.

CICLOPIROX NAIL VARNISH

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
57.50	1	Isopropyl alcohol	575.00
33.00	2	Ethyl acetate	330.00
3.80	3	Polyvinyl butyral	38.00
3.10	4	Cellulose nitrate	31.00
0.60	5	Dibutyl phthalate	6.00
2.00	6	Ciclopirox	20.00

Manufacturing Directions

1. Mix all items to a uniform mixture. Pigments may be added to color the varnish.
2. Prepare a thixotropic paste by slowly stirring ten parts of an organically modified montmorillonite (e.g., bentone 27) into 80 parts toluene and subsequently adding eight parts wetting agent (e.g., anti-terra-U) and two parts methanol. Also prepare a clear varnish by dissolving 22 parts butanol-moist collodion cotton (e.g., type E 510) and eight parts toluene sulfonamide resin (e.g., santolite MS 80) in a mixture of three parts dibutyl phthalate, 20 parts ethyl acetate, ten parts butyl acetate, seven parts ethyl alcohol, and 30 parts toluene; also process 40 parts DC ROT No. 7 calcium varnish (e.g., color pigment C 19021) and 60 parts dibutyl phthalate to give a color paste with a particle size of less than 1 μm.
3. To prepare the pigmented nail varnish, disperse 12 parts thixotropic paste and 0.8 parts antisettling agent (e.g., MPA 2000 X) in 83.7 parts clear varnish, during which operation a temperature of at least 38°C is to be reached; then dissolve one part 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2-pyridone in the thixotropic clear varnish and stir in 2.5 parts color paste. Filter the finished nail varnish through a 70 μm sieve.

CIPROFLOXACIN HYDROCHLORIDE OPTHALMIC OINTMENT

The ciprofloxacin hydrochloride ophthalmic ointment consists of synthetic, sterile, multiple-dose antimicrobials for topical ophthalmic use. Each gram of ophthalmic ointment contains active ingredients ciprofloxacin HCl, 3.33 mg equivalent to 3 mg base. Inactive ingredients are mineral oil and white petrolatum.

CLINDAMYCIN GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Clindamycin USE clindamycin phosphate	11.90
0.15	2	Methyl paraben	1.50
0.20	3	Carbopol 941	2.00
15.00	4	Propylene glycol 400	50.00
5.00	5	Polyethylene glycol	50.00
QS	6	Sodium hydroxide 10% solution for pH adjustment	QS
QS	7	Water purified	QS to 1 kg

Manufacturing Directions

The viscosity of this composition is approximately 1000 cP.

1. Weigh approximately 90% of the purified water into a stainless-steel kettle.
2. Add the propylene glycol 400 and polyethylene glycol. Stir with a propeller mixer.

3. At room temperature, add methyl paraben to step 1 with continued stirring. Mix until dissolved.
4. While continuing to mix, add clindamycin phosphate to step 2. Mix until dissolved.
5. While continuing to mix, add Carbopol 941 slowly to step above. Avoiding clumping.
6. Mix vigorously at room temperature until a uniform and lump-free dispersion is achieved.
7. While mixing, add sufficient sodium hydroxide, 10% solution, to achieve a pH of 5.3 to 5.7. Mix until uniform.
8. Add the remaining water to make 100% and mix until uniform. Please note that a commercial preparation contains an additional component, allantoin.

CLINDAMYCIN LOTION AND GEL

The topical lotion contains clindamycin phosphate USP at a concentration equivalent to 10 mg clindamycin per milliliter. The lotion contains cetostearyl alcohol (2.5%), glycerin, glyceryl stearate SE (with potassium monostearate), isostearyl alcohol (2.5%), methyl paraben (0.3%), sodium lauroyl sarcosinate, stearic acid, and purified water. Topical gel contains clindamycin phosphate USP at a concentration equivalent to 10 mg clindamycin per gram. The gel contains allantoin, carbomer 934P, methyl paraben, polyethylene glycol 400, propylene glycol, sodium hydroxide, and purified water.

CLINDAMYCIN PHOSPHATE SUPPOSITORY

Manufacturing Directions

1. Melt 29 kg of Witepsol H 32® hard fat NF base in a manufacturing kettle by heating to and maintaining at 40°C.
2. Using a preheated filter, transfer 26.614 kg of the molten base to a second manufacturing vessel equipped with a homogenizing mixer.
3. Add 1.386 kg of clindamycin phosphate, equivalent to 1.12 kg of clindamycin free base, to the kettle and mix and homogenize to obtain a uniform dispersion.
4. Transfer the drug dispersion to a jacketed kettle and transport to the form/fill/seal suppository machine.
5. While maintaining mixing and a temperature of 40°C, form the drug dispersion into 2.5 g suppositories using the automated form/fill/seal equipment. The final batch size is 11,200 units.

CLINDAMYCIN PHOSPHATE TOPICAL GEL

The topical gel also contains benzoyl peroxide for topical use. Each gram of topical gel contains, as dispensed, 10 mg (1%) clindamycin as phosphate and 50 mg (5%) benzoyl peroxide in a base of carbomer, sodium hydroxide, dioctyl sodium sulfosuccinate, and purified water.

CLINDAMYCIN PHOSPHATE VAGINAL CREAM

Vaginal cream, 2%, is a semisolid white cream that contains 2% clindamycin phosphate USP at a concentration equivalent to 20 g clindamycin per gram. The pH of the cream is between 3 and 6. The cream also contains benzyl alcohol, cetostearyl alcohol, cetyl palmitate, mineral oil, polysorbate 60, propylene glycol, purified water, sorbitan monostearate, and stearic acid. Each applicatorful of 5 g of vaginal cream contains approximately 100 mg of clindamycin phosphate.

CLINDAMYCIN PHOSPHATE VAGINAL SUPPOSITORY

Each 2.5-g suppository contains clindamycin phosphate equivalent to 100 mg clindamycin in a base consisting of a mixture of glycerides of saturated fatty acids.

CLOBETASOL PROPIONATE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.050	1	Clobetasol propionate (5% excess)	0.525
44.500	2	Propylene glycol	445.000
0.050	3	Sodium citrate	0.500
0.050	4	Citric acid	0.500
5.000	5	Glyceryl monostearate A/S	50.000
4.000	6	Cetostearyl alcohol	40.000
0.600	7	White wax (beeswax bleached)	6.000
0.075	8	Chlorocresol	0.750
1.000	9	Glyceryl monostearate SE	10.000
7.000	10	Propylene glycol	70.000
2.675	11	Propylene glycol	26.750
35.000	12	Purified water	350.000

Manufacturing Directions

1. Aqueous phase
   a. Heat item 12 to 90°C in mixer. Bring down the temperature to 60°C. Dissolve all ingredients to a clear solution. Maintain temperature at 60°C.
   b. Filter through a polyester cloth. Check the weight. Clean the manufacturing vessel with item 12. Adjust the weight with item 12, if required. Record the quantity of extra item 12.
   c. Transfer again to manufacturing vessel. Maintain temperature at 60°C.
2. Oil phase
   a. Melt items 5 to 9 in melting vessel at 70°C to 75°C while stirring. Cool to 60°C. Maintain temperature at 60°C.

3. Dispersed phase
   a. Transfer the oil phase to aqueous phase in the manufacturing vessel through mesh by vacuum while stirring at manual mode 10 rpm, temperature 60°C. Mix at 10 rpm for 10 minutes at 60°C. Homogenize at high speed under vacuum 0.4 bar for 5 minutes at temperature 60°C. Cool down the temperature to 50°C while mixing at 10 rpm.
4. Drug phase
   a. Mix item 1 in item 10 in a water bath at 50°C
   b. Cool to 30°C while mixing at 10 rpm, auto mode under vacuum 0.4 bar, mixing time 20 minutes until a clear solution is obtained. A homogenizer may be used.
   c. Add to dispersed phase from step 4b. Rinse with item 11 and add to dispersed phase at step 3a. Mix and homogenize under vacuum 0.4 bar for 5 minutes, high speed, 10 rpm, temperature 50°C.
   d. Unload the cream in stainless-steel drum and fill.

CLOBETASOL PROPIONATE CREAM, OINTMENT, AND GEL

Cream contains clobetasol propionate 0.5 mg/g in a cream base of propylene glycol, glyceryl monostearate, cetostearyl alcohol, glyceryl stearate, PEG-100 stearate, white wax, chlorocresol, sodium citrate, citric acid monohydrate, and purified water. Ointment contains clobetasol propionate 0.5 mg/g in a base of propylene glycol, sorbitan sesquioleate, and white petrolatum. Gel contains clobetasol propionate 0.5 mg/g in a base of propylene glycol, carbomer 934P, sodium hydroxide, and purified water.

CLOBETASOL PROPIONATE OINTMENT GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.050	1	Clobetasol propionate (5% excess)	0.525
94.460	2	Petrolatum (white soft paraffin)	944.600
0.500	3	Sorbitan sesquioleate (Arlacel 83)	5.000
4.000	4	Propylene glycol	40.000
0.500	5	Propylene glycol	5.000

Manufacturing Directions

1. Melt items 2 and 3 in a fat-melting vessel at temperature 75°C while mixing.
2. Start heating mixer vessel to 75°C. Transfer molten items 2 and 3 to mixer through stainless-steel mesh under vacuum 0.4 to 0.6 bar. Start mixer at 10 rpm manual mode.
3. Cool down to 50°C.
4. In a water bath (temperature 60°C), dissolve item 1 in item 4 using homogenizer for 5 minutes. Add this to mixer with stirring.
5. Rinse with item 5 and add to mixer at temperature 50°C.
6. Start homogenizer under vacuum 0.4 to 0.6 bar while stirring at 10 rpm high speed for 10 minutes.
7. Cool down the temperature to 30°C, 10 rpm, auto mode, vacuum 0.4 to 0.6 bar.
8. Transfer the ointment to a stainless-steel container. Fill.

CLOTRIMAZOLE AND BETAMETHASONE CREAM AND LOTION

Each gram of cream contains 10 mg clotrimazole and 0.643 mg betamethasone dipropionate (equivalent to 0.5 mg betamethasone) in a hydrophilic cream consisting of purified water, mineral oil, white petrolatum, cetearyl alcohol 70/30, ceteareth-30, propylene glycol, sodium phosphate monobasic monohydrate, and phosphoric acid, with benzyl alcohol as preservative. Each gram of lotion contains 10 mg clotrimazole and 0.643 mg betamethasone dipropionate (equivalent to 0.5 mg betamethasone) in a hydrophilic base of purified water, mineral oil, white petrolatum, cetearyl alcohol 70/30, ceteareth-30, propylene glycol, sodium phosphate monobasic monohydrate, and phosphoric acid, with benzyl alcohol as a preservative. Lotion may also contain sodium hydroxide.

CLOTRIMAZOLE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
7.00	1	Cetyl stearyl alcohol	70.00
1.50	2	Cremophor A6	15.00
1.50	3	Cremophor A25	15.00
12.00	4	Liquid paraffin	120.00
0.20	5	Methyl and propyl parabens	2.00
68.80	6	Water purified	688.00
8.00	7	Propylene glycol	80.00
1.00	8	Clotrimazole	1.00

Manufacturing Directions

1. Heat the mixture of items 1 to 5 and item 6 separately to approximately 80°C.
2. Add item 6 to the obtained solution step 1 mixture of items 1 to 5 with rigorous stirring.

3. Heat items 7 and 8 until the active ingredient is dissolved, mix with step 2, and continue to stir during cooling to room temperature.

CLOTRIMAZOLE LOTION

Each gram of lotion contains 10 mg clotrimazole USP dispersed in an emulsion vehicle composed of benzyl alcohol NF (1%), cetearyl alcohol 70/30 (3.7%), cetyl esters wax NF, octyldodecanol NF, polysorbate 60 NF, sodium phosphate dibasic anhydrous R, sodium phosphate monobasic monohydrate USP, sorbitan monostearate NF, and purified water USP.

CLOTRIMAZOLE LOTION

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
40.00	1	Clotrimazole	40.00
50.00	2	White petrolatum	50.00
20.00	3	Mineral oil	60.00
24.00	4	Cetearyl alcohol	72.00
22.50	5	Ceteth-20	22.50
10.00	6	Benzyl alcohol	10.00
100.00	7	Propylene glycol	100.00
0.35	8	Sodium phosphate dibasic anhydrous	0.35
5.00	9	Sodium phosphate monobasic monohydrate	5.00
QS	10	Water purified	QS to 1 kg

Manufacturing Directions

1. Heat 75% of the water to 70°C in a suitable vessel. Add the monobasic sodium phosphate monohydrate, anhydrous dibasic sodium phosphate, propylene glycol, and benzyl alcohol to the vessel with agitation, maintaining the temperature at 70°C.
2. In a separate vessel, melt the petrolatum and heat to 70°C.
3. Add the mineral oil and mix. Add the cetearyl alcohol and 95% of the ceteth-20. Mix and maintain at 70°C.
4. Combine the contents of the two vessels with agitation, maintaining at 70°C.
5. Cool to 38°C with agitation.
6. In a separate vessel, dissolve the remaining ceteth-20 in the remaining water at 65°C with agitation.
7. Cool to room temperature and slurry the clotrimazole with vigorous agitation until smooth uniform slurry is obtained.
8. Add the slurry to the previous emulsion mixture and agitate while cooling to room temperature.

CLOTRIMAZOLE VAGINAL CREAM

The vaginal cream's active ingredient is clotrimazole 2% (100 mg per applicator). The inactive ingredients are benzyl alcohol, cetearyl alcohol, cetyl esters wax, octyldodecanol, polysorbate 60, purified water, and sorbitan monostearate.

CLOTRIMAZOLE VAGINAL CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
40.00	1	Clotrimazole	40.00
150.00	2	White petrolatum	150.00
60.00	3	Mineral oil	60.00
72.00	4	Cetearyl alcohol	72.00
22.50	5	Ceteth-20	22.50
10.00	6	Benzyl alcohol	10.00
100.00	7	Propylene glycol	100.00
0.35	8	Sodium phosphate dibasic anhydrous	0.35
5.00	9	Sodium phosphate monobasic monohydrate	5.00
QS	10	Water purified	QS to 1 kg

Manufacturing Directions

1. Heat 75% of the water to 70°C in a suitable vessel. Add the monobasic sodium phosphate monohydrate, anhydrous dibasic sodium phosphate, propylene glycol, and benzyl alcohol to the vessel with agitation, maintaining the temperature at 70°C.
2. In a separate vessel, melt the petrolatum and heat to 70°C.
3. Add the mineral oil and mix. Add the cetearyl alcohol and 95% of the ceteth-20. Mix and maintain at 70°C.
4. Combine the contents of the two vessels with agitation, maintaining at 70°C.
5. Cool to 38°C with agitation.
6. In a separate vessel, dissolve the remaining ceteth-20 in the remaining water at 65°C with agitation.
7. Cool to room temperature and slurry the clotrimazole with vigorous agitation until smooth uniform slurry is obtained.
8. Add the slurry to the previous emulsion mixture and agitate while cooling to room temperature.

CLOTRIMAZOLE VAGINAL CREAM INSERTS

Each clotrimazole vaginal insert contains 100 mg clotrimazole with inactive ingredients benzyl alcohol, cetostearyl alcohol, cetyl esters wax, octyldodecanol, polysorbate 60, purified water, and sorbitan monostearate. The inserts are made of cornstarch, lactose, magnesium stearate, and povidone.

CLOTRIMAZOLE AND CLINDAMYCIN CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Clotrimazole	20.00
4.00	2	Clindamycin base USE clindamycin hydrochloride	4.54
20.00	3	Sorbitan monostearate	20.00
30.00	4	Tween 60	30.00
130.46	5	Paraffin viscous	130.46
100.00	6	Cetyl stearyl alcohol	100.00
10.00	7	Benzyl alcohol	10.00
670.00	8	Water purified	670.00

Manufacturing Directions

1. One application unit is equivalent to 5 g. This comprises 100 mg clotrimazole and 20 mg clindamycin.
2. Add and dissolve items 1 and 2 in items 7 and 8 in a blender.
3. Add and dissolve remaining items in a separate blender and heat to 40°C.
4. Add into step 2 with vigorous mixing to form a cream base.

CLOTRIMAZOLE AND CLINDAMYCIN SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
100.00	1	Clotrimazole	100.00
20.00	2	Clindamycin base USE clindamycin hydrochloride	22.70
77.30	3	Calcium lactate pentahydrate	77.30
250.00	4	Gelatin	250.00
250.00	5	Water purified	250.00
1250.00	6	Glycerol	1250.00

Manufacturing Directions

1. Dissolve items 1 and 2 in item 5.
2. Heat item 4 in item 6 in a separate vessel and add item 3.
3. Mix well and add to step 1.
4. Fill suppository 2 g each.

CLOTRIMAZOLE AND CLINDAMYCIN SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
100.00	1	Clotrimazole	100.00
20.00	2	Clindamycin base USE clindamycin hydrochloride	22.70
77.30	3	Calcium lactate pentahydrate	77.30
1000.00	4	Macrogol 400	1000.00
800.00	5	Macrogol 6000	800.00
200.00	6	Lactic acid	200.00

Manufacturing Directions

1. Add and mix all ingredients.
2. Heat to 70°C and mix well.
3. Cool to 40°C and fill.

COAL TAR AND ALLANTOIN CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
40.00	1	Lanolin alcohol	40.00
50.00	2	White petroleum jelly	50.00
120.00	3	Paraffin wax 140F	120.00
300.00	4	Mineral oil 70 cS	300.00
20.00	5	Coal tar	20.00
2.50	6	Allantoin	2.50
QS	7	Deionized water	QS to 1 kg
QS	8	Preservative	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Slowly add water phase in increments to the oil phase.
3. Allow each addition time to be fully incorporated.
4. Stir to cool. Fill just above melting point. Further homogenization may improve stability before filling.

COAL TAR AND ALLANTOIN CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
160.00	1	Stearic acid	16.00
60.00	2	Oleyl alcohol	6.00
20.00	3	Lanolin	2.00
20.00	4	Coal tar	2.00
6.00	5	Triethanolamine 99%	0.60
2.50	6	Allantoin	0.25
QS	7	Deionized water	QS to 1 kg
QS	8	Preservative	QS

Manufacturing Directions

1. Heat water (items 7 and 8) and oil phases (all other items) separately to 80°C.
2. Add water phase to oil phase while stirring. Stir to cool.
3. Fill at 40°C. May homogenize.

COAL TAR CREAM

The active ingredient in coal tar cream is 5% coal tar solution USP, equivalent to 0.8% coal tar. Inactive ingredients include acetylated lanolin alcohol, alcohol (4.7%), carbomer-934P, ceteth-2, ceteth-16, cetyl acetate, cetyl alcohol, D&C; red no. 28, fragrance, glyceryl tribehenate, laneth-16, lanolin alcohol, laureth-23, methyl gluceth-20, methylchloroisothia-zolinone, methylisothiazolinone, mineral oil, octyldodecanol, oleth-16, petrolatum, potassium hydroxide, purified water, steareth-16, stearyl alcohol, titanium dioxide.

COLLAGENASE OINTMENT

Collagenase ointment is a sterile enzymatic debriding ointment that contains 250 collagenase units per gram of white petrolatum USP. The enzyme collagenase is derived from the fermentation by *Clostridium histolyticum*. It possesses the unique ability to digest collagen in necrotic tissue exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blend to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17 (alpha)-dihydroequilin, together with smaller amounts of 17 (alpha)-estradiol, equilenin, and 17 (alpha)-dihydroequilin as salts of their sulfate esters.

CONJUGATED ESTROGENS VAGINAL CREAM

Each gram of conjugated estrogens vaginal cream contains 0.625 mg conjugated estrogens USP in a nonliquefying base containing cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, benzyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil. It is applied intravaginally.

CYANOCOBALAMIN GEL

Cyanocobalamin gel for intranasal administration is a solution of cyanocobalamin USP (vitamin B12) for administration as a metered gel to the nasal mucosa. Each bottle of gel contains 2.3 mL of a 500 µg/0.1 mL gel solution of cyanocobalamin with methylcellulose, sodium citrate, citric acid, glycerin, and benzalkonium chloride in purified water. The gel solution has a pH between 4.5 and 5.5. After initial priming, each metered gel delivers an average of 500 µg of cyanocobalamin, and the 2.3 mL of gel contained in the bottle will deliver eight doses.

DBcAMP OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
3.00	1	DBcAMP	35.10
68.49	2	Polyethylene glycol 400	684.90
28.00	3	Polyethylene glycol 4000	280.00

Manufacturing Directions

1. In a glass-lined melting vessel, place 90% of item 3 and item 2 and melt at 70°C to 80°C.
2. Transfer to a homogenizer and cool to 50°C.
3. Prepare a dispersion of item 1 in balance of item 3 in a separate vessel and add to step 2.
4. Rinse the container with item 2 and add rinsings.
5. Mix at 50°C. Cool and fill.

DESONIDE CREAM, OINTMENT, AND LOTION

Cream 0.05%, ointment 0.05%, and lotion 0.05% contain desonide. Each gram of cream contains 0.5 mg of desonide in a base of purified water, emulsifying wax, propylene glycol, stearic acid, isopropyl palmitate, synthetic beeswax, polysorbate 60, potassium sorbate, sorbic acid, propyl gallate, citric acid, and sodium hydroxide. Each gram of ointment contains 0.5 mg of desonide in a base of mineral oil and polyethylene. Each gram of lotion contains 0.5 mg of desonide in a base of sodium lauryl sulfate, light mineral oil, cetyl alcohol, stearyl alcohol, propylene glycol, methyl paraben, propyl paraben, sorbitan monostearate, glyceryl stearate SE, edetate sodium, and purified water and may contain citric acid or sodium hydroxide for pH adjustment.

DESOXIMETASONE EMOLLIENT CREAM, GEL, AND OINTMENT

Desoximetasone emollient cream 0.25%, desoximetasone gel 0.05%, desoximetasone ointment 0.25%, and desoximetasone emollient cream 0.05% contain the active synthetic corticosteroid desoximetasone. Each gram of emollient cream

0.25% contains 2.5 mg desoximetasone in an emollient cream consisting of white petrolatum USP, purified water USP, isopropyl myristate NF, lanolin alcohols NF, mineral oil USP, cetostearyl alcohol NF, aluminum stearate, and magnesium stearate. Each gram of gel 0.05% contains 0.5 mg desoximetasone in a gel consisting of purified water USP, SD alcohol 40 (20% w/w), isopropyl myristate NF, carbomer 940, trolamine NF, edetate disodium USP, and docusate sodium USP. Each gram of ointment 0.25% contains 2.5 mg of desoximetasone in a base consisting of white petrolatum USP, propylene glycol USP, sorbitan sesquioleate, beeswax, fatty alcohol citrate, fatty acid pentaerythritol ester, aluminum stearate, citric acid, and butylated hydroxyanisole. Each gram of emollient cream 0.05% contains 0.5 mg desoximetasone in an emollient cream consisting of white petrolatum USP, purified water USP, isopropyl myristate NF, lanolin alcohols NF, mineral oil USP, cetostearyl alcohol NF, aluminum stearate, edetate disodium USP, lactic acid USP, and magnesium stearate.

DEXAMETHASONE SODIUM PHOSPHATE OINTMENT

Sterile ophthalmic ointment dexamethasone sodium phosphate is a topical steroid ointment containing dexamethasone sodium phosphate equivalent to 0.5 mg (0.05%) dexamethasone phosphate in each gram. Inactive ingredients are white petrolatum and mineral oil.

DEXPANTHENOL CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Dexpanthenol	50.00
10.00	2	White soft paraffin	100.00
5.00	3	Cetostearyl alcohol	50.00
2.00	4	Lanolin anhydrous	20.00
10.00	5	Liquid paraffin	100.00
11.00	6	Propylene glycol	110.00
0.15	7	Methyl paraben	1.50
0.05	8	Propyl paraben	0.50
1.00	9	Tween 60	10.00
1.00	10	Simethicone M30	10.00
0.072	11	Lavender oil	0.072
0.028	12	Rose oil perfume	0.28
64.70	13	Water purified	647.00

Manufacturing Directions

1. Place items 2 to 5 in a melting vessel and heat to 70°C.
2. Combine portion of item 13 (at 70°C), item 1, and item 9 and heat to 70°C and mix for 10 minutes.
3. In a separate container add and dissolve items 7 and 8 in item 6 at 70°C and add to step 2.
4. Add step 1 into step 3. Mix under vacuum and at 70°C for 20 minutes.
5. Cool to 35°C to 40°C and add item 10. Mix again under vacuum.
6. Add items 11 and 12 and mix (without vacuum) and cool down to 25°C.
7. Transfer to storage vessel and fill.

DEXPANTHENOL GEL CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Dexpanthenol (BASF)	50.00
100.00	2	Liquid paraffin	100.00
150.00	3	Lutrol E 400	150.00
180.00	4	Lutrol F 127	180.00
QS	5	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve dexpanthenol and Lutrol E 400 in water, add liquid paraffin, and stir, heating to 60°C to 70°C.
2. Slowly add Lutrol F 127 and stir until it is dissolved.
3. Cool to room temperature, stirring continuously until the air bubbles disappear.

DICLOFENAC DIETHYLAMINE GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Diclofenac diethylamine, 10% excess	11.00
1.20	2	Carbopol 934P	12.00
23.00	3	Isopropyl alcohol	230.00
5.00	4	Propylene glycol	50.00
2.50	5	Liquid paraffin	25.00
2.50	6	Cetiol LC	25.00
2.00	7	Cetomacrogol 1000	20.00
0.90	8	Diethylamine	9.00
0.028	9	Perfume	0.28
0.072	10	Perfume	0.72
68.00	11	Water purified	680.00

Manufacturing Directions

1. Place 90% of item 11 in a mixing vessel, heat to 80°C, stir to produce vortex, and add item 2 to disperse after passing through 1 mm sieve. Mix for 5 minutes, avoiding foam.
2. Transfer step 1 into Becomix and maintain temperature at 70°C.

3. Combine items 5 to 7 in a separate vessel, melt at 70°C, transfer to step 2.
4. Mix at speed II under vacuum of 0.4 to 0.6 bar for 5 minutes at 10 rpm.
5. Cool down to 30°C.
6. Add and dissolve item 8 in item 11 separately and then add to step 5 and mix for 10 minutes.
7. Dissolve item 1 in items 3 and 4 separately and transfer to step 6 through a cloth filter. Mix for 20 minutes.
8. Homogenize at speed I for 5 minutes under vacuum at 10 rpm.
9. Add perfumes and mix for 5 minutes.
10. Fill in appropriate containers.

DICLOFENAC DIETHYLAMMONIUM GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
QS	1	Water purified	465.53
500.00	2	Alcohol 190 proof	500.00
2.00	3	Menthol	2.00
10.00	4	Diclofenac USE diclofenac diethylammonium	12.47
8.00	5	Carbopol 940	8.00
12.00	6	Trolamine	12.00

Manufacturing Directions

1. Place purified water and alcohol in a 316-grade stainless-steel mixing tank.
2. Add menthol crystals to the alcohol–water mixture. Mix for 5 minutes or until completely dissolved.
3. Add diclofenac diethylammonium to the mixing tank. Mix for 10 minutes or until completely dissolved.
4. While mixing, sprinkle in carbomer. Continue mixing slowly at intervals for 1 to 2 hours or until carbomer swells completely in the hydroalcoholic solution.
5. Add trolamine and mix for 10 minutes or until gel forms.
6. Fill into suitable lined collapsible aluminum tube.

DICLOFENAC SODIUM SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
12.50	1	Diclofenac sodium micronized, 1% excess	12.62
530.32	2	Suppocire CM	530.32
353.00	3	Suppocire AS2X	353.00
2.90	4	Crill 3	2.90
1.15	5	Aerosil 200	1.15

Manufacturing Directions

1. Load items 2 to 4 in the fat-melting vessel and heat to 55°C.
2. Transfer to a mixing vessel through filter sieves. Set the temperature to 50°C.
3. Add item 1 and 5 to step 2. Mix at 10 rpm and homogenize at speed I for 15 minutes at 0.6 bar vacuum.
4. Cool down to 50°C to 55°C.
5. Transfer into storage vessel and set temperature at 50°C.
6. Fill 900 mg in a suppository mold.

DICLOFENAC SODIUM SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
25.00	1	Diclofenac sodium micronized, 1% excess	25.25
522.70	2	Suppocire CM	522.70
348.00	3	Suppocire AS2X	348.00
2.90	4	Crill 3	2.90
1.15	5	Aerosil 200	1.15

Manufacturing Directions

1. Load items 2 to 4 in the fat-melting vessel and heat to 55°C.
2. Transfer to a Becomix vessel through filter sieves. Set the temperature to 50°C.
3. Add items 1 and 5 to step 2. Mix at 10 rpm and homogenize at speed I for 15 minutes at 0.6 bar vacuum.
4. Cool down to 50°C to 55°C.
5. Transfer into storage vessel and set temperature at 50°C.
6. Fill 900 mg in a suppository mold.

DICLOFENAC SODIUM SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
50.00	1	Diclofenac sodium micronized, 1% excess	50.50
1045.40	2	Suppocire CM	1045.40
696.00	3	Suppocire AS2X	696.00
5.80	4	Crill 3	5.80
2.30	5	Aerosil 200	2.30

Manufacturing Directions

1. Load items 2 to 4 in the fat-melting vessel and heat to 55°C.
2. Transfer to a mixing vessel through filter sieves. Set the temperature to 50°C.
3. Add items 1 and 5 to step 2. Mix at 10 rpm and homogenize at speed I for 15 minutes at 0.6 bar vacuum.
4. Cool down to 50°C to 55°C.
5. Transfer into storage vessel and set temperature at 50°C.
6. Fill 1800 mg in a suppository mold.

DICLOFENAC SODIUM SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
100.00	1	Diclofenac sodium micronized, 1% excess	101.00
1015.00	2	Suppocire CM	1015.00
675.00	3	Suppocire AS2X	675.00
6.00	4	Crill 3	6.00
2.50	5	Aerosil 200	2.50

Manufacturing Directions

1. Load items 2 to 4 in the fat-melting vessel and heat to 55°C.
2. Transfer to a mixing vessel through filter sieves. Set the temperature to 50°C.
3. Add items 1 and 5 to step 2. Mix at 10 rpm and homogenize at speed I for 15 minutes at 0.6 bar vacuum.
4. Cool down to 50°C to 55°C.
5. Transfer into storage vessel and set temperature at 50°C.
6. Fill 1800 mg in a suppository mold.

DICHLOROBENZYL ALCOHOL TOOTH GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	2,4-dichlorobenzyl alcohol (Myacid)	10.00
2.00	2	Sodium carboxymethylcellulose[a]	20.00
QS	3	Water purified	QS to 1 kg

[a] To obtain thicker gel, the quantity can be increased to 4.00.

Manufacturing Directions

1. Disperse item 2 in item 3 heated to 70°C.
2. Cool and add item and mix well.
3. Cool to 40°C and fill.

DIENESTROL VAGINAL CREAM

The active ingredient in dienestrol vaginal cream is dienestrol 0.01%. It is compounded in a cream base suitable for intravaginal use only. The cream base is composed of glyceryl monostearate, peanut oil, glycerin, benzoic acid, glutamic acid, butylated hydroxyanisole, citric acid, sodium hydroxide, and water. The pH is approximately 4.3. Available in 2.75-oz (78-g) tubes with or without a measured dose applicator.

DIETHYLAMINE SALICYLATE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
22.50	1	White soft paraffin	225.00
12.50	2	Glyceryl monostearate	125.00
5.00	3	Criss-3 (span 60)	50.00
0.10	4	Vitamin E oily	1.00
45.24	5	Water purified	452.40
0.71	6	Sodium phosphate monobasic	7.10
0.13	7	Sodium hydroxide pellets	1.30
0.10	8	Sodium disulfide pure	1.00
0.166	9	Sodium ethylene diamine tetraacetate	1.66
12.00	10	Diethylamine salicylate	120.00
0.12	11	Menthol	1.20
0.50	12	Chlorbutol	5.00
0.30	13	Lavender oil	3.00
0.40	14	Glycerin	4.00
0.20	15	Methyl paraben	2.00
0.12	16	Propyl paraben	1.20

Manufacturing Directions

1. Charge, one by one, items 1 to 4 to a melting vessel at 75°C to 79°C. Hold molten fat at 70°C with continuous stirring at low speed.
2. In a separate vessel, heat 90% of item 5 to 90°C, add, and dissolve parabens by stirring. Cool to 65°C to 70°C.
3. In a separate vessel, take the balance of item 5 and sodium hydroxide pellets and sodium phosphate monobasic and dissolve.
4. Transfer step 3 to the paraben solution and mix for 5 to 10 minutes at slow speed and at 65°C to 70°C.
5. Cool to 25°C. Check and adjust pH 6.8 to 7.2. Add items 8 to 10 and mix to dissolve at 50°C.
6. Filter solution through polyester cloth and keep aside at 50°C.
7. Set Becomix temperature to 70°C, 10 rpm, and vacuum 6 bar.
8. Transfer molten fat at 70°C after passing through a stainless-steel filter to step above while mixing.
9. Homogenize at slow speed for 10 minutes. Temperature 65°C to 70°C.
10. Set Becomix to 50°C and transfer diethylamine salicylate solution to the cream at 50°C while stirring.
11. Continue mixing and add chlorbutol, menthol, lavender oil, and glycerin at 40°C. (Menthol and chlorbutol first dissolve in a separate container.)
12. Homogenize for 10 minutes under vacuum.
13. Cool to 25°C, transfer to storage vessel, fill.

DIFLORASONE DIACETATE CREAM AND OINTMENT

Each gram of cream contains 0.5 mg diflorasone diacetate in a cream base. Each gram of cream contains 0.5 mg diflorasone diacetate in a hydrophilic vanishing cream base of propylene glycol, stearyl alcohol, cetyl alcohol, sorbitan monostearate, polysorbate 60, mineral oil, and purified water. Each gram of ointment contains 0.5 mg diflorasone diacetate in an ointment base. Emollient ointment contains diflorasone diacetate in an emollient occlusive base consisting of polyoxypropylene 15-stearyl ether, stearic acid, lanolin alcohol, and white petrolatum.

DIMETHICONE AND ZINC OXIDE OINTMENT

Active ingredients in dimethicone and zinc oxide ointment are dimethicone, 1%, and zinc oxide, 10%. Inactive ingredients include aloe extract, benzyl alcohol, cod liver oil (contains vitamins A and D), fragrance, glyceryl oleate, light mineral oil, ozokerite, paraffin, propylene glycol, sorbitol, synthetic beeswax, and water.

DINOPROSTONE CERVICAL GEL

Dinoprostone is the naturally occurring form of prostaglandin E_2 (PGE_2). The active constituent of gel is dinoprostone 0.5 mg/3 g (2.5 mL gel); other constituents are colloidal silicon dioxide NF (240 mg/3 g) and triacetin USP (2760 mg/3 g).

DINOPROSTONE VAGINAL INSERT AND SUPPOSITORIES

Dinoprostone vaginal insert is a thin, flat polymeric slab that is rectangular with rounded corners, contained within the pouch of a knitted polyester retrieval system, an integral part of which is a long tape. Each slab is buff colored and semitransparent and contains 10 mg of dinoprostone. The hydrogel insert is contained within the pouch of an off-white knitted polyester retrieval system designed to aid retrieval at the end of the dosing interval. The finished product is a controlled-release formulation that has been found to release dinoprostone in vivo at a rate of approximately 0.3 mg/h. Each insert contains 10 mg of dinoprostone in 241 mg of a cross-linked polyethylene oxide/urethane polymer that is a semiopaque, beige-colored, flat rectangular slab measuring 29 mm × 9.5 mm × 0.8 mm in thickness. The insert and its retrieval system, made of polyester yarn, are nontoxic, and when placed in a moist environment they absorb water, swell, and release dinoprostone. The insert contains 10 mg dinoprostone. The product is wound and enclosed in an aluminum sleeve that is contained in an aluminum-polyethylene pack. Vaginal suppositories are available. Each suppository contains 20 mg of dinoprostone in a mixture of glycerides of fatty acids.

DIPHENHYDRAMINE HYDROCHLORIDE AND ZINC ACETATE OINTMENT

Diphenhydramine hydrochloride and zinc acetate ointment contain diphenhydramine hydrochloride 1% and zinc acetate 0.1%. The extra-strength formulation is diphenhydramine hydrochloride 2% and zinc acetate 0.1%. Inactive ingredients include cetyl alcohol, diazolidinyl urea, methyl paraben, polyethylene glycol monostearate 1000, propylene glycol, propyl paraben, and purified water.

DOCOSANOL LOTION

Docosanol, 10%, is a cold sore/fever blister treatment. Inactive ingredients include benzyl alcohol, light mineral oil, propylene glycol, purified water, sucrose distearate, and sucrose stearate.

ECONAZOLE NITRATE AND BENZOYL PEROXIDE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
200.00	1	PEG-6 and PEG-32 and glyceryl stearate (Tefose 63)	200.00
30.00	2	Mineral oil	30.00
30.00	3	Apricot kernel oil PEG-6 esters (Labrafil M 1944)	30.00
0.50	4	Sorbic acid	0.50
0.50	5	Sodium methyl paraben	0.50
724.00	6	Deionized water	724.00
5.00	7	Benzoyl peroxide	5.00
10.00	8	Econazole nitrate	10.00

Manufacturing Directions

1. Mix and heat items 1 to 6 together and bring temperature to 75°C.
2. Allow to cool while stirring. Add items 7 and 8 at 30°C and mix well until uniform.

ECONAZOLE NITRATE AND BENZOYL PEROXIDE LOTION

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	PEG-6 stearate and cetech-20 and steareth-20 (Tefose 2000)	50.00
30.00	2	Mineral oil	30.00
20.00	3	Cetyl alcohol	20.00
0.70	4	Sodium methyl paraben	0.70
0.30	5	Sorbic acid	0.30
884.00	6	Deionized water	884.00
5.00	7	Benzoyl peroxide	5.00
10.00	8	Econazole nitrate	10.00

Manufacturing Directions

1. Mix and heat items 1 to 3 together and bring temperature to 75°C.
2. Allow to cool while stirring. Mix items 4 to 6 and add to above while stirring.
3. Cool with stirring. Add items 7 and 8 at 30°C while stirring.

EFLORNITHINE HYDROCHLORIDE CREAM

The cream contains 13.9% (139 mg/g) anhydrous eflornithine hydrochloride as eflornithine hydrochloride monohydrate (150 mg/g). Other ingredients include ceteareth-20, cetearyl alcohol, dimethicone, glyceryl stearate, methyl paraben, mineral oil, PEG-100 stearate, phenoxyethanol, propyl paraben, stearyl alcohol, and water.

ENZYME EXTRACT OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
50.00	1	Fumed silica	500.00
18.50	2	Enzyme extract[a]	185.00
0.20	3	Methyl paraben	2.00
0.50	4	Propyl paraben	5.00
0.03	5	Bromopal	0.30
0.02	6	Fragrance	0.20
QS	7	Water purified	QS to 1 kg

[a] This is a generic formula to incorporate proteins, tissue components, or enzyme extracts (in powder form).

ERYTHROMYCIN AND NEOMYCIN OINTMENT

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
10.00	1	Erythromycin-base fine powder 10% excess (900 µg/mg potency)[a]	12.22
3.50	2	Neomycin-base USE neomycin sulfate (200 Waksman units/mg potency)[a]	5.00
100.00	3	Mineral oil light	100.00
QS	4	Petrolatum white	QS to 1 kg

[a] Adjust petrolatum weight to compensate for change in weight of erythromycin base and neomycin.

Manufacturing Directions

1. Heat petrolatum and mineral oil in a steam kettle to 115°C and maintain temperature for at least 3 hours.
2. Strain into mixing tank and cool to 40°C to 45°C.
3. Reserve portion of petrolatum–oil mixture for step 5.
4. Mix erythromycin and neomycin with 95 g of base and stir until thoroughly dispersed.
5. Run through a 200 mesh (74 µm aperture) screen on Homoloid mill directly into main portion of petrolatum–oil mixture.

6. Rinse mill with reserved petrolatum–oil mixture from step 3.
7. Mix 2 hours before cooling. Cool slowly to avoid condensation.
8. Fill into suitable approved containers.

ERYTHROMYCIN GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Erythromycin base	10.00
20.00	2	Lutrol E 400	200.00
20.00	3	Propylene glycol	200.00
20.00	4	Lutrol F 127	200.00
39.00	5	Water purified	390.00

Manufacturing Directions

1. Heat solution of items 1 to 3 to approximately 70°C.
2. Dissolve item 4, mix with item 5, and cool when the air bubbles escape.

ERYTHROMYCIN OINTMENT

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
10.00	1	Erythromycin powder 850 µg/mg, 10% excess[a]	12.94
100.00	2	Mineral oil light	100.00
QS	3	Petrolatum white	QS to 1 kg

[a] Adjust petrolatum weight to compensate for change in weight of erythromycin base calculated from its potency.

Manufacturing Directions

1. Heat petrolatum and mineral oil in a steam kettle to 115°C and maintain temperature for at least 3 hours.
2. Strain into mixing tank and cool to 40°C to 45°C.
3. Reserve portion of petrolatum–oil mixture for step 6.
4. Mix erythromycin with 78 g of base and stir until thoroughly dispersed.
5. Run through a 200 mesh (74 µm aperture) screen on Homoloid mill directly into main portion of petrolatum–oil mixture.
6. Rinse mill with reserved petrolatum–oil mixture from step 3.
7. Mix 2 hours before cooling. Cool slowly to avoid condensation.
8. Fill into suitable approved containers.

ERYTHROMYCIN OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
23.75	1	Isostearyl benzoate	237.50
23.85	2	Bis (2-ethylhexyl) maleate	238.50
10.00	3	Cyclomethicone	100.00
5.00	4	Stearyl alcohol	50.00
10.00	5	Starch	100.00
10.00	6	Microcrystalline cellulose	100.00
15.00	7	Ethylene/vinyl copolymer	150.00
0.10	8	Propyl paraben	1.00
0.10	9	Butylparaben	1.00
0.10	10	Fragrance	1.00
2.00	11	Erythromycin	21.00

Manufacturing Directions

1. Blend items 1 to 4 in a high-shear mixer.
2. Add balance ingredients and mix well.
3. Fill.

ESTRADIOL AND NORETHINDRONE ACETATE TRANSDERMAL SYSTEM

The estradiol/norethindrone acetate transdermal system is an adhesive-based matrix transdermal patch designed to release both estradiol and norethindrone acetate, a progestational agent, continuously on application to intact skin. The patch is an alcohol-free, adhesive-based matrix transdermal drug delivery system comprising three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are a backing, an adhesive layer, and a protective liner. The adhesive matrix containing estradiol and norethindrone acetate is applied to an adhesive backing of polyester/ethylene vinyl acetate laminate film on one side and is protected on the other side by a transparent fluoropolymer-coated release liner. The transparent release liner must be removed before the system can be used. Each system is enclosed in a heat-sealed pouch. The active components of the system are estradiol USP and norethindrone acetate USP. The remaining components of the system are pharmacologically inactive: A silicone and acrylic-based multipolymeric adhesive, povidone USP, oleic acid NF, and dipropylene glycol.

ESTRADIOL TRANSDERMAL SYSTEM

Estradiol transdermal system is designed to deliver 17 (beta)-estradiol continuously and consistently for more than a 3- or 4-day interval on application to intact skin. Three strengths of Alora systems are available, having nominal in vivo delivery of 0.05, 0.075, and 0.1 mg estradiol per day through skin of average permeability (interindividual variation in skin

permeability is approximately 20%). Alora systems have contact surface areas of 18, 27, and 36 cm^2 and contain 1.5, 2.3, and 3.0 mg of estradiol USP respectively. The composition of the systems per unit active surface area is identical. Estradiol USP 17 (beta)-estradiol is a white crystalline powder that is chemically described as estra-1,3,5(10)-triene-3,17(beta)-diol, has an empirical formula of $C_{18}H_{24}O_2$, and has a molecular weight of 272.37. The delivery system consists of three layers. Proceeding from the polyethylene backing film, the adhesive matrix drug reservoir that is in contact with the skin consists of estradiol USP and sorbitan monooleate dissolved in an acrylic adhesive matrix. The polyester overlapped release liner protects the adhesive matrix during storage and is removed before application of the system to the skin.

Manufacturing Directions

Estradiol-containing matrices are prepared by mixing acrylic adhesive (National Starch Durotac 1194), sorbitan monooleate (Arlacel 80), and estradiol at a ratio of 80-*X*/(20/*X*), where *X* is the proportion (wt%) of estradiol. The matrix contains 25 estradiol (8% estradiol was saturated) for optimal permeation.

ESTRADIOL VAGINAL CREAM

Each gram of estradiol vaginal cream USP 0.01% contains 0.1 mg estradiol in a nonliquefying base containing purified water, propylene glycol, stearyl alcohol, white ceresin wax, mono- and diglycerides, hydroxypropylmethylcellulose, 2208 (4000 CPS; CPS refers to centipoise, a designation of viscosity) sodium lauryl sulfate, methyl paraben, edetate disodium, and tertiary butylhydroquinone. Tubes contain 1.5 oz (42.5 g), with a calibrated plastic applicator for delivery of 1, 2, 3, or 4 g. Each gram of estradiol vaginal cream USP 0.01% contains 0.1 mg estradiol in a nonliquefying base containing purified water, propylene glycol, stearyl alcohol, white ceresin wax, mono- and diglycerides, hydroxypropylmethylcellulose, 2208 (4000 CPS) sodium lauryl sulfate, methyl paraben, edetate disodium, and tertiary butyl-hydroquinone.

ESTRADIOL VAGINAL CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/10 kg (g)
7.00	1	Stearyl alcohol	700.00
4.00	2	Glyceryl monostearate (nonemulsifying)	400.00
7.00	3	Ceresin wax 160	700.00
0.02	4	Monotertiary butylhydroquinone	2.00
0.01	5	17-Beta-estradiol	1.00
10.00	6	Propylene glycol	1000.00
0.15	7	Methyl paraben	15.00
0.30	8	Hydroxypropylmethylcellulose 4000 CPS	30.00
0.05	9	Disodium edetate	5.00
0.30	10	Sodium lauryl sulfate	30.00
71.77	11	Water purified	7177.00

Manufacturing Directions

1. Prepare a nonaqueous phase premix by thoroughly mixing stearyl alcohol (700 g), glyceryl monostearate, nonself-emulsifying (400 g), white ceresin wax 160 (160 signifies the approximate melting point in degrees Fahrenheit, 700 g), and monotertiary butylhydroquinone (2 g) while heating to 75°C.
2. Continue mixing with heating until all solids are dissolved and then add 17-beta-estradiol (1 g dry weight). Then continue the mixing until this phase is in the form of a clear solution, at which point hold at 75°C for later use.
3. Mix propylene glycol (1000 g) and methyl paraben (15 g) together until all solids are dissolved. Add hydroxypropylmethylcellulose 4000 CPS (CPS refers to centipoise, a designation of viscosity, 30 g) to the propylene glycol solution and disperse; then add this resulting mixture to an aqueous solution of disodium edetate (5 g) and sodium lauryl sulfate (30 g) in 7117 g purified water. Heat this mixture and hold at 75°C while stirring to facilitate the formation of an oil-in-water emulsion.
4. Then add the hot nonaqueous phase premix, prepared earlier, to this hot aqueous phase slowly while mixing with an appropriate mixer. If the equipment used permits moisture loss, water may be added during this step to compensate for the loss.
5. Allow the resultant hot emulsion to cool to 60°C, at which point thoroughly homogenize using a recirculating homogenizer, homomixer, or other suitable equipment to provide a particle size reduction to a range of 5 to 20 μm for most particles.

6. Pass the fluid emulsion, still at 60°C, through a No. 100 to No. 200 stainless-steel or nylon screen into a vessel equipped for slow stirring.
7. Then cool the emulsion under vacuum while using slow sweep stirring until the temperature reaches 25°C.

ETHYLENEDIAMINE TETRACETATE OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Liquid paraffin	50.00
10.00	2	White paraffin	100.00
30.00	3	Glycerin	300.00
8.00	4	Cetostearyl alcohol	80.00
0.30	5	Methyl paraben	3.00
3.60	6	Polyoxyethylene sorbitan monostearate	36.00
2.00	7	Glyceryl monostearate	20.00
QS	8	Water purified	QS to 1 kg
1.00	9	Ethylene diamine tetraacetate	10.00

Manufacturing Directions

1. Water phase:
   a. Charge purified water, polysorbate 60, and glycerin with agitation in a melting kettle.
   b. Heat the contents to 61°C to 65°C.
   c. Add methyl paraben and mix the composition to dissolve while maintaining temperature.
2. Oil phase:
   a. In a suitable vessel, place liquid paraffin, cetostearyl alcohol, white petrolatum, glycerol monostearate, and white beeswax and mix continuously while heating to 71°C to 75°C.
3. Mixing of phases:
   a. Transfer the mixture of step 2 to the step 1 kettle, with the water phase maintained at less than 300 mbar vacuum.
   b. Add EDTA and dissolve.
   c. With mixing and keeping the temperature at 61°C to 65°C, draw the oil phase into the water phase.
   d. Mix for 15 minutes with agitation and vacuum at 300 mbar and 61°C to 65°C.
   e. While mixing and under vacuum, allow the mixture to cool gradually to room temperature.
4. Fill in appropriate container.

EUCALYPTUS AND MINT OINTMENT

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
160.00	1	Menthol	160.00
40.00	2	Eucalyptus	40.00
800.00	3	Anhydrous lanolin, USP	800.00

Manufacturing Directions

1. Mix lanolin until melted (approximately at 50°C), add remaining ingredients, and mix for 1 hour.
2. Fill hot.

FOOT FRESHENER CREAM

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Qty/L (g)
30.00	1	Alcohol and ceteareth-20 (Cosmowax® EM5483)	30.00
30.00	2	Isopropyl myristate (Crodamol® IPM)	30.00
5.00	3	Cetyl esters (Crodamol® SS)	5.00
20.00	4	Oleyl alcohol	20.00
5.00	5	Propylene glycol	5.00
5.00	6	Carbopol 980	5.00
QS	7	Deionized water	QS to 1 L
300.00	8	Ethanol (DEB100)	300.00
2.00	9	Triclosan (Irgasan® DP300)	2.00
0.50	10	Menthol	0.50
4.00	11	Triethanolamine 99 (to give pH 6 to 7)	~4.00

Manufacturing Directions

1. Preblend ethanol, Irgasan, and menthol and warm to 50°C.
2. Heat water and oil phases separately to 70°C.
3. Add the water phase to the oil phase while stirring.
4. Stir to cool, adding the preblend at 60°C. Adjust pH.

FOOT MOUSSE

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
300.00	1	Ethanol (DEB100)	300.00
1.00	2	Menthol	1.00
QS	3	Deionized water	QS
20.00	4	Undecyleneamide DEA and diethanolamine	20.00
5.00	5	Cetrimonium bromide	5.00
10.00	6	PEG-75 and water	10.00
QS	7	Perfume, preservative, color	QS

Manufacturing Directions

1. Dissolve menthol in ethanol.
2. Add remaining ingredients.
3. Pack into mechanical mousse applicator.

FLUOCINONIDE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.05	1	Fluocinonide	0.50
7.00	2	Crotamiton	70.00
10.00	3	Liquid paraffin	100.00
1.00	4	Polyoxyethylene lauryl ether	10.00
20.00	5	Carboxyvinyl polymer	200.00
1.20	6	Disodium edetate	12.00
4.68	7	Triethanolamine	46.80
QS	8	Water purified	QS to 1 kg

Manufacturing Directions

1. Dissolve fluocinonide (50 mg) in crotamiton (7 g) with warming and thereto add liquid paraffin (10 g), propylene glycol (10 g), polyoxyethylene lauryl ether (1 g), a 4% aqueous solution of carboxyvinyl polymer (20 g), purified water (47 g), and a 1% aqueous solution of disodium edetate (1.2 g).
2. Heat the mixture until approximately 70°C to 80°C and then add a 2% aqueous solution of triethanolamine (4.68 g) to it with stirring and then add further purified water until the amount becomes 100 g.
3. Stir the mixture well and then cool to give a creamy preparation having a viscosity of 65,000 centipoises and a pH of 4.47.

FLUOCINONIDE CREAM, OINTMENT, AND GEL

The cream contains fluocinonide 0.5 mg/g in a specially formulated cream base consisting of citric acid, 1,2,6-hexanetriol, polyethylene glycol 8000, propylene glycol, and stearyl alcohol. This white cream vehicle is greaseless, nonstaining, anhydrous, and completely water miscible. The base provides emollient and hydrophilic properties. In this formulation, the active ingredient is totally in solution. The cream contains fluocinonide 0.5 mg/g in a water-washable aqueous emollient base of cetyl alcohol, citric acid, mineral oil, polysorbate 60, propylene glycol, sorbitan monostearate, stearyl alcohol, and water (purified). Another strength of cream contains fluocinolone acetonide 0.25 mg/g in a water-washable aqueous base of butylated hydroxytoluene, cetyl alcohol, citric acid, edetate disodium, methyl paraben and propyl paraben (preservatives), mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, simethicone, stearyl alcohol, water (purified), and white wax. The gel contains fluocinonide 0.5 mg/g in a specially formulated gel base consisting of carbomer 940, edetate disodium, propyl gallate, propylene glycol, sodium hydroxide or hydrochloric acid (to adjust the pH), and water (purified). This clear, colorless thixotropic vehicle is grease-less, nonstaining, and completely water miscible. In this formulation, the active ingredient is totally in solution. The ointment contains fluocinonide 0.5 mg/g in a specially formulated ointment base consisting of glyceryl monostearate, white petrolatum, propylene carbonate, propylene glycol, and white wax. It provides the occlusive and emollient effects desirable in an ointment. In this formulation, the active ingredient is totally in solution. In another formulation, the ointment contains fluocinolone acetonide 0.25 mg/g in a white petroleum USP vehicle.

FLUOROMETHOLONE OPTHALMIC OINTMENT

The fluorometholone ophthalmic ointment, 0.1%, contains active ingredients fluorometholone 0.1% and the preservative phenylmercuric acetate (0.0008%). Inactives are white petrolatum, mineral oil, and petrolatum and lanolin alcohol.

FLUOROURACIL CREAM

Fluorouracil cream, 0.5%, contains fluorouracil for topical dermatologic use. Cream contains 0.5% fluorouracil, with 0.35% being incorporated into a patented porous microsphere (Microsponge®) composed of methyl methacrylate/glycol dimethacrylate crosspolymer and dimethicone. The cream formulation contains the following other inactive ingredients: Carbomer 940, dimethicone, glycerin, methyl gluceth-20, methyl methacrylate/glycol dimethacrylate crosspolymer, methyl paraben, octyl hydroxy stearate, polyethylene glycol 400, polysorbate 80, propylene glycol, propyl paraben, purified water, sorbitan monooleate, stearic acid, and trolamine.

The 5% cream contains fluorouracil in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60, and parabens (methyl and propyl).

The 1% topical cream contains inactive ingredients benzyl alcohol, emulsifying wax, mineral oil, isopropyl myristate, sodium hydroxide, and purified water.

FLURANDRENOLIDE LOTION

Each milliliter of lotion contains 0.5 mg (1.145 mol) (0.05%) flurandrenolide in an oil-in-water emulsion base composed of glycerin, cetyl alcohol, stearic acid, glyceryl monostearate, mineral oil, polyoxyl 40 stearate, menthol, benzyl alcohol, and purified water.

FLURANDRENOLIDE TOPICAL FILM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.10	1	Flurandrenolide	1.00
9.00	2	Polyvinyl alcohol	90.00
11.00	3	Polyvinylpyrrolidone (PVP)	110.00
9.00	4	Glycerin	90.00
10.00	5	Alcohol	100.00
2.00	6	Benzyl alcohol	20.00
3.00	7	Propylene glycol	30.00
0.02	8	Disodium edetate	0.20
0.10	9	Citric acid	1.00
QS	10	Water purified	QS to 1 kg

Manufacturing Directions

1. Add and dissolve flurandrenolide in propylene glycol, glycerin, and ethyl alcohol.
2. Dissolve all the remaining items (including some water) separately and add to step 1.
3. Mix thoroughly and make up the volume.
4. Spread the formulation manually or with an applicator. On evaporation of the solvents including water more than a period of 20 to 30 minutes, a continuous medicated adherent film of approximately 0.05- to 0.15 mm (average 0.08 mm) thickness is formed. After 18 to 24 hours or another desirable time span, the film is removed with water or is peeled.

FLUTICASONE OINTMENT

Fluticasone ointment, 0.005%, contains fluticasone propionate. Each gram of ointment contains fluticasone propionate 0.05 mg in a base of propylene glycol, sorbitan sesquioleate, microcrystalline wax, and liquid paraffin.

FLUTICASONE PROPIONATE OINTMENT

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.05	1	Fluticasone propionate	0.05
87.00	2	Propylene glycol	87.00
21.00	3	Sorbitan sesquioleate	21.00
200.00	4	Liquid paraffin	200.00
180.00	5	Microcrystalline wax	180.00
481.95	6	White soft paraffin	481.95
30.00	7	Hard paraffin	30.00

Manufacturing Directions

1. Melt microcrystalline wax, hard paraffin, and sorbitan sesquioleate in a fat-melting vessel at 70°C to 75°C while mixing. Add liquid paraffin and mix well.
2. Transfer the mixture in step 1 to the manufacturing vessel through stainless-steel filter. Mix and homogenize for 10 minutes under vacuum at 0.5 bar. Cool the mixture to 40°C to 45°C.
3. Disperse fluticasone propionate in propylene glycol, mix, and homogenize at a temperature of 40°C to 45°C.
4. Transfer the drug mixture from step 3 into the manufacturing vessel from step 2 while mixing. Mix and homogenize for 10 minutes under vacuum at 0.5 bar to obtain uniform homogeneous ointment to contain label amount of fluticasone propionate per gram.
5. Cool to a temperature of 25°C to 30°C with continuous stirring.
6. Fill the ointment into the tube.

FLUTICASONE PROPIONATE CREAM

Each gram of cream contains fluticasone propionate 0.5 mg in a base of propylene glycol, mineral oil, cetostearyl alcohol, ceteth-20, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water, and imidurea as preservative.

FLUTICASONE PROPIONATE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.50	1	Fluticasone propionate	0.50
40.00	2	Propylene glycol	40.00
100.00	3	Liquid paraffin	100.00
70.70	4	Cetostearyl alcohol	70.70
40.00	5	Cetomacrogol 1000	40.00
50.00	6	Isopropyl myristate	50.00
4.80	7	Dibasic sodium phosphate	4.80
1.50	8	Citric acid monohydrate	1.50
2.50	9	Imidurea	2.50
690.00	10	Purified water	690.00

Manufacturing Directions

1. Melt cetostearyl alcohol and cetomacrogol 1000 in a fat-melting vessel at 70°C. Add liquid paraffin and isopropyl myristate and mix well. Hold the temperature between 60°C and 70°C.
2. Add purified water to the manufacturing vessel and heat to 70°C to 80°C.
3. Dissolve dibasic sodium phosphate, citric acid, and imidurea in purified water. Hold the temperature between 60°C and 70°C.
4. Transfer the fat phase of step 1 through a stainless-steel filter to the manufacturing vessel while stirring at a temperature of 60°C to 70°C. Mix and homogenize for 10 minutes under vacuum at 0.5 bar. Cool the mixture to 40°C to 45°C.
5. Disperse fluticasone propionate in propylene glycol at a temperature of 40°C to 45°C.
6. Transfer the drug mixture of step 5 into step 4 to the manufacturing vessel while mixing. Mix and homogenize for 10 minutes under vacuum at 0.5 bar to obtain a uniform homogenous cream to contain labeled amount of drug per gram.
7. Cool the cream to a temperature of 25°C to 30°C with continuous stirring.
8. Transfer into stainless-steel storage container with product identification label.

FOLIC ACID SUPPOSITORY

Manufacturing Directions

1. Folic acid, 0.2%; allantoin, 0.5%; protein hydrolysate, 0.8%; lactose, 8.0%; lactic acid, 1.0%; magnesium sulfate, 1.0%; sodium chloride, 2.0%; polyoxyethylene glycol 1540, 66.5%; polyoxyethylene sorbitan monolaurate, 15.0%; polyoxyethylene sorbitan monostearate, 5%.
2. After mixing folic acid with an adequate amount of lactose, successively add the remainder of lactose, magnesium sulfate, and sodium chloridewhile stirring.
3. Mix rotein hydrolysate immediately with the powder mixture before preparing the suspension.
4. Simultaneously, after melting the polyoxyethylene glycol and polyoxyethylene glycol fatty acid esters and reaching a temperature of 60°C, mix lactic acid with the melt, suspend the powder mixture in the liquid suppository base containing lactic acid, then homogenize the mass in a colloid mill.
5. At a temperature of approximately 55°C, fill the mass into cooled moulds.
6. The percentages given above refer to suppositories weighing 3.5 to 4.0 g each.

6-FORMYLAMINONICOTINAMIDE OINTMENT AND LOTION

Manufacturing Directions

1. Ointment: Dissolve 6-Formylaminonicotinamide 0.1 g in 5 mL of water and 4.9 mL of ethanol. Admix the solution with hydrophilic ointment USP grade (90 g) to a uniform consistency. This ointment also may be stored in opaque jars at room temperature.
2. Lotion: Dissolve 6-Aminonicotinamide 0.2 g in 7.2 mL of 0.2 N HCl and admix the solution with 92.6 g of a water-in-oil lotion prepared from mineral oil, cottonseed oil, isopropyl palmitate, and water with a surfactant such as sorbitan sesquioleate. The ingredients in said water-in-oil lotion are present for example in 10:10:5:70:5 parts by weight respectively. Store the lotion thus prepared in a plastic squeeze bottle.
3. Fill the cream into the tube.

FOSCARNET CREAM

Bill of Materials

Scale (mg/100 g)	Item	Material Name	Qty/kg (mg)
3.00	1	Trisodium phosphonoformate hexahydrate (foscarnet sodium)	30.00
4.40	2	Polyoxyethylene fatty acid ester	44.00
2.00	3	Cetyl alcohol	20.00
2.00	4	Stearic acid	20.00
2.00	5	Liquid paraffin	20.00
2.00	6	Propylene glycol	20.00
1.50	7	Glycerin	15.00
0.07	8	Methyl paraben	0.70
0.03	9	Propyl paraben	0.30
QS	10	Water purified	QS to 1 kg

GAMMA BENZENE HEXACHLORIDE LOTION

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Gamma benzene hexachloride, 1% excess	10.10
2.00	2	Emulsifying wax	20.00
5.00	3	Xylene	50.00
0.50	4	Cetomacrogol 1000	5.00
10.00	5	Liquid paraffin	100.00
72.00	6	Water purified	720.00

Manufacturing Directions

1. Heat items 2, 4, and 5 to 95°C and pass through a stainless-steel sieve.
2. Heat water to 65°C and add to step 1.
3. Dissolve item 1 in item 3 with stirring and add to step 2 at 35°C.
4. Adjust pH to 7.5 to 8.0 if necessary and mix for 2 hours.

GENTAMICIN SULFATE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.100	1	Gentamycin USE gentamycin sulfate[a]	1.82
15.000	2	Petrolatum (white soft paraffin)	150.00
1.800	3	Polyoxyl 20 cetostearyl ether (cetomacrogol 1000)	18.00
7.200	4	Cetostearyl alcohol	72.00
0.100	5	Chlorocresol	1.00
6.000	6	Mineral oil (liquid paraffin)	60.00
0.300	7	Monobasic sodium phosphate	3.00
69.417	8	Purified water	694.17

[a] Considering the potency of the gentamicin sulfate is 700 µg/mg (anhydrous basis) with 15.0% water content. Quantity of gentamicin sulfate per batch will vary according to the actual potency. Required quantity should be calculated as below. Quantity of gentamicin sulfate required per batch is based on potency.

Manufacturing Directions

1. Fat phase: Load items 2 to 6 in a fat-melting vessel. Heat to 70°C. Stir to melt. Hold the molten fat at 70°C while stirring at low speed in the fat-melting vessel.
2. Aqueous phase: Set the mixer at temperature 70°C. Heat 608 g of item 8 to 70°C in mixer.
3. Cream preparation: Transfer the molten fat at 70°C from step 1 into mixer through a stainless-steel filter while mixing at speed 10 rpm, vacuum 0.6 bar.
4. When the transfer is over, start the homogenizer at low speed. Homogenize for 10 minutes with recirculation. Temperature, 65°C to 70°C.
5. Stop the homogenizer, set the mixer at temperature 50°C, speed 10 rpm (manual mode), and vacuum 0.6 bar. Cool the cream to 50°C.
6. Drug phase: Dissolve items 7 and 1 in 86.17 g of item 8 in a stainless-steel container while mixing with a stirrer. Hold the temperature at 50°C.
7. Transfer the drug solution from step 4 to the cream phase in mixer at 50°C while mixing.
8. Start the homogenizer at high speed, mixer speed 10 rpm. Mix and homogenize for 10 minutes under vacuum 0.6 bar.
9. While homogenization is in progress, set the temperature at 25°C so that the cream temperature shall not increase. Continue mixing at 10 rpm under vacuum 0.6 bar until the temperature reaches 25°C.
10. When the cream is cooled to 25°C, unload the cream in stainless-steel container and fill.

GENTAMICIN SULFATE OINTMENT

Each gram of ointment contains gentamicin sulfate USP (equivalent to 3 mg gentamicin) in a base of white petrolatum, with methyl paraben (0.5 mg) and propyl paraben (0.1 mg) as preservatives. Active ingredients are gentamicin sulfate equivalent to 0.3% gentamicin base, prednisolone acetate 0.6%, and the preservative (chloral derivative) 0.5%. Inactives are white petrolatum, mineral oil, petrolatum and lanolin alcohol, and purified water.

GENTAMICIN SULFATE OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.100	1	Gentamycin sulfate (100% excess)	2.00
0.400	2	Cetostearyl alcohol	4.00
0.100	3	Polyoxyl 20 cetostearyl ether (cetomacrogol 1000)	1.00
1.500	4	Mineral oil (liquid paraffin)	15.00
1.000	5	Mineral oil (liquid paraffin)	10.00
96.600	6	Petrolatum (white soft paraffin)	966.00
0.200	7	Purified water	2.00

Manufacturing Directions

1. Melt items 2, 3, and 5 at 70°C in a small container using water bath. Put the melt under homogenizer (keep homogenizer warm to avoid losses caused by sticking).
2. Dissolve item 1 in item 7 and heat to 50°C in water bath. Add step 2 to step 1 and homogenize for 2 to 3 minutes using homogenizer. Maintain the temperature around 50°C.
3. Load item 6 in a fat-melting vessel while stirring at 70°C. Transfer the molten mass through filter to mixer and cool it down to 50°C. Note that the mixer should be warmed before the transfer starts to avoid sticking on the wall. Add step 2 to the step 3 while stirring. Maintain temperature at around 50°C.

4. Rinse the homogenizer with warm item 4 and transfer the rinsing to the mixer.
5. Mix and homogenize for 10 minutes at low speed, mixer speed 10 to 12 rpm, vacuum 0.4 to 0.6 bar, and temperature 50°C.
6. Cool the ointment to 30°C to 35°C with stirring under vacuum 0.4 to 0.6 bar.
7. Transfer the ointment to stainless-steel drum and fill.

GLYCERIN SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
1800.00	1	Glycerin (glycerol)	1800.00
178.00	2	Sodium stearate	178.00
99.00	3	Purified water	99.00

Manufacturing Directions

1. The suppository mass is manufactured at a temperature of 120°C. Care must be taken to see that molten suppository mass does not accidentally spill on the person. The inside of the vessel should not be touched with a bare hand, as it is at a temperature of 120°C. Sodium stearate powder is light and fluffy. Avoid inhaling the dust.
2. Load item 1 into the mixer and heat to 120°C ± 2°C while stirring at low speed.
3. Load item 2 to the mixer containing item 1. Mix until complete solubilization occurs. Cool to 105°C ± 2°C.
4. Add item 3 slowly to the mixer containing mass while stirring. Mix for 20 minutes. Immediately transfer the hot mass to the heated storage vessel or heated vessel of suppository filling machine.
5. Check the temperature; it should be 105°C ± 2°C. Fill weight: 2077 mg/suppository.

GLYCERIN SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
900.00	1	Glycerin (glycerol) excess 0.06%	900.50
89.00	2	Sodium stearate	89.00
49.50	3	Purified water	49.50

Manufacturing Directions

See above; fill weight: 1039 mg/suppository.

GLYCOLIC ACID CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
3.00	1	Polyoxyethylene (40) stearate	30.00
2.00	2	Polyoxyethylene (200) sorbitan monooleate	20.00
8.00	3	Glycerol monostearate	80.00
2.00	4	Lanolin	20.00
1.00	5	Mineral oil	10.00
49.00	6	Water purified	490.00
5.00	7	Propylene glycol	50.00
3.00	8	Sorbitol	30.00
1.00	9	Carbopol 940	10.00
10.00	10	Glycolic acid	100.00
16.00	11	Triisopropanolamine	160.00

Manufacturing Directions

1. Heat items 1 to 5 in a stainless-steel container to 80°C.
2. In a separate container, heat items 6 to 9 to 80°C.
3. Add step 2 to step 1 with agitation.
4. After the mixture is congealed, add glycolic acid and triisopropanolamine.
5. Continue agitation until a uniform consistency is obtained. The pH of the cream is 3.8.

GRAMICIDIN, NEOMYCIN, NYSTATIN, AND TRIAMCINOLONE OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.025	1	Gramicidin	0.025
10.00	2	Liquid paraffin	10.00
0.48	3	Neomycin sulfate	0.48
2.72	4	Nystatin micronized	2.72
1.00	5	Syncrowax	1.00
0.105	6	Triamcinolone acetonide micronized	0.105
86.72	7	White soft paraffin	86.72

Manufacturing Directions

1. Charge items 5 and 7 in a melting vessel and heat to 70°C to melt. Transfer to Becomix through stainless-steel filters and cool to 40°C while mixing.
2. Add items 2 (half quantity) and 4 to a separate vessel and disperse using a spatula. Homogenize twice with

fine-gap setting to make smooth dispersion and add this dispersion to step 1.
3. Charge items 1, 2 (balance quantity), 3, and 6 in a separate stainless-steel vessel and homogenize to a smooth dispersion until here are no lumps.
4. Transfer to step 2.
5. Rinse homogenizer with liquid paraffin and add rinsings.
6. Homogenize the final mixture under a vacuum of 0.4 to 6 bar at 10 rpm and set temperature to 28°C to 30°C.
7. Mix until ointment is smooth, transfer to a stainless-steel vessel, and fill.

HALOBETASOL PROPIONATE CREAM AND OINTMENT

Each gram of cream contains 0.5 mg/g of halobetasol propionate in a cream base of cetyl alcohol, glycerin, isopropyl isostearate, isopropyl palmitate, steareth-21, diazolidinyl urea, methylchloroisothiazolinone, methylisothiazolinone, and water. Each gram of ointment contains 0.5 mg/g of halobetasol propionate in a base of aluminum stearate, beeswax, pentaerythritol cocoate, petrolatum, propylene glycol, sorbitan sesquioleate, and stearyl citrate.

HEMORRHOID CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Lanolin alcohol (Ivarlan 3310)	20.00
448.00	2	Petrolatum	448.00
450.00	3	Petrolatum amber	450.00
30.00	4	Shark liver oil	30.00
10.00	5	Live yeast cell derivative (Biodyne's TRF)	10.00
10.00	6	Deionized water	10.00
20.90	7	Lanolin	20.90
1.00	8	Thyme oil	1.00
0.10	9	Phenyl mercuric nitrate	0.10

Manufacturing Directions

1. Mix and heat items 1 to 4 to 70°C, cool to 50°C, and hold.
2. Separately combine items 5 to 7 and heat to 40°C and mix until homogenous dispersion is achieved; with rapid mixing add this mixture to previous mixture. Mix again and cool to 40°C. Add items 8 and 9.
3. Continue mixing while cooling to 35°C.

HEPARIN GEL CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.186	1	Heparin sodium	1.86
15.00	2	Lutrol E 400	150.00
10.00	3	Liquid paraffin	100.00
23.00	4	Lutrol F 127	230.00
QS	5	Water purified	QS to 1 kg

Manufacturing Directions

1. Dissolve heparin sodium in water. Add Lutrol E 400 and liquid paraffin.
2. Stir and cool to 6°C. Add Lutrol F 127 slowly and stir until it is dissolved.
3. Heat to room temperature when the air bubbles escape.

HEXACHLOROPHENE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
45.80	1	Olive oil, low acidity	45.80
45.00	2	Diglycol stearate S	45.00
5.00	3	Cetyl alcohol	5.00
5.00	4	Lanolin anhydrous	5.00
5.00	5	Petrolatum white	5.00
1.03	6	Polysorbate 40	1.03
5.00	7	Hexachlorophene	5.00
0.10	8	Simethicone	0.10
50.00	9	Glycerin	50.00
1.00	10	Methyl paraben	1.00
10.00	11	Sodium borate	10.00
1.30	12	Sodium lauryl sulfate	1.30
1.76	13	Perfume	1.76
2.00	14	Menthol	2.00
14.02	15	Alcohol	14.02
QS	16	Water purified	779.0 mL

Manufacturing Directions

1. Strain olive oil through voile cloth or equivalent into a suitable stainless-steel jacketed tank.
2. Add diglycol stearate. While heating oil–stearate mix, add cetyl alcohol, lanolin, petrolatum, and polysorbate 40 with mixing. Mix until all are dissolved and temperature of mixture reaches 65°C to 70°C.
3. Add and dissolve hexachlorophene in the oil mix, then add and disperse the simethicone.

4. Start heating another jacketed tank as 820 mL of purified water is added to it. Add and dissolve glycerin, methyl paraben, and borax as purified water is added and as solution is heated to 65°C to 70°C.
5. Stop mixer, add sodium lauryl sulfate, and continue mixing under vacuum.
6. Reserve 4 mL of solution from step 5 in a separate container to rinse equipment in step 2.
7. While both solutions are at 65°C to 70°C, form the primary emulsion by pumping the aqueous solution from step 5 into the oil mixture from step 3 and QS to 200 mL with vigorous agitation.
8. Homogenize primary emulsion through a Troy Mill, or similar device, into the balance of aqueous solution, mixing continually under vacuum. Rinse pump, mill, tank, and lines with reserved solution from step 6. Note that the primary emulsion should be strained through voile cloth or equivalent before being run through the Troy mill.
9. Cool emulsion to 40°C to 50°C with agitation under vacuum.
10. Dissolve perfume and menthol in the alcohol and add.
11. Using purified water, QS to 1 liter.
12. Continue mixing and cooling to 25°C.
13. Fill.

HYDROCORTISONE ACETATE AND PRAMOXINE HYDROCHLORIDE CREAM AND LOTION

The cream contains hydrocortisone acetate, 1% or 2.5%, and pramoxine HCl, 1%, in a hydrophilic cream base containing stearic acid, cetyl alcohol, Aquaphor, isopropyl palmitate, polyoxyl-40 stearate, propylene glycol, potassium sorbate, sorbic acid, triethanolamine lauryl sulfate, and water. The lotion 2.5% contains hydrocortisone acetate, 2.5%, and pramoxine hydrochloride, 1%, in a hydrophilic lotion base containing stearic acid, cetyl alcohol, forlan-L, glycerin, triethanolamine, polyoxyl 40 stearate, diisopropyl adipate, povidone, silicone, potassium sorbate, sorbic acid, and purified water. Topical corticosteroids are anti-inflammatory and antipruritic agents. Other formulations include cream, which contains hydrocortisone acetate, 1% or 2.5%, and pramoxine HCl, 1%, in a hydrophilic base containing stearic acid, cetyl alcohol, Aquaphor, isopropyl palmitate, polyoxyl 40 stearate, propylene glycol, potassium sorbate, sorbic acid, triethanolamine lauryl sulfate, and water; lotion, which contains hydrocortisone acetate, 1% or 2.5%, and pramoxine HCl, 1%, in a base containing forlan-L, cetyl alcohol, stearic acid, diisopropyl adipate, polyoxyl 40 stearate, silicone, triethanolamine, glycerin, polyvinylpyrrolidone, potassium sorbate, sorbic acid, and water; and ointment, which contains hydrocortisone acetate, 1% or 2.5%, and pramoxine HC1, 1%, in an emollient ointment base containing sorbitan sesquioleate, water, Aquaphor, and white petrolatum.

HYDROCORTISONE ACETATE SUPPOSITORIES

Each Anusol-HC 25 mg suppository contains 25 mg hydrocortisone acetate in a hydrogenated cocoglyceride base.

HYDROCORTISONE AND NITROFURAZONE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.20	1	Nitrofurazone, 4% excess	2.08
1.00	2	Hydrocortisone acetate, 5% excess	10.50
7.20	3	Cetostearyl alcohol	72.00
1.80	4	Cetomacrogol 1000	18.00
6.00	5	Liquid paraffin	60.00
15.00	6	White soft paraffin	150.00
1.00	7	Propylene glycol	10.00
0.020	8	Chlorocresol	0.20
69.00	9	Water purified	690.00

Manufacturing Directions

1. Place items 3, 4, 5 (90%), and 6 in a melting vessel after passing through stainless-steel sieve and heat to melt.
2. In a separate vessel, heat two-thirds of item 9 to 50°C and dissolve item 8 in it. Add to step 1.
3. Add and mix item 1 with item 5 (balance) and add to step 2.
4. Dissolve item 2 in balance of item 9 and a portion of item 5 in a separate vessel and homogenize. Add to step 3 with stirring. Mix for several hours.
5. Fill.

HYDROCORTISONE BUTYRATE CREAM AND OINTMENT

The cream, ointment, and topical solution contain the topical corticosteroid hydrocortisone butyrate. Each gram of cream contains 1 mg hydrocortisone butyrate in a hydrophilic base consisting of cetostearyl alcohol, ceteth-20, mineral oil, white petrolatum, citric acid, sodium citrate, propyl paraben and butylparaben (preservatives), and purified water. Each gram of ointment contains 1 mg of hydrocortisone butyrate in a base consisting of mineral oil and polyethylene.

HYDROCORTISONE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.000	1	Hydrocortisone, micronized (3% excess)	10.30
6.000	2	Propylene glycol	60.00
0.100	3	Chlorocresol	1.00
5.000	4	Mineral oil (liquid paraffin)	50.00
2.000	5	Polyoxyl 20 cetostearyl ether (cetomacrogol 1000)	20.00
8.000	6	Cetostearyl alcohol	80.00
18.000	7	Petrolatum (white soft paraffin)	180.00
0.290	8	Monobasic sodium phosphate	2.90
0.035	9	Propyl paraben	0.35
0.100	10	Methyl paraben	1.00
59.600	11	Purified water	596.00

Manufacturing Directions

1. Load 10 g of item 5 and items 4, 6, and 7 in a fat-melting vessel.
2. Heat to 70°C to 75°C while stirring. Cool down the temperature to 65°C.
3. Maintain temperature at 65°C to 70°C.
4. Heat item 11 to 90°C in mixer. Dissolve items 9 and 10 to a clear solution by stirring. Cool down the temperature to 65°C. Maintain temperature at 65°C to 70°C.
5. Add 10 g of item 5 and items 3 and 8 to the parabens solution to dissolve.
6. Mix for 10 to 15 minutes. Maintain temperature at 65°C to 70°C.
7. Transfer the oil phase to the aqueous phase in a mixer vessel through mesh by vacuum while stirring at manual mode, 10 rpm, temperature 60°C.
8. Homogenize at high speed, temperature 60°C, vacuum 0.4 bar, 10 minutes.
9. Cool down temperature to 45°C. Mix item 1 in 48g of item 2 in a separate container at 45°C using homogenizer to make slurry.
10. Add to the dispersed phase while mixing at 10 rpm and temperature 45°C.
11. Rinse the container with 12 g of item 2 and add to the dispersed phase.
12. Mix and homogenize under vacuum 0.4 bar for 10 minutes, low speed, 10 rpm, temperature 45°C.
13. Cool down the temperature to 30°C while mixing at 10 rpm, auto mode, under vacuum 0.4 bar.

HYDROCORTISONE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
70.00	1	Cetyl stearyl alcohol	70.00
15.00	2	Cremophor A 6	15.00
15.00	3	Cremophor A 25	15.00
120.00	4	Liquid paraffin	120.00
2.00	5	Paraben	2.00
688.00	6	Water	688.00
80.00	7	Propylene glycol	80.00
10.00	8	Hydrocortisone	10.00

Manufacturing Directions

1. Heat the mixture of items 1 to 5 and the water separately to approximately 80°C.
2. Add the water to the obtained solution of items 1 to 5 with rigorous stirring.
3. Heat items 7 and 8 until the active ingredient is dissolved, mix with product of step 2, and continue to stir during cooling to room temperature. White cream.

HYDROCORTISONE CREAM

Bill of Materials

Scale (mg/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Hydrocortisone, micronized	10.00
6.00	2	Propylene glycol	60.00
0.10	3	Chlorocresol	1.00
5.00	4	Liquid paraffin	5.00
2.00	5	Cetomacrogol 1000	20.00
8.00	6	Cetostearyl alcohol	80.00
18.00	7	Soft white paraffin	180.00
0.29	8	Sodium phosphate monobasic	2.90
0.035	9	Propyl paraben	0.35
0.10	10	Methyl paraben	1.00
59.60	11	Deionized water	596.00

Manufacturing Directions

1. Load items 4 to 7 in a fat-melting vessel (the oily phase; use only half of item 5) and heat to 70°C to 75°C while stirring.
2. Cool down temperature to 65°C and maintain within the range of 65°C to 70°C.
3. In a Becomix vessel, heat item 11 to 90°C.
4. Add and dissolve items 9 and 10 in step 3. Cool down to 65°C and maintain temperature between 65°C and 70°C.

5. Add item 3, balance of item 5, and item 8 and dissolve by mixing for 10 to 15 minutes at 65°C to 70°C.
6. Transfer the oil phase from step 2 into step 5 through vacuum transfer while stirring at manual 10 rpm and temperature of 60°C.
7. Homogenize at speed II at 60°C and vacuum of 0.4 bar for 10 minutes. Cool down to 45°C.
8. In a separate vessel, place items 1 and 2 at 45°C using Ultra-Turrax homogenizer to make a slurry.
9. Add step 8 into step 7 at 10 rpm and 45°C. Rinse container with item 2 and add to mix for 10 minutes at speed II.
10. Cool down to 30°C while mixing at 10 rpm auto mode and under vacuum of 0.4 bar.
11. Fill appropriate quantity into collapsible tubes.

HYDROCORTISONE CREAM AND OINTMENT

For the 1% cream, the inactive ingredients are aloe vera, benzyl alcohol, ceteareth-20, cetearyl alcohol, cetyl palmitate, glycerin, isopropyl myristate, isostearyl neopentanoate, methyl paraben, and purified water. For the 1% ointment, they are butylparaben, cholesterol, methyl paraben, microcrystalline wax, mineral oil, and white petrolatum. The 0.5% cream includes aloe vera, butylparaben, cetyl palmitate, glyceryl stearate, methyl paraben, polyethylene glycol, stearamido ethyl diethylamine, and purified water. The intensive therapy cream includes cetyl alcohol, citric acid, glyceryl stearate, isopropyl myristate, methyl paraben, polyoxyl 40 stearate, polysorbate 60, propylene glycol, propyl paraben, purified water, sodium citrate, sorbic acid, sorbitan monostearate, stearyl alcohol, and white wax. Another formulation of cream with aloe contains the active ingredient hydrocortisone 1% and the inactive ingredients aloe barbadensis gel, aluminum sulfate, calcium acetate, cetearyl alcohol, glycerin, light mineral oil, maltodextrin, methyl paraben, potato dextrin, propyl paraben, purified water, sodium cetearyl sulfate, sodium lauryl sulfate, white petrolatum, and white wax. Hydrocortisone 0.5% ointment comprises active ingredient hydrocortisone, 0.5%, and inactive ingredients aloe barbadensis extract and white petrolatum. Hydrocortisone 0.5% cream includes aloe barbadensis gel, aluminum sulfate, calcium acetate, cetearyl alcohol, glycerin, light mineral oil, maltodextrin, methyl paraben, potato dextrin, propyl paraben, purified water, sodium cetearyl sulfate, sodium lauryl sulfate, white petrolatum, and white wax.

HYDROCORTISONE GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
10.00	1	Hydrocortisone acetate	10.00
100.00	2	Lutrol E 400	100.00
50.00	3	Cremophor RH 40	50.00
5.00	4	Carpopol 940 (Goodrich)	5.00
495.00	5	Water	495.00
QS	6	Preservative	QS
260.00	7	Water	260.00
8.00	8	Triethanolamine	8.00
QS	9	Water	7.20

Manufacturing Directions

1. Suspend item 1 in a mixture of items 2 and 3 at 70°C that contains item 6.
2. Add item 8 and continue to stir until the gel is cooled to room temperature.

HYDROCORTISONE GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
10.00	1	Hydrocortisone acetate	10.00
150.00	2	Cremophor A 25	150.00
20.00	3	Cremophor RH 40	20.00
QS	4	Preservative	QS
640.00	5	Water	640.00

Manufacturing Directions

1. Suspend item 1 in the mixture of items 2 and 3 at 70°C.
2. Prepare solution of item 4, heat item 5 to 70°C and add slowly to the hot mixture item 4.
3. Continue to stir until the gel is cool (clear, colorless gel).

HYDROCORTISONE GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Hydrocortisone acetate	5.00
60.00	2	Cremophor RH 40	60.00
9.00	3	Triethanolamine	9.00
76.00	4	Water	76.00
600.00	5	Ethanol 96%	600.00
5.00	6	Carbopol 940 (Goodrich)	5.00
245.00	7	Water	245.00

Manufacturing Directions

1. Prepare solution of items 6 and 7 and mix slowly with solution of items 1 to 5.
2. Form a clear, colorless gel.

HYDROCORTISONE OINTMENT

Bill of Materials

Scale (mg/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Hydrocortisone micronized 6% excess	10.60
91.50	2	White soft paraffin	915.00
7.00	3	Liquid paraffin	70.00
0.50	4	Sorbitan sesquioleate (Arlacel 83)	5.00

Manufacturing Directions

1. Charge items 2 and 4 in a melting vessel and melt at 75°C.
2. Transfer to preheated Becomix at 75°C through stainless-steel mesh under 0.4 to 0.6 bar vacuum.
3. Start mixing at 10 rpm manual mode. Cool to 50°C.
4. In a separate vessel, disperse item 1 in item 3, using a spatula, in a water bath maintained at 60°C. Homogenize for 6 minutes using Ultra-Turrax homogenizer.
5. Add to step 3 while mixing.
6. Rinse with item 3 and add and mix.
7. Homogenize dispersion under vacuum at 0.4 to 0.6 bar at 10 rpm.
8. Cool down to 30°C while mixing.
9. Transfer to storage vessel.
10. Fill appropriate quantity at a suitable temperature.

HYDROGEN PEROXIDE AND CARBAMIDE PEROXIDE BLEACHING ORAL DENTIFRICE

Manufacturing Directions

1. Gel composition as weight percent contains sodium fluoride, 0.32 (0.14 w/v fluoride ion); Carbopol 974 P-NF, 1.25; sorbitol (70% soln), 10.00; glycerin, 10.00; carbamide peroxide, 14.00; sodium lauryl sulfate, 1.50; sodium saccharine, 0.20; flavor, 1.25; FD&C yellow 5, 0.15; FD&C red 40, 0.05; water purified, 29.60.
2. Paste composition in weight percent contains sodium fluoride, 0.32; hydrogen peroxide (50% solution), 10.00; Carbopol 943, 0.51; sorbitol (70% soln), 5.18; glycerin, 5.18; sodium lauryl sulfate, 1.50; sodium saccharine, 0.20; flavor, 1.25; polytetrafluoroethylene (Teflon), 52.00; water purified, 29.86.
3. Both phases (steps 1 and 2) are neutralized to a pH of approximately 5.5 and 6.5 with freshly prepared 10% sodium hydroxide and the stripe composition to the main composition is approximately 15:100.
4. The above hydrogen peroxide/carbamide peroxide blend composition is effective and stable when used topically for bleaching tooth surfaces.
5. When extruded from the tube container, the gel composition will be in the form of one or more stripes enclosed in the periphery of the toothpaste surrounded by the paste composition.
6. The gel and the paste composition must be of sufficiently heavy viscosities to prevent migration (bleeding) of the colored gel into the white paste composition.

HYDROGEN PEROXIDE BLEACHING DENTIFRICE PASTE

Manufacturing Directions

1. To 50 g purified water, add 1.5 g of emulsifier Carbopol 934/polyvinylpyrrolidone in 75:25 ratio and dissolve with gradual stirring.
2. To the mixture, add 20 mL of hydrogen peroxide (50%) and mix for additional 5 to 10 minutes.
3. Then adjust the acid composition between pH 5.5 and 6.5 with 10% NaOH.
4. The composition thickens to a gel and set aside.
5. In a separate vessel, add 210 g of methyl methacrylate crosspolymer GMX-0610 obtained from Perspere Corp.
6. In another separate vessel, continuous phase of the invention is prepared comprising the following ingredients: Weight% sodium fluoride, 1.05; propylene glycol, 24.10; sodium lauryl sulfate, 5.04; water, 43.40; vinyl pyrrolidone/acrylic acid*, 1.02; hydroxyethyl cellulose, 2.01; glycerin, 18.85; sodium saccharine, 0.47; flavor, 2.76; sodium benzoate, 0.55; benzoic acid, 0.06; sodium EDTA, 0. 14; sodium hydroxide, (10% solution) 0.55*; dry blend copolymer containing 25% vinyl pyrrolidone and 75% Carbopol.
7. The vinyl pyrrolidone in the mixture delays the solubility of the emulsion further than Carbopol alone.
8. After the bleaching composition (step 1) has been prepared to desired consistency, add 50 g of this composition to 50 g of the water insoluble abrasive suspension (step 2) and disperse the intimate mixture of the two immiscible phases in each other and then, with the aid of the colloidal mill, agitate until extremely fine homogeneous dispersion is obtained.
9. Then add 100 g of the dispersion so obtained to 50 g of the continuous phase (step 3) and mix the two phases in a colloidal mill, and the resultant composition comprises the discontinuous phases (step 1) dispersed homogenously throughout the continuous phase (step 2) and (step 3) of the present invention.
10. The final formulation is as follows expressed as weight in percentage: purified water, 15.75; methyl

methacrylate crosspolymer GMX-0610, 53.71; hydrogen peroxide, 10.00; Carbopol 934, 0.37; hydroxyethyl cellulose, 0.73; sodium fluoride, 0.38 (0.17% F ions); sodium lauryl sulfate, 1.83; propylene glycol, 8.75; glycerin, 6.84; sodium saccharine, 0.17; sodium benzoate, 0.20; benzoic acid, 0.02; sodium EDTA, 0.05; flavor, 1.00; sodium hydroxide (10%) QS pH 6.5, 0.20.

11. Carbopol in this composition sufficiently retards the dissolution of the emulsified hydrogen peroxide to allow the abrasive agent methyl methacrylate crosspolymer GMX-0610 to remove the dental plaque and pellicles from the enamel surface and thus allow the bleaching active hydrogen peroxide to diffuse through the plaque-free enamel with ease.

HYDROGEN PEROXIDE OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Liquid paraffin	50.00
10.00	2	White paraffin	100.00
30.00	3	Glycerin	300.00
8.00	4	Cetostearyl alcohol	80.00
0.30	5	Methyl paraben	3.00
3.60	6	Polyoxyethylene sorbitan monostearate	36.00
2.00	7	Glyceryl monostearate	20.00
QS	8	Water purified	QS to 1 kg
8.00	9	Hydrogen peroxide[a]	80.00

[a] Hydrogen peroxide, at different strengths, is used as an anti-infective in the oral cavity or topically for minor wounds.

Manufacturing Directions

1. Preparation of water phase:
   a. Charge purified water, polysorbate 60, and glycerin with agitation in a melting kettle.
   b. Heat the contents to 61°C to 65°C.
   c. Add methyl paraben and mix the composition to dissolve while maintaining temperature.
2. Preparation of oil phase:
   a. In a suitable vessel, place liquid paraffin, cetostearyl alcohol, white petrolatum, glycerol monostearate, and white beeswax and mix continuously while heating to 71°C to 75°C.
3. Mixing of phases:
   a. Transfer the mixture of step 2 to the step 1 kettle, with the water phase maintained under 300-mbar vacuum.
   b. Add hydrogen peroxide and dissolve.
   c. With mixing and keeping the temperature at 61°C to 65°C, draw the oil phase into the water phase.
   d. Mix for 15 minutes with agitation and vacuum at 300 mbar and 61°C to 65°C.
   e. While mixing and under vacuum, allow the mixture to cool gradually to room temperature.
4. Fill in appropriate container.

HYDROPHILIC OINTMENT USP

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.0250	1	Methyl paraben	0.250
0.015	2	Propyl paraben	0.15
1.00	3	Sodium lauryl sulfate	10.00
12.00	4	Propylene glycol	120.00
25.00	5	Stearyl alcohol	250.00
25.00	6	White petrolatum	250.00
37.00	7	Water purified	370.00

Manufacturing Directions

1. Melt the stearyl alcohol and the white petrolatum on a steam bath and warm to approximately 75°C.
2. Dissolve the other ingredients in the purified water and warm to approximately 75°C.
3. Mix all ingredients together and stir until the mixture congeals.

HYDROQUINONE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.50	1	Ascorbyl palmitate	15.00
1.00	2	Tocopherol acetate	10.00
2.00	3	Linoleic acid	20.00
3.00	4	Safflower oil	30.00
4.00	5	Oleyl alcohol	40.00
1.00	6	Jojoba oil	10.00
8.00	7	SDA 40 anhydrous alcohol	80.00
0.50	8	Benzyl alcohol	5.00
0.50	9	Butylated hydroxyanisole	5.00
0.15	10	Sodium bisulfite	1.50
3.00	11	Petrolatum	30.00
5.00	12	PEG-4 diheptanoate	50.00
4.00	13	Glyceryl stearate SE	40.00
1.80	14	Cetyl alcohol	18.00
2.00	15	Polyacrylamide and C13-14 isoparaffin and laureth-7	20.00
0.20	16	Hydroxyethyl cellulose	2.00
QS	17	Water purified	QS
4.00	18	Hydroquinone	40.00
QS	19	Fragrance	QS

Manufacturing Directions

1. Charge linoleic acid, safflower oil, jojoba oil, petrolatum, behenyl erucate, and cetyl alcohol and heat to 70°C.
2. Add tocopherol to above just before adding the rest of the ingredients (see below).
3. Heat item 15 to 70°C and add and dissolve item 18. Add and disperse item 16.
4. In a separate vessel, add item 1 and BHA and heat to 45°C. Dissolve items 5, 7, and 8 and heat to 45°C. Add sodium bisulfite. Stir to dissolve.
5. Add step 2 to step 1 in a homogenizer and then during homogenization add step 4 and also add tocopherol. Homogenize well.
6. Add items 18 and 19 and mix well. Cool to 35°C and fill.

HYDROQUINONE CREAM AND GEL

Each gram of 4% cream contains 40 mg of hydroquinone USP in a vanishing cream base of purified water USP, stearic acid NF, propylene glycol USP, polyoxyl 40 stearate NF, polyoxyethylene (25) propylene glycol stearate, glycerol monostearate, light mineral oil NF, squalane NF, propyl paraben NF, and sodium metabisulfite NF. The sunblocking 4% cream contains 40 mg hydroquinone USP in a tinted sunblocking-cream base of purified water USP, stearic acid NF, talc USP, polyoxyl 40 stearate NF, polyoxyethylene (25) propylene glycol stearate, propylene glycol USP, glycerol monostearate, iron oxides, light mineral oil NF, squalane NF, edetate disodium USP, sodium metabisulfite NF, and potassium sorbate NF. In another formulation, each gram of 4% cream contains 40 mg hydroquinone USP, 80 mg padimate O USP, 30 mg dioxybenzone USP, and 20 mg oxybenzone USP in a vanishing cream base of purified water USP, glycerol monostearate and polyoxyethylene stearate, ootyldodecyl stearoyl stearate, glyceryl dilaurate, quaternium-26, cetearyl alcohol and ceteareth-20, stearyl alcohol NF, propylene glycol USP, diethylaminoethyl stearate, polydimethylsiloxane, polysorbate 80 NF, lactic acid USP, ascorbic acid USP, hydroxyethyl cellulose, quaternium-14 and myristalkonium chloride, edetate disodium USP, and sodium metabisulfite NF. Each gram of 4% gel contains 40 mg hydroquinone USP, 50 mg padimate O USP, and 30 mg dioxybenzone USP in a hydroalcoholic base of alcohol USP, purified water USP, propylene glycol USP, entprol, carbomer 940, edetate disodium USP, and sodium metabisulfite NF.

HYDROQUINONE GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.50	1	Ascorbyl palmitate	15.00
1.00	2	Tocopherol acetate	10.00
4.00	3	Linoleic acid	40.00
17.75	4	Safflower oil	177.50
12.00	5	Oleyl alcohol	120.00
12.00	6	SDA 40 anhydrous alcohol	120.00
0.50	7	Benzyl alcohol	5.00
0.50	8	Butylated hydroxyanisole	5.00
16.60	9	Cyclomethicone	166.00
0.15	10	Sodium bisulfite	1.50
2.00	11	Sorbitol laurate	20.00
5.00	12	C18-C36 acid glyco ester	50.00
5.00	13	Tribehenin	50.00
7.50	14	Petrolatum	75.00
15.00	15	Behenyl erucate	150.00
4.00	16	Hydroquinone	40.00
QS	17	Fragrance	QS

Manufacturing Directions

1. Place ascorbyl palmitate and butylated hydroxyanisole in a suitable vessel and dissolve in oleyl alcohol, SDA anhydrous alcohol, and benzyl alcohol. Heat to 45°C.
1. Add sodium bisulfite and mix while keeping it covered. Keep it aside.
3. In a separate vessel, place items 11 to 16 and heat to 70°C.
4. Cool to 55°C and then add tocopherol acetate, linoleic acid, and safflower oil.
5. Add step 4 into step 2 while mixing to minimize air entrapment.
6. Add item 16 and mix well. Add item 17 and mix well.
7. Cool to 30°C and fill.

IBUPROFEN AND DOMPERIDONE MALEATE SUPPOSITORY

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
22.50	1	Domperidone maleate	22.50
600.00	2	Ibuprofen	600.00
120.00	3	Polysorbate 60	120.00
1800.00	4	Witepsol H 185	1800.00

Manufacturing Directions

1. Disperse the polysorbate in the molten Witepsol; then add the ibuprofen and domperidone.
2. Then inject the mixture into molds to produce a suppository shape and cool to ambient temperature.
3. The suppository contains 600 mg ibuprofen and 22.5 mg domperidone maleate.

IBUPROFEN CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Ibuprofen	50.00
24.00	2	Glyceryl stearate and PEG-75 stearate (Gelot 64)	240.00
5.00	3	Labrafil M 1944	50.00
3.00	4	Octyldodecyl myristate	30.00
0.07	5	Sodium methyl paraben	0.70
0.03	6	Sorbic acid	0.30
1.00	7	Stearic acid	10.00
15.00	8	Ethoxydiglycol (Transcutol)	150.00
0.150	9	Lavender oil	1.50
46.75	10	Water purified	467.50

Manufacturing Directions

1. Place item 9 in Becomix and heat to 80°C. Add items 2 to 7 one by one and mix for 20 minutes.
2. Homogenize at speed I under vacuum. Cool to 25°C.
3. In a separate container, place items 1, 8, and 9. Dissolve and filter through polyester filter.
4. Add step 3 into step 2.
5. Mix well and fill.

IBUPROFEN GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Ibuprofen	50.00
10.00	2	Alcohol	100.00
20.00	3	Propylene glycol	200.00
22.00	4	Lutrol F 127	220.00
QS	5	Preservatives	QS
43.00	6	Water purified	430.00

Manufacturing Directions

1. Heat solution of items 1 to 3 to 70°C to 80°C.
2. Dissolve item 4 and cool.
3. Add solution of item 5.
4. Fill.

IBUPROFEN GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Ibuprofen	50.00
10.00	2	Alcohol	100.00
10.00	3	Propylene glycol	100.00
15.00	4	Lutrol F 127	150.00
1.00	5	Isopropyl myristate	10.00
QS	6	Preservatives	QS
59.00	7	Water purified	590.00

Manufacturing Directions

The addition of item 5 to the formulation makes the product less sticky and is preferred.

1. Heat solution of items 1 to 3 to 70°C to 80°C.
2. Dissolve items 4 and 5 and cool. Add solution of item 6.
3. Fill.

IBUPROFEN GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Ibuprofen	51.00
27.35	2	Propylene glycol	273.50
10.00	3	Isopropyl alcohol	100.00
5.00	4	Isopropyl alcohol	50.00
0.10	5	Potassium sorbate	1.00
2.50	6	Carbopol 940	25.00
0.20	7	Sodium methyl paraben	2.00
0.0025	8	FD&C red No. 40	0.025
22.50	9	Ethoxydiglycol (Transcutol)	225.00
0.150	10	Lavender oil	1.50
27.09	11	Water purified	270.90

Manufacturing Directions

1. Place and mix items 2,3, and 11 in a stainless-steel vessel.
1. Add and dissolve item 5 in step 1 by stirring.
2. Add and dissolve item 6 in step 1 after passing through a stainless-steel sieve.
3. Mix and homogenize suspension.

4. Dissolve item 7 in item 11 and add to step 4.
6. Add and dissolve item 8 in item 11 separately and add to step 5.
7. Place item 2 in a separate vessel, dissolve, and add to step 7.
8. Combine items 9 and 10 in a separate container, mix, and transfer to step 8.
9. Mix thoroughly, transfer to storage vessel, and fill.

IBUPROFEN GEL CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Ibuprofen	50.00
12.00	2	Propylene glycol	120.00
12.00	3	Isopropyl alcohol	120.00
12.00	4	Lutrol F 127	120.00
44.00	5	Water purified	440.00
15.00	6	Nonionic hydrophilic cream: DAB 1996	150.00

IBUPROFEN GEL CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Polysorbate 60	50.00
10.00	2	Cetyl stearyl alcohol	100.00
10.00	3	Glycerin	100.00
25.00	4	White petrolatum	250.00
50.00	5	Water purified	500.00

Manufacturing Directions

1. Prepare solution of items 1 to 3 and cool to approximately 8°C. Dissolve item 4 in items 5 and 6.
2. Maintain cool until the air bubbles escape.

IBUPROFEN GEL CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Ibuprofen	50.00
24.00	2	Glyceryl stearate and PEG-75 stearate (Gelot 64)	240.00
5.00	3	Labrafil M 1944	50.00
3.00	4	Octyldodecyl myristate	30.00
0.07	5	Sodium methyl paraben	0.70
0.03	6	Sorbic acid	0.30
1.00	7	Stearic acid	10.00
15.00	8	Ethoxydiglycol (Transcutol)	150.00
0.150	9	Lavender oil	1.50
46.75	10	Water purified	467.50

Manufacturing Directions

1. Place item 9 in Becomix and heat to 80°C. Add items 2 to 7 one by one and mix for 20 minutes.
2. Homogenize at speed I under vacuum. Cool to 25°C.
3. In a separate container, combine items 1, 8, and 9; dissolve and filter through polyester filter.
4. Add step 3 into step 2. Mix well and fill.

IMIQUIMOD CREAM

Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base consisting of isostearic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methyl paraben, and propyl paraben.

INDOMETHACIN GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Indomethacin	10.00
10.00	2	Cremophor RH 40	100.00
15.00	3	Lutrol F 127	150.00
74.00	4	Water purified	740.00

Manufacturing Directions

1. Dissolve indomethacin in Cremophor RH 40 at 60°C to 70°C.
2. Add the water slowly (60–70°C), stir the mixture well, and dissolve Lutrol F 127.
3. Cool to room temperature.
4. Fill.

INDOMETHACIN GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Indomethacin	10.00
20.00	2	Propylene glycol	200.00
20.00	3	Lutrol E 400	200.00
21.00	4	Lutrol F 127	210.00
38.00	5	Water purified	380.00

Manufacturing Directions

1. Heat solution of items 1 to 3 to approximately 70°C.
2. Dissolve item 4 with stirring for approximately 30 minutes.
3. Add and mix item 5 and cool to form a yellow gel.
4. Fill.

INDOMETHACIN GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Indomethacin	10.00
15.00	2	Alcohol	150.00
22.00	3	Lutrol E 400	220.00
23.00	4	Lutrol F 127	230.00
39.00	5	Water purified	390.00

INDOMETHACIN SUPPOSITORIES

The suppositories for rectal use contain 50 mg of indomethacin and the following inactive ingredients: Butylated hydroxyanisole, butylated hydroxytoluene, edetic acid, glycerin, polyethylene glycol 3350, polyethylene glycol 8000, and sodium chloride.

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
100.00	1	Indomethacin	100.00
0.082	2	Butylated hydroxyanisole	0.082
0.082	3	Butylated hydroxytoluene	0.082
0.163	4	Edetic acid	0.163
128.00	5	Glycerin	128.00
128.00	6	Polyethylene glycol 6000	128.00
1630.00	7	Polyethylene glycol 4000	1630.00

Manufacturing Directions

1. Charge the polyethylene glycol 6000, polyethylene glycol 4000 (16.3 kg), and glycerol to the Becomix machine.
2. Heat to 70°C to melt, stir until homogenous, and cool to 60°C to 65°C.
3. Maintain temperature at 60°C to 65°C. Apply a head of nitrogen gas to hopper, then add the parabens to the hopper.
4. Stir until dissolved.
5. Charge indomethacin slowly to hopper while stirring. Stir until completely dissolved. A clear yellow melt is produced.
6. Charge edetic acid to the hopper and stir for 15 minutes to disperse it (material does not dissolve), then cool to 55°C to 60°C.
7. Stir the mixture for 30 minutes, maintaining the temperature at 55°C to 60°C, then commence filling into molds at filling limits 1.581 g to 1.679 g.

INDOMETHACIN SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
50.00	1	Indomethacin	50.00
8.30 ljg	2	Butyl hydroxytoluene	8.30 mg
141.00	3	Lutrol E 4000	141.00
14.00	4	Lutrol E 6000	14.00
16.30 ljg	5	EDTA	16.30 mg
3.00	6	Water purified	3.00

Manufacturing Directions

1. Prepare solution of items 5 and 6.
2. Mix with the melted mixture of items 1 to 4 and fill into the molds of suppositories. Fill 1.6 g/suppository.

INSECT BITE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
180.00	1	Trilaneth-4 phosphate, glyceryl stearate, and PEG-2 stearate	180.00
20.00	2	Hydrogenated palm/kernel oil PEG-6 esters	20.00
80.00	3	Mineral oil	80.00
0.30	4	Sodium methyl paraben	0.30
0.70	5	Sorbic acid	0.70
646.70	6	Deionized water	646.70
10.00	7	Benzocaine	10.00
10.00	8	Butamben	10.00
2.00	9	Menthol	2.00
0.30	10	Resorcinol	0.30
50.00	11	Ethoxydiglycol	50.00

Manufacturing Directions

1. Dissolve items 7 to 10 in item 11.
2. Mix and heat items 1 to 6 to 75°C.
3. Allow to cool slowly with constant stirring.
4. At 35°C add this to previous mixture.
5. Homogenize if necessary.

KERATOLYTIC CREAM

Bill of Materials

Scale (mg/10 g)	Item	Material Name	Qty/kg (g)
150.00	1	Polawax (self-emulsifying wax)	15.00
150.00	2	PPG-2 myristyl ether propionate (Crodamol PMP)	15.00
50.00	3	Sorbitol isostearate	5.00
35.00	4	Safflower oil, super-refined	3.50
20.00	5	Avocado oil, super-refined	2.00
20.00	6	Cetyl palmitate	2.00
50.00	7	Salicylic acid	5.00
1.50	8	Propyl paraben	0.15
1.00	9	Butylated hydroxyanisole	0.10
487.50	10	Deionized water	48.75
10.00	11	Sodium borate	1.00
3.00	12	Methyl paraben	0.30
2.00	13	Imidazolidinyl urea	0.20
20.00	14	Hydrolyzed collagen + hyaluronic acid (Cromoist HTA)	2.00

Manufacturing Directions

1. Dissolve item 7 in item 2 with mixing and heating to 70°C.
2. Add balance of items 1 to 9 and mix with heat to 80°C and mix items 10 to 13 together separately and heat to 80°C.
3. Add this mixture to the first mixture with mixing and cool to 40°C.
4. Add item 14 with mixing and cool to the desired fill temperature.
5. Adjust pH if necessary to 3 to 4 with 10% triethanolamine solution.

KETOCONAZOLE CREAM

The ketoconazole 2% cream contains the broad-spectrum synthetic antifungal agent ketoconazole, 2%, formulated in an aqueous cream vehicle consisting of propylene glycol, stearyl and cetyl alcohols, sorbitan monostearate, polysorbate 60, isopropyl myristate, sodium sulfite anhydrous, polysorbate 80, and purified water.

KETOCONAZOLE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
2.00	1	Ketoconazole micronized	20.00
20.00	2	Propylene glycol	200.00
8.00	3	Stearyl alcohol	80.00
2.00	4	Cetyl alcohol	20.00
2.00	5	Span 60	20.00
1.50	6	Tween 60	15.00
1.00	7	Isopropyl myristate	10.00
0.20	8	Sodium sulfite anhydrous	2.00
0.10	9	Tween 80	1.00
QS	10	Water purified	QS to 1 kg

Manufacturing Directions

1. Place items 3 to 5 in a steam-jacketed kettle. Heat to 75°C and then begin stirring to ensure complete melting. Maintain temperature, keep stirring.
2. Combine items 2 and 10 in a separate heating vessel and heat to 75°C. Add item 6 and stir, preferably under vacuum of 0.5 bar to avoid frothing and add to step 1, passing through a 100 mesh screen by a pump. Rinse with item 10 and add rinsings.
3. Stir for 1 hour. Cool to 40°C while stirring.
4. In a separate vessel, add 10% of item 10 and item 1 to make a slurry, heat to 40°C, and pass through colloid mill after adding another 10% of item 10.

5. Separately dissolve in 5% of item 10, item 8, and add to step above. Mix for 30 minutes.
6. Pass again through colloid mill and add to step 3, mix, and pass again through colloid mill.
7. Fill in appropriate containers.

KOJIC DIPALMITATE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.20	1	Kojic dipalmitate	2.00
6.00	2	Finetex TN	60.00
3.00	3	Bernel FAO	30.00
2.00	4	CarboSil M-5 (fumed silica)	20.00
0.30	5	Microtitanium dioxide	3.00
0.50	6	Lecithin Z-3	5.00
5.00	7	Bentone TN (hectorite compound)	50.00
2.00	8	Mineral oil	20.00
8.00	9	Isopropyl myristate	80.00
0.08	10	Fragrance	0.80

Manufacturing Directions

1. Heat the Kojic dipalmitate, Finetex, FAO, bentone, and isopropyl myristate to 70°C in a jacketed kettle.
2. Transfer to a homogenizer mill.
3. Slowly add, with high-shear agitation, the CarboSil and the microtitanium dioxide.
4. Mill and cool to 45°C to 50°C.
5. Add, with milling, the remaining ingredients except the fragrance and SD alcohol. Cool with milling (and cooling jacket if needed) to 25°C to 30°C.
6. Add, with mixing, the fragrance and alcohol. Package immediately.

LACTIC ACID CREAM

The cream is a formulation of 12% lactic acid neutralized with ammonium hydroxide, as ammonium lactate, with a pH of 4.4 to 5.4. The cream also contains cetyl alcohol, glycerin, glyceryl stearate, laureth-4, light mineral oil, magnesium aluminum silicate, methylcellulose, methyl and propyl parabens, PEG-100 stearate, polyoxyl 40 stearate, propylene glycol, and water. Lactic acid is a racemic mixture of 2-hydroxypropanoic acid.

LANOLIN CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
60.00	1	Stearic acid	60.00
145.00	2	White petrolatum jelly	145.00
116.00	3	Mineral oil 25 cS	116.00
10.00	4	Lanolin	10.00
20.00	5	Cetearyl alcohol	20.00
QS	6	Deionized water	QS to 1 kg
14.00	7	Triethanolamine 99%	14.00
QS	8	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring. Stir to cool, adding triethanolamine at 60°C and perfuming at 40°C to 50°C.
3. This cream serves as a base for drugs as well. Triethanolamine may be omitted, because it gives a higher pH.

LIDOCAINE ADHESIVE SYSTEM GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
8.00	1	Lidocaine base	80.00
5.00	2	Dipropylene glycol	50.00
8.00	3	Lecithin 60% in propylene glycol	80.00
10.00	4	Karaya gum	100.00
2.00	5	Bentonite (Polargel)[a]	20.00
0.10	6	Zinc oxide	1.00
6.00	7	Glycerin	60.00

[a] Optional ingredients.

Manufacturing Directions

1. Blend the lidocaine base, the propylene glycol, lecithin, and glycerin at approximately 70°C to 90°C until the entire drug is dissolved.
2. Cool the solution to 20°C to 35°C before adding the karaya gum and clay.
3. Once the karaya gum and clay are added, apply the final composition to a suitable backing material such as a nonwoven polyester film (e.g., the film sold under the trademark Sontara 8100, manufactured by DuPont de Nemours, EI and Co, Wilmington, DE) and warm to approximately 100°C to accelerate the formation of the gel into its final, finite form.

LIDOCAINE AND PRILOCAINE TOPICAL ADHESIVE SYSTEM CREAM

Lidocaine, 2.5%, and prilocaine, 2.5%, are emulsions in which the oil phase is a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1 by weight. This eutectic mixture has a melting point below room temperature; therefore, both local anesthetics exist as liquid oil rather than as crystals. It is also packaged in the anesthetic disc, which is a single-dose unit contained within an occlusive dressing. The anesthetic disc is composed of a laminate backing, an absorbent cellulose disc, and an adhesive tape ring. The disc contains 1 g of emulsion, the active contact surface being approximately 10 cm^2. The surface area of the entire anesthetic disc is approximately 40 cm^2.

LIDOCAINE AND TRIBENOSIDE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Tribenoside	50.00
2.00	2	Lidocaine hydrochloride	20.00
5.00	3	Cetyl alcohol	50.00
9.00	4	Stearic acid	90.00
10.00	5	Liquid paraffin	100.00
2.00	6	Isopropyl palmitate	20.00
4.45	7	Cetomacrogol 1000	44.50
1.55	8	Crill 3	15.50
0.180	9	Methyl paraben	1.80
0.05	10	Propyl paraben	0.50
6.00	11	Sorbitol 70% solution	60.00
54.80	12	Water purified	548.00

Manufacturing Directions

1. Mix and dissolve items 9 and 10 in portion of item 12 at 90°C.
2. Place item 11 into Becomix and heat to 60°C.
3. Add item 2 to step 3 and dissolve, maintaining temperature at 60°C.
4. Place items 3, 4, 7, and 8 in a melting vessel and melt at 70°C. Cool to 55°C.
5. Add items 1, 5, and 6 to a fat-melting vessel and melt at 60°C.
6. Transfer step 5 to step 4 and mix well. Cool down to 25°C.
7. Transfer to storage vessel and fill.

LIDOCAINE AND TRIBENOSIDE OINTMENT

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Tribenoside	5.00
2.00	2	Lidocaine	2.00
79.20	3	White soft paraffin	79.20
0.30	4	Hard paraffin	0.30
3.50	5	Microcrystalline wax	3.50

Manufacturing Directions

1. Place items 3 to 5 in a melting vessel and heat to 70°C to melt, transfer to Becomix, and maintain 40°C to 45°C.
2. In a portion of the melt above, add items 1 and 2 in a separate vessel and homogenize for 5 minutes. Transfer to step 1 using the melt to rinse and adding rinsings.
3. Allow to cool to 40°C. Transfer to storage vessel and fill.

LIDOCAINE AND TRIBENOSIDE SUPPOSITORIES

Bill of Materials

Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
40.00	1	Lidocaine	40.00
400.00	2	Tribenoside	400.00
281.00	3	Witepsol E 85	281.00
1124.60	4	Witepsol W 35	1124.60
4.40	5	Miglyol 812 N	4.40

Manufacturing Directions

1. Load items 3 and 4 in a fat-melting vessel and heat to 50°C. Transfer molten material to Becomix through filter sieves, keeping a small portion on the side.
2. Add items 1, 2, and 4 to product of step 1, rinsing the container of item 2 with the molten portions kept aside in step 1.
3. Mix for 20 minutes at 10 rpm (manual), temperature 50°C, homogenize at speed II for 4 minutes under 0.6 bar vacuum. Check for clarity; if not clear, homogenize again.
4. Set the temperature to 39°C and mix at 10 rpm.
5. Fill 1850 mg in suppository molds.

LIDOCAINE ANORECTAL CREAM

Anorectal cream (lidocaine 5%) is a topical anesthetic cream. Each gram of anorectal cream contains lidocaine 50 mg, benzyl alcohol, carbomer 940, cholesterol, hydrogenated lecithin, isopropyl myristate, polysorbate 80, propylene glycol, triethanolamine, vitamin E acetate, and water.

LIDOCAINE, EUGENOL, AND MENTHOL DENTAL OINTMENT

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
55.2	1	Beeswax white	55.2
150.0	2	Lanolin anhydrous	150.0
723.7	3	Petrolatum	723.7
40.0	4	Lidocaine base	40.0
1.2	5	Saccharin sodium powder	1.2
QS	6	Water purified	3.0 mL
1.0	7	Eugenol	1.0
5.0	8	Menthol	5.0
0.8	9	Oil peppermint	0.8
20.16	10	Metaphen ointment base	20.16

Manufacturing Directions

1. Melt beeswax white, lanolin, and petrolatum white together at 70°C to 80°C and strain into a suitable container.
2. Do not heat above 70°C to 80°C.
3. Melt Lidocaine base and strain into the container while mixing.
4. Dissolve the sodium saccharin in purified water heated to 70°C. Add to the container while mixing. Cool down to 45°C to 50°C while mixing.
5. Liquefy eugenol, menthol, and peppermint oil together by mixing all three items.
6. Warm gently to 35°C to 40°C if necessary. Strain into the container while mixing. Gently melt metaphen ointment base and strain into the container while mixing.
7. Mix thoroughly until congealed.

LIDOCAINE GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/1000 Tablets (g)
20.00	1	Lidocaine hydrochloride	2
560.00	2	Water	56
200.00	3	Propylene glycol pharma	20
220.00	4	Lutrol F 127	22

Manufacturing Directions

1. Prepare solution of items 1 to 3 at room temperature, heat to 70°C or cool to 6°C, and slowly add item 4 to the well-stirred solution until it is dissolved.
2. Maintain the temperature until the air bubbles escape. A clear, colorless gel is obtained.

LIDOCAINE GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/1000 Tablets (g)
50.00	1	Lidocaine hydrochloride	5
500.00	2	Water	50
150.00	3	Propylene glycol pharma	15
100.00	4	Liquid paraffin	10
200.00	5	Lutrol F 127	20

Manufacturing Directions

1. Prepare solution of items 1 to 3 at room temperature and mix with item 4.
2. Heat to 70°C or cool to 6°C and slowly add item 5 to the well-stirred solution until it is dissolved. Maintain cool until the air bubbles escape. A gel cream is obtained.

LIDOCAINE OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Lidocaine base	50.00
28.00	2	Polyethylene glycol (PEG-3350)	280.00
40.00	3	Polyethylene glycol (PEG-400)	400.00
25.00	4	Propylene glycol	250.00
2.00	5	Purified water	20.00

Manufacturing Directions

1. Load items 2 and 3 into a fat-melting vessel and heat to 70°C.
2. Cool to 40°C while stirring at slow speed (10–12 rpm).
3. Maintain the temperature between 40°C and 45°C under continuous stirring.
4. Heat 200 g of item 4 to 40°C to 45°C in a stainless-steel container.

5. Dissolve item 1 by stirring with stirrer. Add item 5 with continuous stirring.
6. Maintain the temperature between 40°C and 45°C with continuous stirring.
7. Filter through cloth filter. Transfer the drug solution into mixer previously set with temperature at 40°C to 45°C.
8. Rinse the stainless-steel container with 50 g of item 4.
9. Add the rinsing into mixer. Transfer the molten mass from the fat-melting vessel at 40°C through a stainless-steel filter to the mixer containing the drug solution while mixing at 10 to 12 rpm.
10. When the transfer is over, start the homogenizer at low speed, vacuum 0.6 bar, with stirrer speed at 10 rpm (manual mode).
11. Mix and homogenize for 10 minutes with recirculation at temperature 40°C to 45°C.
12. Stop the homogenizer, set the mixer at temperature 25°C, with stirrer speed at 10 rpm (manual mode).
13. Cool the cream to 25°C. When the ointment is cooled to 25°C, unload the ointment in stainless-steel container.

LINDANE LOTION

Lindane lotion USP, 1%, is an ectoparasiticide and ovicide effective against *Sarcoptes scabiei* (scabies). In addition to the active ingredient, lindane, it contains glycerol monostearate, cetyl alcohol, stearic acid, trolamine, carrageenan, 2-amino-2-methyl-1-propanol, methyl paraben, butyl paraben, perfume, and water to form a nongreasy lotion, which is the highly purified gamma isomer of 1,2,3, 4, 5, 6-hexachlorocyclohexane. Cream spreads easily and can be washed off readily with water. It has a slight acetic odor. Each gram of cream contains mafenide acetate equivalent to 85 mg of the base. The cream vehicle consists of cetyl alcohol, stearyl alcohol, cetyl esters wax, polyoxyl 40 stearate, polyoxyl 8 stearate, glycerin, and water, with methyl paraben, propyl paraben, sodium metabisulfite, and edetate disodium as preservatives.

MAFENIDE ACETATE CREAM

The cream is a soft, white, nonstaining, water-miscible antiinfective cream for topical administration to burn wounds.

MALATHION LOTION

The lotion contains 0.005 g of malathion per milliliter in a vehicle of isopropyl alcohol (78%), terpineol, dipentene, and pine needle oil.

MANDELIC ACID CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
2.00	1	Polyoxyethylene (40) stearate	20.00
1.00	2	Polyoxyethylene (20) sorbitan monooleate	10.00
5.00	3	Glycerol monostearate	50.00
3.00	4	Beeswax	30.00
2.00	5	Mineral oil	20.00
71.00	6	Water purified	710.00
5.00	7	Propylene glycol	50.00
0.50	8	Carbopol 934	5.00
5.00	9	DL-mandelic acid	50.00
1.7 mL	10	Ammonium hydroxide concentrated	17.00 mL

Manufacturing Directions

1. Heat items 1 to 5 in a stainless-steel container to 80°C.
1. In a separate container, heat items 6 to 8 to 80°C.
2. Add step 2 to step 1 with agitation.
4. After the mixture is congealed, add mandelic acid and ammonium hydroxide.
5. Continue agitation until a uniform consistency is obtained. The pH of the cream is 4.

MEDICATED FOOT CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Lanolin	5.00
90.00	2	Stearic acid	90.00
5.00	3	Cetyl alcohol	5.00
40.00	4	Isopropyl palmitate	40.00
10.00	5	Oleyl alcohol	10.00
20.00	6	Mineral oil and lanolin alcohol (liquid base CB3929)	20.00
7.50	7	Oil of wintergreen	7.50
3.00	8	Oil of thyme	3.00
5.00	9	Oil of pine	5.00
5.00	10	Menthol	5.00
5.00	11	Camphor	5.00
QS	12	Deionized water	QS to 1 kg
80.00	13	Glycerin	80.00
18.00	14	Triethanolamine 99%	18.00
QS	15	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately at 65°C to 70°C.
2. Add water phase to oil phase while stirring.
3. Add the triethanolamine drop-wise.
4. Stir to cool.

This product can be used as a disinfecting and soothing cream for the feet.

MENTHOL, METHYL SALICYLATE, AND MENTHOL CREAM AND OINTMENT

This cream and ointment contain menthol in an alcohol base gel, combinations of methyl salicylate, and menthol in cream and ointment bases, as well as a combination of methyl salicylate, menthol, and camphor in a nongreasy cream base; all are suitable for topical application. The varieties include the ointment (methyl salicylate, 18.3%; menthol, 16%), the cream (methyl salicylate, 15%; menthol, 10%), an arthritis formula cream (methyl salicylate, 30%; menthol, 8%), an ultrastrength pain-relieving cream (methyl salicylate, 30%; menthol, 10%; camphor, 4%), vanishing gel (2.5% menthol), and cream (10% menthol) with a fresh scent.

MERCURIC OXIDE OINTMENT

Manufacturing Directions

1. Prepare an oleaginous ointment composition containing yellow mercuric oxide as its active ingredient using the following ingredients in the relative weight percentages indicated: White petrolatum USP, 54.55; mineral oil NF, 31.50; microcrystalline wax, 5.00; stearic acid NF, 0.40; boric acid NF, 2.50; yellow mercuric oxide, 1.05; wheat germ oil, 5.00.
2. Charge the white petrolatum, mineral oil, microcrystalline wax, and stearic acid NF into a suitably sized No. 316 stainless-steel tank with an agitator. Heat the ointment base while mixing to 80°C to 85°C until the base is completely melted.
3. Then filter the ointment base through a 0.22 μm membrane-filtering unit into the main No. 316 stainless-steel mixing tank.
4. When the ointment base has cooled down to approximately 45°C, withdraw a portion of the base into a stainless-steel container.
5. Then add the boric acid (sterilized) to the base and disperse with the aid of a homomixer for 10 minutes.
6. Then add the yellow mercuric oxide (sterilized) to the mixture and disperse for at least 30 minutes until a homogeneous slurry is achieved.
7. Add the slurry to the main ointment batch and mix until the batch is homogeneous and free of lumps. Then cool the batch to approximately 28°C and add the filtered wheat germ oil thereto. Mix the resulting ointment for approximately 15 minutes until homogeneous.

MESALAMINE SUPPOSITORY

The rectal suppository contains 500 mg of mesalamine in a base of hard fat NF.

METHOTREXATE CATAPLASMS

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Diisopropanolamine	50.00
3.00	2	Methotrexate	30.00
10.00	3	Polysodium acrylate	100.00
10.00	4	Gelatin	100.00
30.00	5	Glycerin	300.00
QS	6	Water purified	QS to 1 kg

Manufacturing Directions

1. Mix diisopropanolamine and methotrexate with a portion of purified water.
2. Mix the resulting aqueous mixture with an aqueous solution of the corresponding base components (polysodium acrylate, gelatin, and glycerin) in the remaining portion of the purified water.
3. Cast the mass in step 2 on a release sheet; apply a nonwoven fabric backing to a surface of the mass.

METHOTREXATE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
7.00	1	Stearic acid	70.00
0.50	2	Behenyl alcohol	5.00
7.00	3	Squalene	70.00
2.00	4	Polyethylene glycol monostearate	20.00
5.00	5	Glyceryl monostearate (self-emulsifying type)	50.00
0.10	6	Butyl hydroxybenzoate	1.00
0.10	7	Methyl hydroxybenzoate	2.00
5.00	8	1,3-Butylene glycol	50.00
3.00	9	Methotrexate	30.00
5.00	10	Diisopropanolamine[a]	50.00
QS	11	Water purified	QS to 1 kg

[a] May be omitted.

Manufacturing Directions

1. Mix diisopropanolamine and methotrexate with a portion of purified water.

2. Mix the resulting aqueous mixture under heat with a liquid mixture of stearic acid, behenyl alcohol, squalane, polyethylene glycol stearate, glyceryl monostearate acid, and butyl parahydroxybenzoate and also with an aqueous mixture of methyl parahydroxybenzoate, 1,3-butylene glycol, and the remaining portion of the purified water.
3. Cool the resulting mass whereby the cream is obtained.

METHOTREXATE GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
92.00	1	Hydrocarbon gel	920.00
5.00	2	Diisopropanolamine	50.00
3.00	3	Methotrexate	30.00

Manufacturing Directions

1. Mix diisopropanolamine and methotrexate and stir with gelated hydrocarbon gel, whereby the ointment is obtained. An alternate formulation mixes methotrexate directly into gel with item 2.

METHOTREXATE LOTION

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Stearic acid	10.00
0.50	2	Behenyl alcohol	5.00
1.00	3	Polyoxyethylene sorbitan monooleate	10.00
1.00	4	Glyceryl monostearate (self-emulsifying type)	10.00
0.10	5	Butyl hydroxybenzoate	1.00
0.10	6	Methyl hydroxybenzoate	2.00
5.00	7	1,3-Butylene glycol	50.00
1.00	8	Carboxyvinyl polymer	10.00
3.00	9	Methotrexate	30.00
5.00	10	Diisopropanolamine[a]	50.00
QS	11	Water purified	QS to 1 kg

[a] May be omitted.

Manufacturing Directions

1. Mix diisopropanolamine and methotrexate with a portion of purified water.
2. Mix the resulting aqueous mixture under heat with a liquid mixture of stearic acid, behenyl alcohol, polyoxyethylene sorbitan monostearate, glyceryl monostearate, and butyl parahydroxybenzoate and also with an aqueous mixture of methyl parahydroxybenzoate, 1,3-butylene glycol, and another portion of the purified water.
3. Cool the resulting mixture to room temperature and mix with a water-base dispersion of carboxyvinyl polymer in the remaining water, whereby the lotion is obtained.

METHOXSALEN LOTION

Each milliliter of lotion contains 10 mg methoxsalen in an inert vehicle containing alcohol (71% v/v), propylene glycol, acetone, and purified water.

METHYL SALICYLATE AND MENTHOL CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
130.00	1	Methyl salicylate	130.00
60.00	2	Menthol	60.00
20.00	3	Eucalyptus oil	20.00
5.00	4	Lanolin	5.00
1.00	5	Chloroxylenol	1.00
150.00	6	Glyceryl stearate and PEG-100 stearate	150.00
73.00	7	Cetearyl alcohol	73.00
70.00	8	Glyceryl stearate	70.00
QS	9	Deionized water	QS to 1 kg
QS	10	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70˚C.
2. Add water phase to oil phase while stirring. Stir to cool.
3. Fill at 30˚C.

METHYL SALICYLATE AND MENTHOL LOTION

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
110.00	1	Methyl salicylate	110.00
50.00	2	Menthol	50.00
200.00	3	Lutrol E 400	200.00
60.00	4	Cremophor RH 40	60.00
70.00	5	Propylene glycol pharma	70.00
320.00	6	Lutrol F 127	320.00
190.00	7	Water	190.00

Manufacturing Directions

1. Dissolve item 6 in solution of items 1 to 5 and mix with item 7.
2. The clear gel can be diluted with water. Because of the high concentration of the active ingredients and of Lutrol F127, the consistency of the colorless clear gel is extremely hard. By reducing the concentration of the active ingredients, the amount of Lutrol F 127 could be reduced too, and the consistency of the gel will be normal.

METHYL SALICYLATE AND MENTHOL LOTION

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Methyl salicylate	150.00
70.00	2	Menthol	70.00
10.00	3	Lanolin oil	10.00
30.00	4	PEG-40 stearate	30.00
20.00	5	Glyceryl stearate	20.00
QS	6	Deionized water	QS
1.50	7	Carbopol 980	1.50
10.00	8	Potassium hydroxide (10% aqueous solution)	10.00
QS	9	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases (except potassium hydroxide) separately to 65°C to 70°C.
2. Add water phase to oil phase while stirring. Add potassium hydroxide solution to neutralize.
3. Stir to cool. Fill at 30°C.

METHYL SALICYLATE AND MENTHOL OINTMENT

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Polawax	150.00
100.00	2	Methyl salicylate	100.00
50.00	3	Menthol	50.00
100.00	4	Mineral oil 70 cS	100.00
QS	5	Deionized water	QS to 1 kg
QS	6	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70˚C.
2. Add water to oil phase while stirring. Stir to cool. Fill at 30°C.

METHYL SALICYLATE CLEAR GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
25.00	1	Hydroxypropyl cellulose	25.00
QS	2	Deionized water	QS to 1 kg
400.00	3	Ethanol DEB 100	400.00
100.00	4	Menthol	100.00
150.00	5	Methyl salicylate	150.00
25.00	6	DEA-oleth-3-phosphate	25.00

Manufacturing Directions

1. Hydrate hydroxypropyl cellulose in water at 60°C to 65°C.
2. Stir to cool. Add ethanol.
3. Add remaining ingredients and stir until homogenous.

METHYL SALICYLATE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
30.00	1	Tromethamine magnesium aluminum silicate (Veegum PRO)	30.00
30.00	2	Hydroxypropyl cellulose	30.00
350.00	3	Deionized water	350.00
350.00	4	Ethanol	350.00
40.00	5	Cocoyl sarcosine (Vanseal CS)	40.00
25.00	6	Oleath-10	25.00
25.00	7	PEG-25 hydrogenated castor oil	25.00
50.00	8	Isopropyl myristate	50.00
20.00	9	Triethanolamine	20.00
5.00	10	Camphor	5.00
5.00	11	Menthol	5.00
2.00	12	Eucalyptus oil	2.00
65.00	13	Methyl salicylate	65.00
QS	14	Preservatives	QS

Manufacturing Directions

1. Dry blend items 1 and 2 and slowly add them to items 2 and 4, agitating to ensure homogenous dispersion.
2. Combine items 5 to 9 separately and items 10 to 14 separately and mix them together. Add this mixture to the first mix and then mix until uniform.

METHYL SALICYLATE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
15.00	1	Magnesium aluminum silicate (Veegum)	1.50
547.00	2	Deionized water	54.70
2.00	3	Simethicone emulsion	0.20
30.00	4	Propylene glycol	3.00
150.00	5	Methyl salicylate	15.00
50.00	6	Menthol	5.00
6.00	7	Polysorbate	0.60
50.00	8	C18-C36 acid	5.00
150.00	9	Glyceryl stearate and PEG-100 stearate	15.00
QS	10	Preservatives	QS

Manufacturing Directions

1. Add item 1 slowly to water and mix vigorously to smooth dispersion.
2. Add items 3 and 4, mixing one at a time. Heat to 75°C to 80°C.
3. Separately mix and heat items 5 to 9 to 75°C to 80°C and add the two parts while mixing. Cool while mixing and add item 10 at 40°C.

METHYL SALICYLATE HEAT RUB LOTION

Bill of Materials

Scale (mg/mL)	Item	Material Name	Qty/L (g)
25.00	1	PPG-5-Cetech-10-phosphate (Crodafos SG)	25.00
40.00	2	Emulsifying wax, NF (Polawax)	40.00
45.00	3	PPG-1 cetyl ether (Procetyl 10)	45.00
10.00	4	Menthol	10.00
10.00	5	Camphor	10.00
75.00	6	Methyl salicylate	75.00
30.00	7	Glycerin	30.00
10.00	8	Gelatin, NF (Crodyne BY-19)	10.00
3.00	9	Diethanolamine	3.00
742.00	10	Deionized water	742.00
10.00	11	Propylene glycol, diazolidinyl urea, methyl paraben, and propyl paraben	10.00

Manufacturing Directions

1. Premix items 4, 5, and 6 with item 3.
2. When completely dissolved, add items 1 and 2 and heat to 75°C to 80°C.
3. Dissolve item 8 in water and add items 7 and 9.
4. Heat to 80°C. Slowly add this part to previous part using good mechanical mixing.
5. Allow to cool while mixing to 40°C and then add item 11.
6. Cool to 30°C and fill.

METHYL SALICYLATE LOTION

Bill of Materials

Scale (mg/mL)	Item	Material Name	Qty/L (g)
25.00	1	PPG-5-cetech-10-phosphate (Crodafos SG)	25.00
40.00	2	Emulsifying wax NF (Polawax)	40.00
45.00	3	PPG-1 cetyl ether (Procetyl 10)	45.00
10.00	4	Menthol	10.00
10.00	5	Camphor	10.00
75.00	6	Methyl salicylate	75.00
30.00	7	Glycerin	30.00
10.00	8	Gelatin (Crodyne BY-19)	10.00
3.00	9	Diethanolamine	3.00
742.00	10	Deionized water	742.00
10.00	11	Propylene glycol, diazolidinyl urea, methyl paraben, and propyl paraben	10.00

Manufacturing Directions

1. Premix items 4, 5, and 6 with item 3.
2. When completely dissolved, add items 1 and 2 and heat to 75˚C to 80˚C.
3. Dissolve item 8 in water and add items 7 and 9.
4. Heat to 80˚C. Add this part to previous part slowly, using good mechanical mixing.
5. Allow to cool while mixing to 40˚C and then add item 11. Cool to 30˚C and fill.

METHYL SALICYLATE, THYME, PINE, AND MENTHOL FOOT CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Lanolin	5.00
90.00	2	Stearic acid	90.00
5.00	3	Cetyl alcohol	5.00
40.00	4	Isopropyl palmitate	40.00
10.00	5	Oleyl alcohol	10.00
20.00	6	Mineral oil and lanolin alcohol (liquid base CB3929)	20.00
7.50	7	Oil of wintergreen	7.50
3.00	8	Oil of thyme	3.00
5.00	9	Oil of pine	5.00
5.00	10	Menthol	5.00
5.00	11	Camphor	5.00
QS	12	Deionized water	QS to 1 kg
80.00	13	Glycerin	8.00
18.00	14	Triethanolamine 99%	1.80
QS	15	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately at 65°C to 70°C.
2. Add water phase to oil phase while stirring. Add the triethanolamine dropwise.
3. Stir to cool. This product can be used as a disinfectant and soothing cream for the feet.

METOCLOPRAMIDE SUPPOSITORIES

Bill of Materials

Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
005.00	1	Metoclopramide (5.0% excess)	5.25
894.75	2	Hard fat (Suppocire AM)	894.75
QS	3	Ethanol 95%[a]	35.00

[a] To be evaporated during manufacturing process.

Manufacturing Directions

1. Load item 2 in the fat-melting vessel and heat to 65°C ± 2°C.
2. Transfer the molten mass in a stainless-steel container through clean polyester cloths.
3. Wash the mixer with purified water (65°C ± 2°C). Set the temperature to 65°C ± 2°C. Transfer the molten mass to the mixer.
4. Heat 32.5 g of item 3 in a stainless-steel container using a water bath at 65°C ± 2°C.
5. Dissolve item 1 in hot item 3 (step 4) by a stirrer. Maintain temperature at 65°C.
6. Add the ethanol–drug solution to the molten suppository base in mixer at 65°C ± 2°C while mixing.
7. Wash the drug container with 2.5 g of hot item 3 (65°C ± 2°C) and add the rinsing to the mixer while mixing.
8. Set the mixer under vacuum with air circulation. Maintain temperature at 50°C ± 2°C, mixing 10 rpm manual mode. Homogenize under vacuum with air circulation at temperature 50°C ± 2°C for 1 hour 45 minutes.
9. After completion of evaporation, continue the mixing of the mass under vacuum 0.4 to 0.6 bar while cooling it to 40°C ± 2°C.
10. Heat the storage vessel; set temperature at 40°C ± 2°C.
11. Transfer the molten mass from the mixer to the storage vessel.
12. Hold the molten mass 40°C ± 2°C while mixing continuously at low speed.
13. Fill 900 mg/suppository.

METOCLOPRAMIDE SUPPOSITORIES

Bill of Materials

Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
10.00	1	Metoclopramide (5% excess)	10.50
1339.50	2	Hard fat (Suppocire AM)	1339.50
QS	3	Ethanol 95%[a]	62.00

[a] To be evaporated during manufacturing process.

Manufacturing Directions

1. Load item 2 in the fat-melting vessel and heat to 65°C ± 2°C.
2. Transfer the molten mass in a stainless-steel container through clean polyester cloths.
3. Wash the mixer with purified water (65°C ± 2°C). Set the temperature to 65°C ± 2°C. Transfer the molten mass to the mixer.
4. Heat 57 g of item 3 in a stainless-steel container using a water bath at 65°C ± 2°C.
5. Dissolve item 1 in hot item 3 (step 4) by a stirrer. Maintain temperature at 65°C.
6. Add the ethanol–drug solution to the molten suppository base in the mixer at 65°C ± 2°C while mixing.
7. Wash the drug container with 5 g of hot item 3 (65° C ± 2°C) and add the rinsing to the mixer while mixing.

8. Set the mixer under vacuum with air circulation. Maintain temperature at 50°C ± 2°C, mix, homogenize under vacuum with air circulation at temperature 50°C ± 2°C for 1 hour 45 minutes.
9. After completion of evaporation, continue the mixing of the mass under vacuum 0.4 to 0.6 bar while cooling to 40°C ± 2°C.
10. Heat the storage vessel, set temperature at 40° ± 2°C.
11. Transfer the molten mass from mixer to the storage vessel.
12. Hold the molten mass at 40°C ± 2°C while mixing continuously at low speed.
13. Fill 1350 mg/suppository.

METOCLOPRAMIDE SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
20.00	1	Metoclopramide (5% excess)	21.00
1779.00	2	Hard fat (Suppocire AM)	1779.00
QS	3	Ethanol 95%[a]	90.00

[a] To be evaporated during manufacturing process.

Manufacturing Directions

Fill weight: 1800 mg/suppository.

Precaution: The molten suppository mass must be kept under stirring throughout the storage period, during manufacturing, and during filling to avoid the sedimentation of the active drug.

1. Load item 2 in the fat-melting vessel and heat to 65°C ± 2°C.
2. Transfer the molten mass in a stainless-steel container through clean polyester cloths.
3. Wash the mixer with purified water (65 ± 2°C). Set the temperature to 65°C ± 2°C. Transfer the molten mass to the mixer.
4. Heat 82.5 g of item 3 in a stainless-steel container using a water bath at 65°C ± 2°C.
5. Dissolve item 1 in hot item 3 (step 4) by a stirrer. Maintain temperature at 65°C.
6. Add the ethanol–drug solution to the molten suppository base in the mixer at 65°C ± 2°C while mixing.
7. Wash the drug container with 7.5 g of hot item 3 (65°C ± 2°C) and add the rinsing to the mixer while mixing.
8. Set the mixer under vacuum with air circulation. Maintain temperature at 50°C ± 2°C, homogenize under vacuum with air circulation at temperature 50°C ± 2°C for 1 hour 45 minutes.
9. After completion of evaporation, continue the mixing of the mass under vacuum 0.4 to 0.6 bar while cooling to 40°C ± 2°C.
10. Heat the storage vessel, set temperature at 40°C ± 2°C.
11. Transfer the molten mass from mixer to the storage vessel.
12. Hold the molten mass at 40°C ± 2°C while mixing continuously at low speed.
13. Fill 1800 mg/suppository.

METOCLOPRAMIDE SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
10.00	1	Metoclopramide base 5% excess	10.50
1339.00	2	Suppocire AM	1339.00
QS	3	Alcohol	QS

Manufacturing Directions

1. Add and melt item 2 in a melting vessel at 65°C. Transfer to mixing vessel through filter sieve at 65°C.
2. Heat item 3 to 65°C in a separate vessel and add item 1 to dissolve. Add to step 1.
3. Set mixing vessel under vacuum with air circulation and at 50°C. Homogenize at speed II.
4. Completely evaporate alcohol and continue to mix at 0.4 to 0.6 bar and cool down to 40°C.
5. Fill suppository mold.

METRONIDAZOLE CREAM

The topical cream contains metronidazole USP at a concentration of 7.5 mg/g (0.75%) in an emollient cream consisting of emulsifying wax, sorbitol solution, glycerin, isopropyl palmitate, benzyl alcohol, lactic acid or sodium hydroxide to adjust pH, and purified water. Metronidazole is a member of the imidazole class of antibacterial agents and is classified therapeutically as an antiprotozoal and antibacterial agent. For metronidazole cream, 1%, each gram contains 10 mg micronized metronidazole USP in a base of purified water USP, stearic acid NF, glyceryl monostearate NF, glycerin USP, methyl paraben NF, trolamine NF, and propyl paraben NF.

METRONIDAZOLE GEL SOLUTION

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Metronidazole	10.00
5.00	2	Hydroxy-beta-cyclodextrin	50.00
0.15	3	Methyl paraben	1.50
0.03	4	Propyl paraben	0.30
5.00	5	Glycerin	50.00
1.50	6	Hydroxyethyl cellulose	15.00
0.05	7	Disodium edetate	0.50
QS	8	Water purified	QS to 1 kg

METRONIDAZOLE LOTION

Metronidazole lotion contains metronidazole USP at a concentration of 7.5 mg/g (0.75% w/w) in a lotion consisting of benzyl alcohol, carbomer 941, cyclomethicone, glycerin, glyceryl stearate, light mineral oil, PEG-100 stearate, polyethylene glycol 400, potassium sorbate, purified water, steareth-21, stearyl alcohol, and sodium hydroxide or lactic acid to adjust pH. Metronidazole is an imidazole and is classified therapeutically as an antiprotozoal and antibacterial agent.

METRONIDAZOLE VAGINAL GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.20	1	Metronidazole	1.20
21.00	2	Lutrol F 127	21.00
40.00	3	Lutrol E 400	40.00
37.80	4	Water purified	37.80

Manufacturing Directions

1. Heat mixture of items 1 to 3 to 70°C to 80°C and slowly add the water heated to approximately 70°C.
2. Maintain the temperature until the air bubbles disappear.

MICONAZOLE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
7.00	1	Cetostearyl alcohol	70.00
1.50	2	Cremophor A6	15.00
1.50	3	Cremophor A 25	15.00
12.00	4	Liquid paraffin	120.00
0.10	5	Parabens mixture	1.00
67.80	6	Water purified	678.00
8.00	7	Propylene glycol	80.00
2.00	8	Miconazole nitrate	20.00

Manufacturing Directions

1. Heat the mixture of items 1 to 5 and the water separately to approximately 80°C.
2. Add the water to the obtained solution with rigorous stirring.
3. Heat items 7 and 8 until the active ingredient is dissolved, mix with step 2, and continue to stir during cooling to room temperature.

MICONAZOLE MOUTH GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
2.00	1	Miconazole nitrate	20.00
0.10	2	Orange flavor	1.00
20.00	3	Lutrol F 127	200.00
10.00	4	Cremophor RH 40	100.00
10.00	5	Propylene glycol	100.00
5.00	6	Kollidon 90F	50.00
0.30	7	Saccharin sodium	3.00
52.60	8	Water purified	526.00

Manufacturing Directions

1. Dissolve items 1 and 2 in the molten mixture of items 3 and 4.
2. Heat solution of items 6 to 8 to 90°C and mix slowly with step 1.
3. Let cool to room temperature when the air bubbles have escaped.

MICONAZOLE NITRATE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
21.00	1	Miconazole nitrate (5% excess)	21.00
200.0	2	Tefose 63	200.0
30.00	3	Labrafil M[a]	30.00
30.00	4	Mineral oil (liquid paraffin)	30.00
0.05	5	Butylated hydroxyanisole	0.05
2.00	6	Benzoic acid	2.00
720.00	7	Purified water	720.00

[a] Synonyms: Labrafil M 1944 CS, oleoyl macrogolglycerides, apricot kernel oil PEG-6 complex.

Manufacturing Directions

1. Melt items 2, 3, and 4 (fatty phase) in fat-melting vessel.
2. Heat to 65°C to 70°C.
3. Disperse items 5 and 1 in the fatty phase while mixing at high speed for 20 minutes.
4. Add item 7 to the mixer and heat to 80°C to 90°C.
5. Dissolve item 6 and cool down to 65°C to 70°C.
6. Transfer the fatty phase to the mixer with vacuum at 0.2 to 0.3 bar.
7. Start cooling down while mixing at 10 rpm and homogenize at high speed for 20 minutes, then cool down to 25°C to 28°C while mixing at a vacuum of 0.2 to 0.3 bar (65–45°C) or 0.5 to 0.7 bar (45–25°C).

MICONAZOLE NITRATE VAGINAL SUPPOSITORIES

Bill of Materials

Scale (mg/ovule)	Item	Material Name	Qty/1000 Ovules (g)
200.00	1	Miconazole nitrate micronized	200.00
1250.00	2	Hard fat (Witepsol H 37)	1250.00
1250.00	3	Hard fat (Witepsol H 35®)	1250.00

Manufacturing Directions

Fill weight: 2700 mg/ovule. The following are additional requirements: All particle sizes must be below 30 gm and 60% to 80% must be less than 20 µm.

Precaution: The molten suppository mass must be kept under stirring throughout the storage period, during the manufacturing, and during filling to avoid the sedimentation of the active drug. Check the molten witepsols for phase separation by draining approximately 18mL to 37 mL of molten witepsols in a glass beaker.

1. Load items 2 and 3 in the fat-melting vessel and heat to 50°C ± 3°C.
2. Check the molten mass for phase separation.
3. Transfer the molten mass to the mixer through filter sieves. Set the temperature at 40°C ± 2°C.
4. Load item 1 to the mixer containing molten Witepsol (items 2 and 3).
5. Carefully mix the powder with the Witepsol melt.
6. Set the mixer at temperature 40°C ± 2°C, speed 10 rpm (manual mode), and mix for 10 minutes.
7. Set the mixer at temperature 40°C ± 2°C, speed 10 rpm (manual mode), vacuum 0.6 bar.
8. Homogenize at low speed while mixing for 5 minutes.
9. Homogenize at high speed while mixing for 3 minutes.
10. Continue mixing of the mass under vacuum in mixer.
11. Heat the storage vessel, set the temperature at 40°C ± 2°C.
12. Transfer the molten mass from the mixer to the storage vessel.
13. Hold the mass at 40°C ± 2°C, while mixing continuously at low speed. Fill.

MICONAZOLE NITRATE VAGINAL SUPPOSITORIES (400 MG)

Bill of Materials

Scale (mg/ovule)	Item	Material Name	Qty/1000 Ovules (g)
400.00	1	Miconazole nitrate micronized	200.00
1150.00	2	Hard fat (Witepsol H 37)	1250.00
1150.00	3	Hard fat (Witepsol H 35)	1250.00

Manufacturing Directions

1. Load items 2 and 3 in the fat-melting vessel and heat to 50°C ± 3°C.
2. Check the molten mass for phase separation.
3. Transfer the molten mass to the mixer through filter sieves. Set the temperature at 40°C ± 2°C.
4. Load item 1 to the mixer containing molten Witepsol (items 2 and 3).
5. Carefully mix the powder with the Witepsol melt.
6. Set the mixer at temperature 40°C ± 2°C, speed 10 rpm (manual mode), and mix for 10 minutes.
7. Set the mixer at temperature 40°C ± 2°C, mix under vacuum 0.6 bar.
8. Homogenize at low speed while mixing for 5 minutes.

9. Homogenize at high speed while mixing for 3 minutes.
10. Continue mixing of the mass under vacuum in mixer.
11. Heat the storage vessel, set the temperature at 40°C ± 2°C.
12. Transfer the molten mass from the mixer to the storage vessel.
13. Hold the mass at 40°C ± 2°C while mixing continuously at low speed.
14. Fill 2700 mg.

MINOXIDIL GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
20	1	Minoxidil	20
5	2	Carbopol 934	5
5	3	Propylene glycol	5
3	4	Ethanol	3
QS	5	Triethanolamine	QS
2	6	Water	2

Manufacturing Directions

1. Dissolve minoxidil in the mixture of ethanol: propylene glycol:water in 50:30:20 proportion, adjust pH to 7.4 with triethanolamine, and gel the solution by adding 0.5% Carbopol 934 with constant stirring at 900 rpm to 1000 rpm.

MINOXIDIL GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
20	1	Minoxidil	20
40	2	HPMC	40
5	3	Propylene glycol	5
3	4	Ethanol	3
QS	5	Triethanolamine	QS
2	6	Water	2
40	7	HPC	40

Manufacturing Directions

1. Dissolve minoxidil in the mixture of ethanol: propylene glycol:water in 50:30:20 proportion, adjust pH to 7.4 with triethanolamine, and gel the solution by adding 4% HPMC and 4% HPC with constant stirring at 900 rpm to 1000 rpm.

MINOXIDIL GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
20	1	Minoxidil	20
60	2	HPMC	60
5	3	Propylene glycol	5
3	4	Ethanol	3
QS	5	Triethanolamine	QS
2	6	Water	2

Manufacturing Directions

1. Dissolve minoxidil in the mixture of ethanol: propylene glycol:water in 50:30:20 proportion, adjust pH to 7.4 with triethanolamine, and gel the solution by adding 6% HPMC with constant stirring at 900 rpm to 1000 rpm.

MINOXIDIL GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
20	1	Minoxidil	20
80	2	HPC	80
5	3	Propylene glycol	5
3	4	Ethanol	3
QS	5	Triethanolamine	QS
2	6	Water	2

Manufacturing Directions

1. Dissolve minoxidil in the mixture of ethanol: propylene glycol:water in 50:30:20 proportion, adjust pH to 7.4 with triethanolamine, and gel the solution by adding 8% HPC with constant stirring at 900 rpm to 1000 rpm.

MOMETASONE FUROATE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.20	1	Mometasone furoate micronized	2.00
40.00	2	Isopropyl alcohol	400.00
0.15	3	Hydroxypropyl cellulose	1.50
0.226	4	Sodium acid phosphate	0.226
30.00	5	Propylene glycol	300.00
QS	6	Water purified	QS to 1 kg
QS	7	Phosphoric acid to adjust pH (10% w/v solution)	QS

Manufacturing Directions

1. Place item 2 in a suitable vessel, add item 1, and mix for 25 minutes to dissolve completely.
2. Add item 3 slowly to step 1 and mix for 15 minutes to disperse evenly.
3. In a separate vessel, dissolve item 4 in a suitable quantity of item 6 and add to step above and mix for 10 minutes. Circulate cold water in the jacket to aid in gel formation.
4. Add item 5 to step above and mix until uniform.
5. Check and adjust the pH to 4.5 ± 0.2 with 10% w/v phosphoric acid solution. Mix the batch for at least 2 hours for pH adjustment and check the final pH.
6. Adjust the volume; pass through a 100 mesh screen.
7. Fill in a suitable container.

MOMETASONE FUROATE LOTION

Each gram of cream, 0.1%, contains 1 mg mometasone furoate in a cream base of hexylene glycol, phosphoric acid, propylene glycol stearate, stearyl alcohol and ceteareth-20, titanium dioxide, aluminum starch ocetenylsuccinate, white wax, white petrolatum, and purified water. Each gram of ointment, 0.1%, contains 1 mg mometasone furoate in an ointment base of hexylene glycol, phosphoric acid, propylene glycol stearate, white wax, white petrolatum, and purified water. Each gram of lotion, 0.1%, contains 1 mg of mometasone furoate in a lotion base of isopropyl alcohol (40%), propylene glycol, hydroxypropyl cellulose, sodium phosphate, and water. It may also contain phosphoric acid and sodium hydroxide used to adjust the pH to approximately 4.5.

MONOBENZONE CREAM

Each gram of benoquin cream contains 200 mg monobenzone USP in a water-washable base consisting of purified water USP, cetyl alcohol NF, propylene glycol USP, sodium lauryl sulfate NF, and white wax NF.

MULTIVITAMIN ORAL GEL VETERINARY

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
18,700 IU	1	Vitamin A palmitate 1.7 million IU/g (BASF)	1.10
1.06	2	Vitamin E acetate (BASF)	10.60
0.50	3	Butyl hydroxytoluene	500.00
20.00	4	Cremophor RH 40	20.00
725.00	5	Water	725.00
0.35	6	Thiamine hydrochloride (BASF)	3.55
0.03	7	Riboflavin (BASF)	0.35
0.17	8	Pyridoxine hydrochloride (BASF)	1.77
0.03	9	Cyanocobalamin gelatin coated 1%	0.35
0.35	10	Nicotinamide	3.53
0.03	11	Folic acid	0.35
0.35	12	Dexpanthenol (BASF)	3.53
0.30	13	EDTA sodium	3.00
0.43	14	Ferrous sulfate (7 H2 0)	4.38
0.63	15	Manganese chloride (4 H2 0)	6.38
0.11	16	Potassium iodide	1.15
50.00	17	Kollidon 90 F	50.00
100.00	18	Lutrol F 127	100.00
100.00	19	Lutrol F 127	100.00

Manufacturing Directions

1. Heat mixture of items 1 to 4 to approximately 60°C to obtain a clear solution and slowly add the water (item 5) to the well-stirred solution.
2. Dissolve items 6 to 16 and item 17 separately in this mixed solution at room temperature, cool to approximately 6°C, add item 19, and stir until all Lutrol F 127 is dissolved.
3. Maintain the cool temperature until the air bubbles have escaped.

MULTIVITAMIN ORAL GEL WITH LINOLEIC AND LINOLENIC ACID

Bill of Materials

Scale (mg/mL)	Item	Material Name	Qty/100 mL (g)
0.050	1	Evening primrose oil (EPO Pure, Prima Rosa/SA)	5.0 mL
0.30	2	Vitamin A palmitate 1.7 million IU/g (BASF)	0.30
0.190	3	Vitamin E acetate (BASF)	0.19
0.00150	4	Vitamin D_3 40 million IU/g	150 µg
200.00	5	Cremophor RH 40	20.0
550.00	6	Water	55.0
0.030	7	Thiamine hydrochloride (BASF)	0.03
0.030	8	Riboflavin (BASF)	0.03
0.150	9	Pyridoxine hydrochloride (BASF)	0.15
0.001	10	Cyanocobalamin, crystalline	10 µg
0.001	11	Calcium D-pantothenate (BASF)	0.10
0.005	12	Nicotinamide	0.50
10.00	13	Ascorbic acid, crystalline (BASF)	1.0
140.00	14	Lutrol F 127	14.0
50.00	15	Lutrol F 127	5.0

Manufacturing Directions

1. Prepare mixture of items 1 to 5 and heat to approximately 65°C.
2. Add the warm water (item 6 at 65°C) slowly to the well-stirred mixture as before.
3. Dissolve items 7 to 14 at 20°C to 25°C in this clear solution.
4. Cool the obtained solution to approximately 5°C and dissolve the rest of Lutrol F 127 item 15.
5. Maintain the cool temperature until the air bubbles have escaped.
6. A clear yellow gel was obtained. 5 mL of evening primrose oil epopure contains 3.5 g linoleic acid and 0.45 g gamma-linolenic acid.

MUPIROCIN CALCIUM CREAM

Mupirocin calcium cream 2% contains the dihydrate crystalline calcium hemisalt of the antibiotic mupirocin. Cream is a white cream that contains 2.15% w/w mupirocin calcium (equivalent to 2.0% mupirocin free acid) in an oil-and-water-based emulsion. The inactive ingredients are benzyl alcohol, cetomacrogol 1000, cetyl alcohol, mineral oil, phenoxyethanol, purified water, stearyl alcohol, and xanthan gum.

MUPIROCIN OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
2.00	1	Mupirocin crystalline USE mupirocin calcium dihydrate equivalent	20.00
1.00	2	Hydrocortisone	10.00
87.30	3	White soft paraffin	873.00
4.85	4	Softisan 649	48.50

Manufacturing Directions

1. Heat appropriate proportions of white soft paraffin and Softisan 649 together to meet at 60°C to 70°C.
2. Mix thoroughly.
3. Allow to cool with stirring to room temperature.
4. Add items 2 and 3 with stirring.
5. Pass ointment through a mill (such as triple roller mill).

MUPIROCIN OINTMENT

Each gram of mupirocin ointment, 2%, contains 20 mg mupirocin in a bland water-miscible ointment base (polyethylene glycol ointment NF) consisting of polyethylene glycol 400 and polyethylene glycol 3350. Mupirocin is a naturally occurring antibiotic. The nasal ointment, 2%, contains the dihydrate crystalline calcium hemisalt of the antibiotic mupirocin. It is a white to off-white ointment that contains 2.15% w/w mupirocin calcium (equivalent to 2% pure mupirocin free acid) in a soft, white ointment base. The inactive ingredients are paraffin and a mixture of glycerin esters (Softisan®).

NAFTIFINE HYDROCHLORIDE CREAM

The cream, 1%, contains the synthetic, broad-spectrum antifungal agent naftifine hydrochloride. It is for topical use only. The active ingredient is naftifine hydrochloride, 1%; the inactive ingredients are benzyl alcohol, cetyl alcohol, cetyl esters wax, isopropyl myristate, polysorbate 60, purified water, sodium hydroxide, sorbitan monostearate, and stearyl alcohol. Hydrochloric acid may be added to adjust pH.

NAFTIFINE HYDROCHLORIDE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
39.00	1	Urea	390.00
0.15	2	Carbopol 940	1.50
5.94	3	Petrolatum	59.40
12.06	4	Mineral oil	120.60
1.875	5	Glyceryl stearate	187.50
0.626	6	Cetyl alcohol	6.26
3.00	7	Propylene glycol	30.00
0.05	8	Xanthan gum	0.50
0.15	9	Trolamine	1.50
1.00	10	Naftifine hydrochloride[a]	10.00

[a] This formulation can serve as a generic formula for topical antifungals.

NANOXYNOL SUPPOSITORY WITH BACTERIAL CULTURE

Bill of Materials

Scale (mg/ suppositoiy)	Item	Material Name	Qty/1000 Suppositories (g)
125.00	1	Benzalkonium chloride or methyl benzethonium chloride	125.00
110.00	2	Imidiazolidinyl urea	110.00
11.00	3	Diazolidinyl urea	11.00
400.00	4	Hydroxypropylmethylcellulose	400.00
200.00	5	Microcrystalline cellulose	200.00
100.00	6	Ascorbic acid	100.00
110.00	7	Nanoxynol 9	110.00
QS	8	Lactic acid for pH adjustment	QS
1 million	9	Encapsulated lactobacilli (bacteria)[a]	1 billion
30.00	10	Magnesium stearate	30.00
30.00	11	Silicon dioxide	30.00
30.00	12	Lactose	30.00
QS	13	Sterile normal saline	QS

[a] Encapsulation methods: Viable lyophilized lactobacilli bacteria that have been lyophilized after the removal of the media are used for encapsulation. The organisms are grown to log phase in nutrient media. The removal of the nutrient media is done by centrifugation at 14,000 *g* at 0°C to 4°C and then washing with sterile, balanced salts and 5% glucose solution at least three times after the initial centrifugation. The bacteria are then "snap frozen" with liquid nitrogen and lyophilized under high vacuum. The freshly obtained, washed, and lyophilized bacteria are suspended in 10 mL of 5% glucose saline solution in such volume so as to obtain a heavy suspension of bacteria that contains between 1 and 10 billion organisms per milliliter at 0°C to 4°C. The suspension of bacteria is rapidly, but gently, stirred while 0.2 mL to 0.4 mL of sodium alginate solution (1.5% weight by volume) is added. The above mixture is then transferred into a 4-L round-bottom flask by using a nitrogen stream through a sheathed 14-gauge needle. The 4-L round-bottom flask was previously washed with a 5% albumin solution and, thereafter, heated for at least 10 hours at 65°C, and the needle and the tubing used in the process have also been treated this way. Thereafter, the above mixture is forced through a 30-gauge multibeveled needle under pressure, using a large syringe and nitrogen stream. Very small droplets are generated at the end of the needle, which are dried by the nitrogen and airstream around the 30-gauge needle, and the droplets are collected in an aqueous solution of 1.3% to 2% calcium chloride, where they gel. Thereafter, they are washed at least three times with 0.08% to 0.13% 2-(N-cyclohexyl-amino) ethanesulfonic acid (CHES) solution and 1.0% to 1.5% calcium chloride solution. The gelled droplets or little spheres are further washed with at least a fivefold excess of the 0.1% CHES 1.1% calcium chloride and normal saline solution. The resultant spheres are then "snap frozen" in liquid nitrogen and then lyophilized. After these steps, the encapsulated organisms can be used in the formulation below.

Manufacturing Directions

1. Add the benzalkonium chloride or methylbenzethonium chloride, imidiazolidinyl urea, and diazolidinyl urea slowly, while thoroughly stirring, to a suspension of hydroxypropylmethylcellulose and microcrystalline cellulose in a sterile normal saline solution (quantity sufficient to make a thick paste) at 35°C to 37°C.
2. Slowly lower the pH to approximately 6.0 to 6.3 with reagent grade lactic acid. (This step binds the antimicrobials to the "cellulose" excipients.)
3. Stir the suspension for 2 hours and then slowly add ascorbic acid that was dissolved in approximately 10 mL to 15 mL sterile saline with gentle stirring.
4. The material is, at this point, a very thick paste. Now add spermicide (Nonoxynol 9) and thoroughly mix. After this step, perform the process at 0°C to 4°C.
5. Then lower the pH of the mixture to 4.3 to 4.5 with reagent-grade lactic acid.
6. Then add freshly obtained encapsulated lactobacilli bacteria to achieve a final concentration of at least 1 million viable bacteria per suppository. (In as much as the goal is to achieve a final concentration of at least 1 million viable bacteria per suppository, a four- to sixfold excess of bacteria are usually added because some loss of the viability occurs during the various mixing processes. This means that approximately 500 mg of the encapsulated bacteria are usually added.) It is important to mix these organisms not only thoroughly to ensure uniformity but also quickly because moisture adversely affects the viability of the organisms.
7. Rapid and thorough mixing can be done, for example, by spreading the paste in a thin layer on a sterile glass plate and then using a replicator to spread the bacteria evenly over the paste.

8. Add magnesium stearate and silicon dioxide, with or without lactose.
9. After the materials are thoroughly mixed at 0°C to 4°C, press them into a mold and dry in a desiccating jar under vacuum at 0°C to 4°C. [Drying at room temperature (25°C) or at higher temperatures decreases the number of viable bacteria.]
10. Then seal the suppositories in air- and moisture-proof containers until used. During storage they should be protected from moisture and extreme temperatures to ensure the viability of the lactobacilli.

NEOMYCIN AND BACITRACIN OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
50,000 IU	1	Bacitracin zinc, 8% excess (69 IU/mg)	7.80
0.50	2	Neomycin sulfate, 8% excess	5.40
85.00	3	White soft paraffin	850.00
5.00	4	Hard paraffin	50.00
10.00	5	Liquid paraffin	100.00
0.10	6	Edetate disodium	1.00

Manufacturing Directions

1. Place items 3 and 4 and half of item 5 in a melting vessel and heat to 100°C; bubble nitrogen gas to remove moisture and reduce oxygen load.
2. In a separate vessel, place balance of item 5 and mix items 1 and 2 to make a paste.
3. Add step 2 to step 1 and mix at 30°C for 2 hours.

NEOMYCIN GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.50	1	Neomycin sulfate	0.50
50.00	2	Propylene glycol	50.00
5.00	3	Parabens	5.00
200.00	4	Lutrol F 127	200.00
745.00	5	Water	745.00

Manufacturing Directions

1. Dissolve the parabens and Lutrol F 127 in water heated to approximately 80°C.
2. Add the propylene glycol and dissolve neomycin sulfate.
3. Either cool to room temperature when the air bubbles escape or dissolve parabens in hot water, cool to 5°C to 10°C, dissolve Lutrol F 127, add propylene glycol, and dissolve neomycin sulfate.
4. Maintain the cool temperature until the air bubbles have escaped.

NEOMYCIN, POLYMYXIN B SULFATE, AND BACITRACIN ZINC OPTHALMIC OINTMENT

The neomycin and polymyxin B sulfates and bacitracin zinc ophthalmic ointment is a sterile antimicrobial ointment for ophthalmic use. Each gram contains neomycin sulfate equivalent to 3.5 mg neomycin base, polymyxin B sulfate equivalent to 10,000 polymyxin B units, bacitracin zinc equivalent to 400 bacitracin units, and white petrolatum, QS.

NICOTINE POLYMER GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
66.70	1	N-30 PVP	667.00
28.60	2	Lauryl methylacrylate	286.00
5.00	3	Sodium stearate	50.00
1.25	4	Hydrogen peroxide (30%)	12.50
QS	5	Water purified	QS to 1 kg

Manufacturing Directions

1. Carry out the emulsion copolymerization of 66.7 parts N-30 vinyl pyrrolidone and 28.6 parts lauryl methacrylate in 200 parts water containing five parts sodium stearate and 1.25 parts 30% hydrogen peroxide as catalyst.
2. Heat the mixture with stirring and carry out the polymerizationat 75°C for approximately 10 hours. The conversion is approximately 92%.
3. Spray dry the emulsion at approximately 210°C to yield a fine off-white powder.
4. The nitrogen content of the copolymer is 8.6%, indicating an item 1 content of 68%.
5. Prepare a gel base by vigorously mixing the following ingredients (in parts by weight): Copolymer prepared above, 6.75; propylene glycol, hydroxypropyl cellulose, isopropyl myristate, stearic acid, cetyl alcohol, fumed silica, 12.45; and ethanol, 80.80. The resultant gel has a viscosity of 12,000 cps and a specific gravity of 0.8.
6. To 40 g of the above gel, add 140 mg nicotine. Mix thoroughly to obtain a composition containing 3.5 mg/g (2.8 mg/mL).

NITROFURAZONE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.20	1	Nitrofurazone, 4% excess	2.08
7.20	2	Cetostearyl alcohol	72.00
1.80	3	Cetomacrogol 1000	18.00
6.00	4	Liquid paraffin	60.00
15.00	5	White soft paraffin	150.00
1.00	6	Propylene glycol	10.00
0.020	7	Chlorocresol	0.20
69.00	8	Water purified	690.00

Manufacturing Directions

1. Place items 3, 4, 5 (90%), and 6 in a melting vessel after passing it through a stainless-steel sieve and heat to melt. In a separate vessel, heat two-thirds of item 9 to 50°C and dissolve item 8 in it. Add to step 1.
2. Add and mix item 1 with item 5 (balance) and add to step 2.
3. Fill.

NONDETERGENT NEUTRAL DRY SKIN CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
60.00	1	Stearic acid	60.00
145.00	2	White petrolatum jelly	145.00
116.00	3	Mineral oil (25 cS)	116.00
10.00	4	Lanolin	10.00
20.00	5	Cetearyl alcohol	20.00
QS	6	Deionized water	QS to 1 kg
14.00	7	Triethanolamine (99%)	14.00
QS	8	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring.
3. Stir to cool, adding triethanolamine at 60°C and perfuming at 40°C to 50°C.
4. This cream serves as a base for drugs as well.
5. Triethanolamine may be omitted, because it gives a higher pH.

NYSTATIN CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
80.00	1	Cetostearyl alcohol	80.00
20.00	2	Polyoxyl 20 cetostearyl ether (Cetomacrogol 1000)	20.00
80.00	3	Mineral oil (liquid paraffin)	80.00
2.00	4	Methyl paraben	2.00
100,000 IU	5	Nystatin microfine[a] (30% excess) 5420 IU/mg	24.00
1.00	6	Propyl paraben	1.00
100.00	7	Propylene glycol	100.00
4.86	8	Dibasic sodium phosphate	4.86
2.36	9	Monobasic sodium phosphate	2.36
180.00	10	Petrolatum (soft white paraffin)	180.00
506.00	11	Purified water	506.00

[a] Particle size NLT 90% less than 45 pm and 100% less than 80 pm.

Manufacturing Directions

1. Add item 3 to the fat-melting vessel.
2. Heat to 70°C while stirring.
3. Add items 1, 2, and 10 to the fat-melting vessel while stirring.
4. Mix well and maintain the temperature at 65°C to 70°C.
5. Load 466 g of item 11 and item 7 into mixer and heat to 90°C.
6. Add items 4 and 6 to dissolve while stirring on manual mode.
7. Mix for 15 minutes at 10 rpm.
8. Cool to 65°C to 70°C.
9. Add items 8 and 7 to the parabens solution to dissolve.
10. Mix for 5 to 10 minutes at 10 rpm.
11. Maintain temperature at 65°C to 70°C.
12. Take a sample of approximately 0.40 mL from mixer and cool to 25°C.
13. Check the pH (6.3–7.0).
14. Withdraw 80 g of preservative/buffer solution from mixer at 65°C to 70°C in a stainless-steel container.
15. Cool the solution in stainless-steel container to 30°C to 35°C.
16. Disperse item 5 carefully using a spatula.
17. Homogenize using homogenizer to make a smooth dispersion.
18. Transfer the molten fat to the mixer containing the preservative/buffer solution through a stainless-steel sieve by vacuum at 0.6 bar while mixing at 10 rpm in manual mode at a temperature of 65°C.

19. Homogenize and mix the cream for 10 minutes at low speed (10 rpm, manual mode) and vacuum of 0.6 bar.
20. Cool to 40°C ± 5°C.
21. Transfer the 104 g of drug phase (35°C ± 5°C) to the mixer while mixing.
22. Rinse the stainless-steel container of the drug phase with 40 g of item 11 (25–35°C) and transfer to the mixer while mixing.
23. Rinse the homogenizer and the container with item 11 and transfer the rinsing to the mixer.
24. Mix for 5 minutes.
25. Set the mixer at a mixing speed of 10 rpm (manual mode) and the homogenizer at low speed with a vacuum of 6 bar.
26. Mix and homogenize for 15 minutes.
27. Cool to 30°C with mixer speed of 10 rpm and vacuum of 6 bar.
28. Transfer the cream to a stainless-steel drum.

NYSTATIN OINTMENT

Bill of Materials

Scale mg/g	Item	Material Name	Qty/kg (g)
21.05	1	Nystatin microfine[a]	21.05
22.00	2	Cetostearyl alcohol	22.00
8.00	3	Paraffin (hard paraffin)	8.00
100.00	4	Mineral oil (liquid paraffin)	100.00
848.95	5	Petrolatum (white soft paraffin)	848.95

[a] Actual quantity to be calculated as per the actual potency; adjust with soft paraffin. Meets the current USP requirements with following additional requirement: Particle size not less than 90% less than 45 µm, 100% less than 80 µm.

Manufacturing Directions

1. Melt items 2, 3, and 5 at 70°C in a fat-melting vessel.
2. Disperse item 1 in 80 g of item 4 in a separate stainless-steel container by using a spatula.
3. Pass the dispersion through homogenizer twice, then transfer the dispersion to mixer.
4. Rinse the homogenizer and container with 20 g of item 4 and transfer the rinsings to the mixer.
5. Homogenize the dispersion at high speed for 15 minutes. Set the mixer at 40°C to 45°C.
6. Transfer the molten mass from the fat-melting vessel to the mixer at 45°C to 50°C.
7. Mix for 10 minutes at manual mode and 10 minutes at auto mode at 12 rpm and vacuum 0.4 to 0.6 bar.
8. Homogenize at high speed for 10 minutes with recirculation. Mix until the temperature of the ointment reaches 28°C to 30°C.
9. Transfer the ointment to a stainless-steel drum. Keep tightly closed.

NYSTATIN, NEOMYCIN SULFATE, GRAMICIDIN, AND TRIAMCINOLONE ACETONIDE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
22.96	1	Nystatin microfine[a]	22.96
4.43	2	Neomycin sulfate[b]	4.43
0.28	3	Gramicidin[c]	0.28
1.00	4	Triamcinolone acetonide micronized	1.00
80.00	5	Cetostearyl alcohol	80.00
20.00	6	Polyoxyl 20 cetostearyl ether (cetomacrogol 1000)	20.00
80.00	7	Mineral oil (liquid paraffin)	80.00
2.00	8	Methyl paraben	2.00
1.00	9	Propyl paraben	1.00
60.00	10	Propylene glycol	60.00
4.86	11	Dibasic sodium phosphate	4.86
2.36	12	Monobasic sodium phosphate	2.36
180.00	13	Petrolatum (white soft paraffin)	180.00
531.86	14	Purified water	531.86

[a] Actual quantity to be calculated as per the actual potency. Difference in quantity to be adjusted by purified water. Meets current USP requirements with the following additional requirement: Particle size NLT 90% less than 45 µm, 100% less than 80 µm.

[b] Meets the current USP requirements with the following additional requirement: Particle size 99% less than 20 µm, 75% less than 10 µm.

[c] Meets the current USP requirements with the following additional requirement: Particle size 98% less than 50 µm.

Manufacturing Directions

1. Load items 5, 6, 7, and 13 in a fat-melting vessel and heat to 70°C. Stir to melt. Maintain temperature 70°C to 75°C. Heat 420 g of item 14 to 90°C in mixer.
2. Dissolve items 8 and 9 by stirring. Mix for 15 minutes at 10 to 12 rpm.
3. Cool to 65°C to 70°C. Dissolve items 11 and 12 in 71.86 g of item 14 at 40°C to 45°C in a stainless-steel drum.
4. Check the pH limit 6.3 to 7.0 (at 25°C).
5. Dissolve item 2 into 79.08 g phosphate solution. The solution should be clear.
6. Disperse item 1 in the neomycin–phosphate solution above.
7. Homogenize twice to make a smooth dispersion. The dispersion should be smooth with no lumps.
8. Add 50 g of item 10 in a separate stainless-steel container and heat to 40°C to 45°C, then dissolve item 3 by using homogenizer. The solution should be clear. Disperse item 4 in the clear solution of gramicidin–propylene glycol by using the homogenizer. Homogenize until there are no lumps.

9. Maintain temperature at 40°C to 45°C.
10. Transfer the melt from the step above to the mixer through a stainless-steel sieve while mixing at temperature 65°C.
11. Homogenize at high speed for 10 to 12 minutes at 60°C to 65°C, vacuum 0.6 bar. Scrape the sides and blade. Cool down to 50°C. Transfer the homogenized dispersion from the mixer.
12. Rinse the container with 10 g item 10. Add to the mixer and mix for 10 minutes. Transfer the dispersion to the mixer.
13. Rinse the container with 40 g item 14. Add to the mixer and mix for 10 minutes.
14. Homogenize at high speed for 20 minutes at temperature 45°C, mixer speed 10 to 12 rpm, and vacuum 0.6 bar.
15. Cool down to 25°C to 30°C while mixing. Transfer the cream to stainless-steel drum.

NYSTATIN, NEOMYCIN SULFATE, GRAMICIDIN, AND TRIAMCINOLONE ACETONIDE OINTMENT

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
22.96	1	Nystatin microfine[a]	22.96
4.43	2	Neomycin sulfate[a]	4.43
0.28	3	Gramicidin[a]	0.28
1.00	4	Triamcinolone acetonide micronized	1.00
100.00	5	Mineral oil (liquid paraffin)	100.00
10.00	6	Syncrowax	10.00
861.33	7	Petrolatum (white soft paraffin)	861.33

[a] Actual quantity to be calculated as per the actual potency. Difference in quantity to be adjusted by white soft paraffin.

Manufacturing Directions

1. Melt item 7 at 70°C in a fat-melting vessel.
2. Add item 6 to the melt while mixing. Transfer the melt to the mixer through filters and cool to 40°C while mixing.
3. Add 60 g of item 5 in stainless-steel container and disperse item 1 manually by using a spatula. Homogenize two times with homogenizer (gap setting 1) to make smooth dispersion and then transfer to the mixer.
4. Add 20 g of item 5 in a stainless-steel container and disperse items 2, 3, and 4 by using homogenizer to make a smooth dispersion. Homogenize until no lumps.
5. Transfer the dispersion to the mixer. Rinse the homogenizer and stainless-steel container with 20 g of item 5 and transfer the rinsing to the mixer.
6. Mix for 10 minutes, mixer speed 10 rpm, vacuum 0.4 to 0.6 bar, and set thermostat at 28°C to 30°C. Homogenize at high speed for 20 minutes with recirculation.
7. Mix until the temperature of the ointment reaches 28°C to 30°C.
8. Transfer the ointment to a stainless-steel drum. Keep tightly closed.

OCTYL METLIOXYCINNAINATE, OCTYL SALICYLATE, AND OXYBENZONE GEL

The active ingredients in octyl methoxycinnamate, octyl salicylate, and oxybenzone gel are octyl methoxycinnamate, 7.5%, octyl salicylate, 4%, and oxybenzone, 3%. The inactive ingredients are purified water, C12–15 alkyl benzoate, cetearyl alcohol and ceteareth-20, cetyl alcohol, glyceryl monostearate, propylene glycol, petrolatum, diazolidinyl urea, triethanolamine, disodium ethylene diamine tetraacetate, xanthan gum, acrylates/C10–30 alkyl acrylate crosspolymer, to-copheryl acetate, iodopropynyl butylcarbamate, fragrance, carbomer.

OLIBANUM GUM CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Gum olibanum powder	50.00
26.00	2	Emulsifying ointment	260.00
0.15	3	Methyl paraben	1.50
0.15	4	Propyl paraben	1.50
QS	5	Water purified	QS to 1 kg

Manufacturing Directions

1. Take the naturally occurring gum olibanum exudate in dry state as it is.
2. Powder the lumps (1 kg) in an edge runner mill for 30 minutes.
3. Pass the powdered raw gum olibanum through a 100 mesh sieve.
4. Disperse weighed quantity of the powder in appropriate quantity of water along with methyl paraben (0.15%).
5. Melt weighed quantity of emulsifying ointment in another vessel and disperse propyl paraben (0.15%) in it (oily phase).
6. Heat the dispersion containing gum olibanum powder and methyl parabento the same temperature as that of emulsifying ointment.
7. Add the aqueous dispersion containing gum olibanum powder to the molten emulsifying ointment and stir the mixture continuously at 10,000 rpm for 1 hour using a homogenizer to obtain cream consistency.

OXICONAZOLE CREAM AND LOTION

The cream and lotion formulations contain the antifungal active compound oxiconazole nitrate. Both formulations are for topical dermatologic use only. The cream contains 10 mg oxiconazole per gram of cream in a white to off-white, opaque cream base of purified water USP, white petrolatum USP, stearyl alcohol NF, propylene glycol USP, polysorbate 60 NF, and cetyl alcohol NF, with benzoic acid USP 0.2% as a preservative. The lotion contains 10 mg oxiconazole per gram of lotion in a white to off-white, opaque lotion base of purified water USP, white petrolatum USP, stearyl alcohol NF, propylene glycol USP, polysorbate 60 NF, and cetyl alcohol NF, with benzoic acid USP, 0.2%, as a preservative.

OXYMORPHONE HYDROCHLORIDE SUPPOSITORIES

The rectal suppository is available in a concentration of 5 mg of oxymorphone hydrochloride in a base consisting of polyethylene glycol 1000 and polyethylene glycol 3350.

OXYTETRACYCLINE OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
3.00	1	Oxytetracycline hydrochloride micronized	3.00
93.00	2	White soft paraffin	93.00
3.70	3	Liquid paraffin	3.70
0.02	4	Vitamin E oily	0.02

Manufacturing Directions

1. Charge item 2 in a fat-melting vessel and heat to 75°C.
2. In a separate vessel, add and mix items 1, 3, and 4 and mix manually using a spatula.
3. Transfer step 1 to Becomix through a stainless-steel mesh. Cool down to 50°C.
4. Add step 2 to step 3 and mix for 20 minutes. Check for smoothness of dispersion.
5. Homogenize under 0.4 to 0.6 bar vacuum and cool down to 30°C.
6. Fill.

PANTHENOL AND CHLORHEXIDINE LOTION

Bill of Materials

Scale (mg/mL)	Item	Material Name	Qty/1000 Tablets (g)
25.00	1	D-Panthenol (adjusted for potency)	26.25
2.50	2	DL-Lactone pure	2.50
1.00	3	Sequestrene disodium	1.00
3.00	4	Chlorhexidine hydrochloride micropowder	3.00
5.00	5	POEG 300-stearate[a]	5.00
50.00	6	Paraffin oil low viscosity	50.00
5.00	7	Polydimethylsiloxane M 350	5.00
3.00	8	Perfume PCV 1155/8	3.00
–	9	Purified water	QS to 1 L

[a] POEG 300 is a mixture of monoesters and diesters of polyoxyethylene glycol 300, with palmitic and stearic acids and free polyoxyethylene glycol 300.

Manufacturing Directions

1. Aqueous phase: Prepare a solution of DL-lactone (previously liquefied at approximately 100°C) in water.
2. Add the DL-lactone solution to the main part of water at 70°C.
3. Incorporate the D-panthenol (previously liquefied at approximately 45°C).
4. Admix and dissolve sequestrene disodium.
5. Fatty phase: Melt at approximately 65°C under stirring POEG 300-stearate, paraffin oil, and polydimethylsiloxane M 350.
6. Emulsion: Add the fatty phase at 65°C to the aqueous phase at approximately 45°C. Cool to approximately 36°C while stirring and homogenizing.
7. Chlorhexidine suspension: Suspend chlorhexidine in water. Lotion: Add the chlorhexidine suspension to the emulsion at approximately 36°C. Stir, homogenize, and deaerate.
8. Finally, add the perfume, homogenize again, and filter.

PANTHENOL OINTMENT

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Protegin X	50.00
18.00	2	Cetyl alcohol	18.00
12.00	3	Stearyl alcohol	12.00
40.00	4	Wax white	40.00
250.00	5	Wool fat deodorized	250.00
130.00	6	Vaseline® (white)	130.00
50.00	7	Almond oil	50.00
150.00	8	Paraffin oil	150.00
50.00	9	D-Panthenol	50.00
250.00	10	Deionized water	250.00

Manufacturing Directions

1. Place wool fat, Vaseline, almond oil, and paraffin in a heating vessel. Heat and melt the fats together at 80°C with stirring to keep the fatty phase at this temperature until further processing.
2. In a separate container, add protegin X, cetyl alcohol, stearyl alcohol, and wax white; melt these fats with stirring at 80°C. Add to above. The final temperature in the melt should be approximately 70°C. Keep this temperature until further processing.
3. Transfer D-panthenol into a suitable container by pouring and then rinsing it with hot deionized water 1.67 kg, continue to mix another 5 minutes, check the final weight, and make up for evaporated water.
4. Place into kettle and heat to 70°C while stirring. Transfer the melted fatty mass under vacuum (–0.3 atm) through the inline sieve (mesh size 0.150 mm). After the addition, evacuate again to –0.3 atm, then stir for another 15 minutes and homogenize for 5 minutes under the same condition.
5. Cool to 30°C. (The cooling should be within 4 hours.) When this temperature is reached, continue stirring until the ointment has reached 24°C to 26°C. Stop cooling. Then evacuate to –0.3 atm and stir for 5 minutes.
6. Transfer the ointment in a mixer and mix for 5 minutes with electric mixture. Fill the ointment.

PANTHENOL LOTION

Bill of Materials

Scale (mg/mL)	Item	Material Name	Qty/L Tablets (g)
26.25	1	D-Panthenol (2.5%)[a]	26.25
2.50	2	DL-Lactone (pure)	2.50
1.00	3	Sequestrene disodium	1.00
3.00	4	Chlorhexidine hydrochloride (micropowder)	3.00
5.00	5	POEG 300-stearate[b]	5.00
50.00	6	Paraffin oil (low viscosity)	50.00
5.00	7	Polydimethylsiloxane M 350	5.00
3.00	8	Perfume PCV 1155/8	3.00
–	9	Purified water	QS to 1 L

[a] Based on 100% content; adjust for assay.

[b] POEG 300 is a mixture of monoesters and diesters of polyoxyethylene glycol 300, with palmitic and stearic acids and free polyoxyethylene glycol 300.

Manufacturing Directions

1. Aqueous phase: Prepare a solution of DL-lactone (previously liquefied at approximately 100°C) in water.
2. Add the DL-lactone solution to the main part of water at 70°C.
3. Incorporate the D-panthenol (previously liquefied at approximately 45°C).
4. Admix and dissolve sequestrene disodium.
5. Fatty phase: Melt at approximately 65°C under stirring POEG 300 stearate, paraffin oil, and polydimethylsiloxane M 350.
6. Emulsion: Add the fatty phase at 65°C to the aqueous phase at approximately 45°C.
7. Cool to approximately 36°C while stirring and homogenizing.
8. Chlorhexidine suspension: Suspend chlorhexidine in water.
9. Lotion: Add the chlorhexidine suspension to the emulsion at approximately 36°C.
10. Stir, homogenize, and deaerate.
11. Finally, add the perfume, homogenize again, and filter.

PANTOPRAZOLE–CHOLESTEROL COMPLEX SUPPOSITORY

1. Dissolve 7 g of cholesterol and 5 g of ethocel in 100 mL of dichloromethane.
2. Suspend 5 g of pantoprazole sodium sesquihydrate in the solution.
3. Spray dry the suspension in a laboratory spray dryer.
4. Spray conditions: Drying gas nitrogen, inlet temperature 51°C; pump output 10%. Heat 100 g of cetyl alcohol to 65°C. Spray congealing: Slowly add 50 g of pantoprazole sodium sesquihydrate.
5. Stir the mixture until a homogeneous suspension is obtained and subsequently spray through a nozzle in a spray dryer.
6. A white free-flowing powder is obtained with particle size in the range 10 to 40 microns.
7. By variation of the spraying conditions, larger or smaller particles can be obtained.
8. Fuse 194.7 g of suppository base (Adeps solidus/Neutralis) to give a clear mass at 40°C to 45°C.
9. After cooling the mass to 39°C to 40°C, introduce the preparation obtained above (15.3 g) homogeneously using a stirrer.
10. Cool the suspension obtained to 37°C to 38°C and cast into suppositories of 2.1 g each containing 45.6 mg of pantoprazole sodium sesquihydrate.

PAPAIN CHEWING GUM

Formulation

Gum base, 31.20%; sorbitol, 28.08%; mannitol, 5.23%; papain, 1.00%; acesulfame K, 0.16%; aspartame, 0.16%; menthol powder, 1.00%; liquid flavor, 0.47%; isomalt PF, 11.70%; isomalt DC, 16.00%; anticaking agents (magnesium stearate, talc, or silica gel), 4.00%; flavor, 2.00%.

PAPAIN OINTMENT

The ointment is an enzymatic debriding-healing ointment that contains standardized papain USP (not less than 521,700 USP units per gram of ointment), urea USP, 10%, and chlorophyllin copper complex sodium, 0.5%, in a hydrophilic base composed of purified water USP, propylene glycol USP, white petrolatum USP, stearyl alcohol NF, polyoxyl 40 stearate NF, sorbitan monostearate NF, boric acid NF, chlorobutanol (anhydrous) NF (as a preservative), and sodium borate NF. In another formulation, each gram of enzymatic debriding ointment contains papain (8.3×10^5 USP units of activity) and 100 mg urea in a hydrophilic ointment base composed of purified water, emulsifying wax, glycerin, isopropyl palmitate, potassium phosphate monobasic, fragrance, methyl paraben, and propyl paraben.

PENCICLOVIR CREAM

The cream contains penciclovir, an antiviral agent active against herpes viruses for topical administration as a 1% white cream. Each gram of cream contains 10 mg penciclovir and the following inactive ingredients: Cetomacrogol 1000 BP cetostearyl alcohol, mineral oil, propylene glycol, purified water, and white petrolatum.

PEPPERMINT CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
25.00	1	Sorbitol stearate	25.00
15.00	2	Polysorbate 60	15.00
300.00	3	Peppermint oil	300.00
20.00	4	Cetyl alcohol	20.00
40.00	5	Stearic acid	40.00
10.00	6	Triethanolamine 99%	10.00
2.00	7	Carbopol 980	2.00
QS	8	Deionized water	QS
QS	9	Preservative, color	QS

Manufacturing Directions

1. Hydrate Carbopol in water 60°C to 65°C.
2. Add remaining water-phase ingredients.
3. Heat oil and water phases separately to 70°C to 75°C.
4. Add water phase to oil phase while stirring. Stir to cool, neutralizing at 65°C with triethanolamine.

PERMETHRIN CREAM AND LOTION

Permethrin cream, 5%, is a topical scabicidal agent for the treatment of infestation with *S. scabiei* (scabies). It is available in an off-white vanishing cream base. Each gram of cream, 5%, contains permethrin 50 mg (5%) and the inactive ingredients butylated hydroxytoluene, carbomer 934P, coconut oil, glycerin, glyceryl stearate, isopropyl myristate, lanolin alcohols, light mineral oil, polyoxyethylene cetyl ethers, purified water, and sodium hydroxide. Formaldehyde 1 mg (0.1%) is added as a preservative. Each fluid ounce of lotion contains permethrin 280 mg (1%) as its active ingredient and balsam fir Canada, cetyl alcohol, citric acid, FD&C yellow No. 6, fragrance, hydrolyzed animal protein, hydroxyethyl cellulose, polyoxyethylene 10 cetyl ether, propylene glycol, stearalkonium chloride, water, isopropyl alcohol 5.6 g (20%), methyl paraben 56 mg (0.2%), and propyl paraben 22 mg (0.08%) as its inactive ingredients.

PETROLATUM AND LANOLIN OINTMENT

Active ingredients in petrolatum and lanolin ointment are petrolatum, 53.4%, and lanolin, 15.5%. Inactive ingredients

are cod liver oil (contains vitamins A and D), fragrance, light mineral oil, microcrystalline wax, and paraffin.

PHENYLEPHRINE OINTMENT, CREAM, SUPPOSITORIES, AND GEL

The ointment contains petrolatum, 71.9%, mineral oil, 14%, shark liver oil, 3%, and phenylephrine HCl, 0.25%. The cream contains petrolatum, 18%, glycerin, 12%, shark liver oil, 3%, and phenylephrine HCl, 0.25%. The suppositories contain cocoa butter, 85.5%, shark liver oil, 3%, and phenylephrine HCl, 0.25%. The cooling gel contains phenylephrine HCl, 25%, and witch hazel, 50%.

PIROXICAM OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Piroxican	10.00
1.00	2	Carbopol 940	10.00
30.00	3	Alcohol	300.00
30.00	4	Propylene glycol	300.00
1.50	5	Diethanolamine	15.00
0.50	6	Hydroxyethyl cellulose	5.00
0.50	7	PVP K-30	5.00
QS	8	Water purified	QS to 1 kg

Manufacturing Directions

Blend all items uniformly together to produce an ointment formulation having a pH of 7.9. Neutralize the Carbopol using item 5.

PIROXICAM AND DEXPANTHENOL GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.50	1	Piroxicam	5.00
25.00	2	1,2-Propylene glycol	250.00
5.00	3	Alcohol	50.00
0.40	4	Triethanolamine	~4.00
23.00	5	Lutrol F 127	230.00
46.00	6	Water purified	460.00

Manufacturing Directions

1. Prepare the solution of piroxicam in propylene glycol and dexpanthenol at 70°C to 80°C.
   a. Add ethanol and Lutrol F 127.
   b. Stir the highly viscous mixture. Add 50% of the hot water (70°C).
   c. Adjust the pH with triethanolamine to approximately 7.
   d. Add the rest of the water, cool to room temperature when the air bubbles escape, and adjust the pH to approximately 8.

or

1. Dissolve piroxicam in propylene glycol, dexpanthenol, and triethanolamine.
   a. Cool the mixture of Lutrol F 127 and water to approximately 5°C and mix with the piroxicam solution.
   b. Add the ethanol.
   c. Maintain the cool temperature until the air bubbles escape.

POLYMYXIN, BACITRACIN, HYDROCORTISONE, AND ZINC OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
18.00	1	Wax	180.00
69.80	2	Petrolatum	698.00
7.50	3	Polymyxin B sulfate	75.00
0.60	4	Bacitracin	6.00
4.00	5	Zinc oxide	40.00
0.50	6	Hydrocortisone acetate	5.00

Manufacturing Directions

1. Add items 1 and 2 to a melting vessel. Heat to 75°C.
2. Add items 3 to 5 one by one and mix to dissolve.
3. Cool to 40°C and fill.

POVIDONE–IODINE AND LIDOCAINE GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
10.00	2	Lidocaine hydrochloride	10.00
10.00	3	Sodium chloride	10.00
200.00	4	Lutrol F 127	200.00
79.00	5	Sodium hydroxide solution, 1 M	79.00
61.10	6	Water	61.10

Manufacturing Directions

1. Dissolve items 1 to 3 in item 6, cool to approximately 6°C, dissolve item 4, and adjust the pH value (4.5–5.0) with item 5.
2. Maintain the cool temperature until the air bubbles escape. Viscosity (Brookfield, 23°C) 54,000 mPa.

POVIDONE–IODINE BAR SOAP

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	PVP–iodine 30/06	50.00
10.00	2	Fragrance	10.00
75.00	3	Water	75.00
940.00	4	Syndet base	940.00

Manufacturing Directions

1. Dissolve PVP–iodine in water and mix the solution with the fragrance and the syndet base.
2. Pass the blend four times through a three-roller mill.
3. Blend three times through a plodder with a narrow sieve hole disk.
4. Pass the blended material through a wide sieve hole disk combined with a mouth hole disk.
5. Heat the area of the two disks to 50°C using a heating collar.
6. Cut the bar in pieces on a lab stamper.
7. Composition of the syndet base (in sequence of concentration): Disodium lauryl sulfosuccinate, sodium lauryl sulfate, cetyl stearyl alcohol, paraffin, glycerol stearate, water, titanium dioxide.

POVIDONE–IODINE BAR SOAP

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	PVP–iodine 30/06	50.00
75.00	2	Water	75.00
241.5	3	Texapon® K 12	241.5
241.5	4	Setacin® F special paste	241.5
241.5	5	Emcol® 4400.1	241.5
145.00	6	Cetyl stearyl alcohol	145.00
96.50	7	Paraffin	96.50
226.00	8	Glycerol monostearate	226.00

Manufacturing Directions

1. Heat mixture of items 3 to 8 to 75°C to 80°C and cool to approximately 50°C stirring well.
2. Add solution of items 1 and 2 and let cool to room temperature, stirring continuously.
3. Pass the blend four times through a three-roller mill and let dry overnight at room temperature.
4. Cut the bar into pieces on a lab stamper.

POVIDONE–IODINE BAR SOAP

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	PVP–iodine 30/06	50.00
75.00	2	Water	75.00
241.5	3	Texapon® K 12	241.5
241.5	4	Setacin® F special paste	241.5
241.5	5	Emcol® 4400.1	241.5
145.00	6	Cetyl stearyl alcohol	145.00
96.50	7	Paraffin	96.50
226.00	8	Glycerol monostearate	226.00

Manufacturing Directions

1. Heat mixture of items 3 to 8 to 75°C to 80°C and cool to approximately 50°C stirring well.
2. Add solution of item 1 and let cool to room temperature, stirring continuously.
3. Pass the blend four times through a three-roller mill and let dry overnight at room temperature.
4. Cut the bar into pieces on a lab stamper.

POVIDONE–IODINE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
241.00	2	Citric acid solution, 0.1 M	241.00
369.00	3	Na_2HPO_4 solution, 0.2 M	369.00
20.00	4	Cremophor A 6	20.00
20.00	5	Cremophor A 25	20.00
100.00	6	Cetyl stearyl alcohol	100.00
100.00	7	Liquid paraffin	100.00
50.00	8	Glycerol	50.00

Manufacturing Directions

1. Prepare a basic cream from the emulsifying agents and the fatty substances, items 4 to 8.
2. Stir in the PVP–iodine dissolved in the buffer solutions made from items 2 and 3.
3. Brown cream having a pH of 4.5 is obtained.

POVIDONE–IODINE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
100.00	2	Liquid paraffin	100.00
100.00	3	Vaseline	100.00
50–80	4	Cetyl stearyl alcohol	50–80
20.00	5	Cremophor A 6	20.00
20.00	6	Cremophor A 25	20.00
50.00	7	Propylene glycol pharma	50.00
530–560	8	Water	530–560

Manufacturing Directions

This cream is suitable for veterinary mastitis treatment.

1. Dissolve PVP–iodine in the solvents, items 7 and 8.
2. Mix items 2 to 6 by heating, stir the solution in the previous mixture, and cool by stirring.

POVIDONE–IODINE GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
359.00	2	Citric acid solution, 0.1 M	359.00
181.00	3	$NA_2HPO_4 \bullet 12H_2O$ solution, 0.2 M	181.00
50.00	4	Lutrol E 400	50.00
100.00	5	Liquid paraffin	100.00
150.00	6	Lutrol F 127	150.00
70.00	7	Lutrol F 127	70.00

Manufacturing Directions

1. Dissolve item 1 in a solution of items 2 to 4, mix with item 5, and dissolve item 6 at approximately 20°C.
2. Cool to 5°C to 8°C and dissolve item 7. Maintain cool until all air bubbles have disappeared (brown turbid gel).

POVIDONE–IODINE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
241.00	2	Citric acid (0.1-M solution)	241.00
369.00	3	Na2HPO4 (0.2-M solution)	369.00
20.00	4	Cremophor A 6	20.00
20.00	5	Cremophor A 25	20.00
100.00	6	Cetyl stearyl alcohol	100.00
100.00	7	Liquid paraffin	100.00
50.00	8	Glycerol	50.00

Manufacturing Directions

1. Prepare a basic cream from the emulsifying agents and the fatty substances (items 4–8).
2. Stir in the PVP–iodine dissolved in the buffer solutions made from items 2 and 3.
3. A brown cream having a pH of 4.5 is obtained.

POVIDONE–IODINE GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
10.00	2	Sodium chloride	10.00
200.00	3	Lutrol F 127	200.00
79.00	4	Sodium hydroxide solution, 1 M	79.00
610.00	5	Water	610.00

Manufacturing Directions

1. Dissolve items 1 and 2 in item 5 and cool to approximately 6°C.
2. Dissolve Lutrol F 127 and item 2 and adjust the pH value with item 4.
3. Maintain cool until all air bubbles have escaped. Viscosity 61,000 mPa to 54,000 mPa (Brookfield, 23°C); pH value (20% in water) 2.2 to 4.6.

POVIDONE–IODINE GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
600.00	2	Lutrol E 400	600.00
46.00	3	Sodium hydroxide, 1 M solution	46.00
4.00	4	Water	4.00
250.00	5	Lutrol E 4000	250.00

Manufacturing Directions

1. Prepare solution of items 1 to 4, heat to approximately 60°C, incorporate item 6, stir very well, and cool to room temperature.
2. A transparent ointment like a gel having a pH of 4 is achieved, miscible and washable with water.

POVIDONE–IODINE GEL CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
359.00	2	Citric acid (0.1-M solution)	359.00
181.00	3	$NA_2HPO_4 \cdot 12H_2O$ (0.2-M solution)	181.00
50.00	4	Lutrol E 400	50.00
100.00	5	Liquid paraffin	100.00
150.00	6	Lutrol F 127	150.00
70.00	7	Lutrol F 127	70.00

Manufacturing Directions

1. Dissolve item 1 in solution of items 2 to 4, mix with item 5, and dissolve item 6 at approximately 20°C.
2. Cool to 5°C to 8°C and dissolve item 7.
3. Maintain cool temperature until all air bubbles have disappeared.
4. A brown, turbid gel is obtained.

POVIDONE–IODINE GELS

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
10.00	2	Sodium chloride	10.00
200.00	3	Lutrol F 127	200.00
79.00	4	Sodium hydroxide (1-M solution)	79.00
610.00	5	Water	610.00

Manufacturing Directions

1. Dissolve items 1 and 2 in item 5 and cool to approximately 6°C.
2. Dissolve Lutrol F 127 and item 2 and adjust the pH value with item 4.
3. Maintain cool until all air bubbles escape.
4. Viscosity (Brookfield, 23°C) is 61,000 mPa to 54,000 mPa; pH value (20% in water) is 2.2 to 4.6.

POVIDONE–IODINE GLUCOSE OINTMENT

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	PVP–iodine 30/06, with excess	26.00
45.00	2	Ethanol (96%)	45.00
849.00	3	Glucose	849.00
34.00	4	Lutrol E 4000	34.00
6.00	5	Glycerol	6.00
6.00	6	Water	6.00

Manufacturing Directions

1. Dissolve Lutrol E 4000 in the hot mixture of glycerol and water and add the glucose warmed to 60°C to 80°C.
2. Incorporate item 4 to obtain a brown, viscous, and turbid paste.

POVIDONE–IODINE GLUCOSE OINTMENT

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	PVP–iodine 30/06, with excess	26.00
45.00	2	Ethanol 96%	45.00
849.00	3	Glucose	849.00
34.00	4	Lutrol E 4000	34.00
6.00	5	Glycerol	6.00
6.00	6	Water	6.00

Manufacturing Directions

1. Dissolve Lutrol E 4000 in the hot mixture of glycerol and water and add the glucose warmed to 60°C to 80°C.
2. Incorporate solution in the obtained paste (brown viscous and turbid paste).

POVIDONE–IODINE MASTITIS CREAM FOR CATTLE

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
100.00	2	Liquid paraffin	100.00
100.00	3	Vaseline	100.00
50–80	4	Cetyl stearyl alcohol	50–80
20.00	5	Cremophor A 6	20.00
20.00	6	Cremophor A 25	20.00
50.00	7	Propylene glycol	50.00
QS	8	Water	530–560

Manufacturing Directions

1. Dissolve PVP–iodine in the solvents (items 7 and 8).
2. Mix items 2 to 6 by heating, stir the solution in the previous mixture, and cool by stirring.

POVIDONE–IODINE SOFT GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
10.00	1	PVP–iodine 30/06	10.00
25.00	2	Natrosol® HR 250	25.00
QS	3	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve PVP–iodine and Natrosol HR 250 in the water and stir well to produce a clear, brown gel.
2. Viscosity (Brookfield, 23°C) is 31,500 mPa.

POVIDONE–IODINE TRANSPARENT OINTMENT

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
600.00	2	Lutrol E 400	600.00
46.00	3	Sodium hydroxide (1-M solution)	46.00
4.00	4	Water	4.00
250.00	5	Lutrol E 4000	250.00

Manufacturing Directions

1. Prepare solution of items 1 to 4, heat to approximately 60° C, incorporate item 6 (stirring very well), and cool to room temperature.
2. The transparent ointment, similar to a gel, has a pH of 4 and is miscible and washable with water.

POVIDONE–IODINE VAGINAL OVULE

Bill of Materials

Scale (mg/ovule)	Item	Material Name	Qty/1000 Ovules (g)
100.00	1	PVP–iodine 30/06	5.00
200.00	2	Lutrol E 400	10.00
170.00	3	Lutrol E 4000	85.00

Manufacturing Directions

1. Melt the Lutrol E grades by gentle heating.
2. Stir in the micronized PVP–iodine product in small portions into the melt.
3. After a uniform suspension has been obtained, pour it into polyethylene molds.
4. The homogeneous brown-colored ovule has a weight of 2 g.

POVIDONE–IODINE VAGINAL OVULE

Bill of Materials

Scale (mg/ovule)	Item	Material Name	Qty/kg (g)
200.00	1	PVP–iodine 30/06	200.00
100.00	2	Lutrol E 400	100.00
100.00	3	Lutrol E 1500	100.00
700.00	4	Lutrol E 4000	700.00

Manufacturing Directions

1. Melt the Lutrol E grades by gentle heating.
2. Stir in the micronized PVP–iodine product in small portions into the melt.
3. After a uniform suspension has been obtained, pour it into polyethylene molds.
4. The homogeneous brown-colored ovule has a weight of 2 g.

POVIDONE–IODINE VAGINAL OVULES

Bill of Materials

Scale (mg/ovule)	Item	Material Name	Qty/1000 Ovules (g)
100.00	1	PVP–iodine 30/06 M 10	5
200.00	2	Lutrol E 400	10
170.00	3	Lutrol E 4000	85

Manufacturing Directions

1. Melt the Lutrol E grades by gentle heating. Stir the micronized PVP–iodine product in small portions into the melt.
2. After a uniform suspension has been obtained, pour it into polyethylene molds. The result is a homogeneous brown-colored ovule having a weight of 2 g.

POVIDONE–IODINE VAGINAL OVULES

Bill of Materials

Scale (mg/ovule)	Item	Material Name	Qty/kg (g)
200.00	1	PVP–iodine 30/06 M 10	200.00
100.00	2	Lutrol E 400	100.00
100.00	3	Lutrol E 1500	100.00
700.00	4	Lutrol E 4000	700.00

Manufacturing Directions

1. Melt the Lutrol E grades by gentle heating. Stir the micronized PVP–iodine product in small portions into the melt.
2. After a uniform suspension has been obtained, pour it into polyethylene mold. The result is a homogeneous brown-colored ovula having a weight of 2 g.

PRAMOXINE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Cetyl alcohol[a]	150.00
50.00	2	Cetyl esters wax[a]	50.00
0.72 mL	3	Water purified	720 mL
1.80	4	Methyl paraben	1.80
0.20	5	Propyl paraben	0.20
20.00	6	Sodium lauryl sulfate	20.00
50.00	7	Glycerin	50.00
10.00	8	Pramoxine hydrochloride	10.00

[a] Beeswax 75.00 mg/g can be added and adjusted with items 1 and 2.

Manufacturing Directions

1. Phase A: Add the cetyl alcohol (item 1) and the cetyl esters wax (item 2) to a suitable jacketed stainless-steel tank fitted with efficient agitation. Heat to 60°C to 65°C and mix until materials are melted and phase is uniform.
2. Preheat a suitable jacketed stainless-steel batch tank to 60°C to 65°C. Strain phase A (step 1) into the batch tank, maintaining temperature at 60°C to 65°C and gentle agitation.
3. Phase B: Charge 530 mL of purified water (item 3) into a suitable jacketed stainless-steel tank fitted with a high-speed mixer. Adjust the water temperature to 80°C to 90°C and add methyl paraben (item 4) and propyl paraben (item 5). Stir until dissolved, ensuring that no solids are entrained in the bottom valve. Commence cooling to 60°C to 65°C.
4. Add the sodium lauryl sulfate (item 6) with care and stir to dissolve.
5. Add the glycerin (item 7) and mix until uniform. *Caution*: Do not create excessive foam.
6. Cool to 60°C to 65°C.
7. Strain phase A and sweep mix. Rinse through with 12 mL of purified water.
8. Phase C: In a suitable jacketed stainless-steel tank fitted with high-speed agitation, place 166 mL of purified water and raise the temperature to 60°C to 65°C. Add the pramoxine hydrochloride (item 8) and mix until dissolved. Strain the solution via a 100- to 150-gm aperture mesh into the mass from step

above. Rinse through with 12 mL of purified water. Reduce agitation rate to prevent air entrainment and commence cooling to 32°C to 36°C. Please note that you should maintain cooling water at 10° C below batch temperature until 45°C, switching then to full cooling.

9. Fill.

PRAMOXINE HYDROCHLORIDE AND ZINC ACETATE LOTION AND OINTMENT

The lotion contains pramoxine hydrochloride, 1%, and zinc acetate, 0.1%, and inactive ingredients alcohol USP, camphor, citric acid, diazolidinyl urea, fragrance, glycerin, hydroxypropylmethylcellulose, methyl paraben, oil of lavender, oil of rosemary, polysorbate 40, propylene glycol, propyl paraben, purified water, and sodium citrate. The ointment contains active ingredients pramoxine HCl, 1%, zinc oxide, 12.5%, and mineral oil as well as benzyl benzoate, calcium phosphate dibasic, cocoa butter, glyceryl monooleate, glyceryl monostearate, kaolin, peruvian balsam, and polyethylene wax.

PRAMOXINE SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
1782.00	1	Witepsol H 15®	1782.00
18.00	2	Pramoxine hydrochloride	18.00

Manufacturing Directions

1. Conventional method:
   a. In a suitable jacketed stainless-steel tank, premelt the Witepsol H 15 at 35°C to 45°C.
   b. Transfer 200 g of premelted Witepsol H 15 from step 1 into a suitable premix tank fitted with an efficient agitator. Slowly add the pramoxine and mix for 15 minutes.
   c. Run the premix through a suitable colloid mill into a jacketed stainless-steel batching tank fitted with a suitable homogenizer. Maintain the temperature at 40°C.
   d. Flush the premix tank, lines, and colloid mill with 50 g of premelted Witepsol H 15 from step 1 into the batching tank. Homogenize the contents of the batch tank at high speed for 15 minutes.
   e. Add the balance of the premelted Witepsol H 15 from step 1 to the contents of the batching tank. Homogenize for 15 minutes, then cool with mixing to 27°C to 38°C.
   f. Commence batch recirculation through a 150-gm aperture screen. Maintain until the batch is filled. Fill 1.8 g/suppository.
2. CTurbomixer/emulsifier method:
   a. In a suitable jacketed stainless-steel tank fitted with a turbomixer/emulsifier, premelt the Witepsol H 15 at 35°C to 45°C.
   b. After melting, adjust the mixer/emulsifier in a batching tank containing the premelted mass to maximum speed and slowly add the pramoxine and mix.
   c. Homogenize the contents of the batching tank at 38°C with mixer at high speed. Then cool to 35°C to 36°C, always maintaining the whole mass under agitation.
   d. Filter the mass through a 150-gm screen and maintain the blending until the batch is filled.
3. Fill 1.8 g/suppository.

PRAMOXINE SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
1781.00	1	Witepsol W 32	1781.00
17.10	2	Pramoxine base	17.10
1.01	3	Pramoxine hydrochloride	1.01

Manufacturing Directions

This formula is less irritating and preferred.

1. In a suitable stainless-steel tank fitted with an efficient agitator, melt Witepsol W 32 (No. 3) at approximately 45°C.
2. Activate mixer and maintain temperature of 40°C to 50°C.
3. Weigh pramoxine base into a separate suitable stainless-steel container.
4. Slowly add pramoxine hydrochloride to step 3 and premix using homomixer or similar. Take precaution to minimize spread of powder to adjacent areas.
5. Continue to mix for 15 minutes. Make certain that pramoxine hydrochloride is completely dispersed and the mixture is free of lumps.
6. Verify that Witepsol W 32 from step 2 is completely melted and is less than 50°C, then add the premix to it from step 5.
7. Continue mixing at least 15 minutes while maintaining temperature less than 50°C.
8. Commence batch recirculation through a 150-gm aperture stainless-steel screen. Maintain until batch is filled.

9. Cool batch slowly, approximately 3°C per hour, until it reaches 31°C.
10. Maintain product temperature at 31°C to 33.5°C with constant recirculation or mixing throughout filling operation. Adjust mixing as necessary to prevent aeration of the product.

PRANOPROFEN OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Pranoprofen	10.00
2.00	2	Triisopropanolamine	20.00
5.00	3	Carboxyvinyl polymer solution (Hiviswako 104)	50.00
52.00	4	Alcohol	520.00
QS	5	Water purified	QS to 1 kg

Manufacturing Directions

1. To 52 g of ethanol add 1 g of pranoprofen and 2 g of triisopropanolamine. To the mixture add 30 g of a 5% carboxyvinyl polymer solution and 15 g of purified water.
2. The pH of ointment thus obtained is 6.6, and the viscosity, which is measured at 20°C and 20 rpm, is 460 poises.

PREDNICARBATE EMOLLIENT CREAM

Prednicarbate emollient cream, 0.1%, contains prednicarbate. Each gram of emollient cream, 0.1%, contains 1 mg of prednicarbate in a base consisting of white petrolatum USP, purified water USP, isopropyl myristate NF, lanolin alcohols NF, mineral oil USP, cetostearyl alcohol NF, aluminum stearate, edetate disodium USP, lactic acid USP, and magnesium stearate DAB 9.

PROCHLORPERAZINE SUPPOSITORIES

Prochlorperazine suppositories contain prochlorperazine base. Each suppository contains 2.5, 5, or 25 mg of prochlorperazine with glycerin, glyceryl monopalmitate, glyceryl monostearate, hydrogenated coconut oil fatty acids, and hydrogenated palm kernel oil fatty acids.

PROGESTERONE GEL

Progesterone gel is a bioadhesive vaginal gel containing micronized progesterone in an emulsion system, which is contained in single-use, one-piece polyethylene vaginal applicators. The carrier vehicle is an oil-in-water emulsion containing the water-swellable, but insoluble polymer, polycar-bophil. The progesterone is partially soluble in both the oil and the water phases of the vehicle, with the majority of the progesterone existing as a suspension. The active ingredient, progesterone, is present in either a 4% or an 8% concentration (w/w). Each applicator delivers 1.125 g of gel containing either 45 mg (4% gel) or 90 mg (8% gel) of progesterone in a base containing glycerin, mineral oil, polycarbophil, carbomer 934P, hydrogenated palm oil glyceride, sorbic acid, sodium hydroxide, and purified water.

PROMETHAZINE HYDROCHLORIDE SUPPOSITORIES

Each rectal suppository contains 12.5, 25, or 50 mg promethazine hydrochloride with ascorbyl palmitate, silicon dioxide, white wax, and cocoa butter.

PROMETHAZINE SUPPOSITORY

Each rectal suppository contains 12.5, 25, or 50 mg promethazine hydrochloride with ascorbyl palmitate, silicon dioxide, white wax, and cocoa butter. Promethazine hydrochloride is a racemic compound; the empirical formula is $C_{17}H_{20}N_2S.HCl$ and its molecular weight is 320.88. Phenergan suppositories are for rectal administration only.

PSORIASIS CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
40.00	1	Lanolin alcohol	40.00
50.00	2	White petroleum jelly	50.00
120.00	3	Paraffin wax 140F	120.00
300.00	4	Mineral oil (70 cS)	300.00
20.00	5	Coal tar	20.00
2.50	6	Allantoin	2.50
QS	7	Deionized water	QS to 1 kg
QS	8	Preservative	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Slowly add water phase in increments to the oil phase.
3. Allow each addition time to be fully incorporated.
4. Stir to cool.
5. Fill just above melting point.
6. Further homogenization may improve stability prior to filling.

PSORIASIS CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
160.00	1	Stearic acid	16.00
60.00	2	Oleyl alcohol	6.00
20.00	3	Lanolin	2.00
20.00	4	Coal tar	2.00
6.00	5	Triethanolamine (99%)	0.60
2.50	6	Allantoin	0.25
QS	7	Deionized water	QS to 1 kg
–	8	Preservative	QS

Manufacturing Directions

1. Heat water and oil phases separately to 80°C.
2. Add water phase to oil phase while stirring.
3. Stir to cool.
4. Pass through homogenizer.
5. Fill at 40°C.

RESORCINOL ACNE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Polychol 10 (Laneth-10)	20.00
5.00	2	Lanolin alcohols (Super Hartolan)	5.00
55.00	3	Cetyl alcohol C90	55.00
60.00	4	Polawax	60.00
14.00	5	Sulfur	14.00
QS	6	Deionized water	QS
40.00	7	Veegum regular	40.00
20.00	8	Propylene glycol	20.00
20.00	9	Resorcinol	20.00
QS	10	Perfume, preservative	QS

Manufacturing Directions

1. Hydrate Veegum in water. Add rest of water-phase ingredients and heat to 70˚C.
2. Heat oil phase to 70˚C. Disperse sulfur in oil phase.
3. Add oil phase to water phase while stirring. Stir to cool. Fill.

RUBEFACIENT ANALGESIC OINTMENT

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Polawax, NF	150.00
100.00	2	Methyl salicylate	100.00
50.00	3	Menthol	50.00
100.00	4	Mineral oil (70 cS)	100.00
QS	5	Deionized water	QS to 1 kg
QS	6	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring. Stir to cool.
3. Fill at 30°C.

SALICYLIC ACID CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Glyceryl stearate and PEG-75 stearate	150.00
5.00	2	Stearic acid	5.00
80.00	3	Mineral oil	80.00
665.00	4	Deionized water	665.00
100.00	5	Salicylic acid	100.00

Manufacturing Directions

1. Mix and heat items 1 to 4 to 75°C.
2. Allow to cool with gentle stirring.
3. At 30°C, add item 5. Homogenize if necessary.

SALICYLIC ACID CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/100 g (g)
150.00	1	Polawax (self-emulsifying wax)	15.00
150.00	2	PPG-2 myristyl ether propionate (Crodamol PMP)	15.00
50.00	3	Sorbitol isostearate	5.00
35.00	4	Safflower oil, super refined	3.50
20.00	5	Avocado oil, super refined	2.00
20.00	6	Cetyl palmitate	2.00
50.00	7	Salicylic acid	5.00
1.50	8	Propyl paraben	0.15
1.00	9	Butylated hydroxyanisole	0.10
487.50	10	Deionized water	48.75
10.00	11	Sodium borate	1.00
3.00	12	Methyl paraben	0.30
2.00	13	Imidazolidinyl urea	0.20
20.00	14	Hydrolyzed collagen + hyaluronic acid (Cromoist HTA)	2.00

Manufacturing Directions

1. Dissolve item 7 in item 2 with mixing and heating to 70°C.
2. Add balance of items 1 to 9 and mix with heat to 80°C.
3. Mix together items 10 to 13 separately and heat to 80°C.
4. Add this mixture to earlier mixture with mixing and cool to 40°C.
5. Add item 14 with mixing and cool to desired fill temperature.
6. Adjust pH if necessary to 3 to 4 with 10% triethanolamine solution.

SALICYLIC ACID GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
422.00	1	Witch hazel distilled, 14% alcohol	422.00
5.00	2	Salicylic acid	5.00
5.00	3	Aloe vera gel	5.00
10.00	4	Sorbitol	10.00
500.00	5	Polyglyceiylmethylacrylate	500.00
10.00	6	Propylene glycol	10.00
0.80	7	Methyl paraben	0.80
0.20	8	Propyl paraben	0.20

Manufacturing Directions

1. Premix items 1 to 4. Add item 5 with low-shear mixing until homogenous.
2. Mix items 6 to 8 together and then add them to the formulation.

SCOPOLAMINE TRANSDERMAL THERAPEUTIC SYSTEM

The transdermal scopolamine system is a circular flat patch designed for continuous release of scopolamine following application to an area of intact skin on the head, behind the ear. Each system contains 1.5 mg of scopolamine base. The transdermal system is a film 0.2 mm thick and 2.5 cm^2, with four layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are a backing layer of tan-colored, aluminized polyester film; a drug reservoir of scopolamine, light mineral oil, and polyisobutylene; a microporous polypropylene membrane that controls the rate of delivery of scopolamine from the system to the skin surface; and an adhesive formulation of mineral oil, polyisobutylene, and scopolamine. A protective peel strip of siliconized polyester, which covers the adhesive layer, is removed before the system is used. The inactive components, light mineral oil (12.4 mg) and polyisobutylene (11.4 mg), are not released from the system.

SELENIUM SULFIDE DETERGENT LOTION

Bill of Materials

Scale (mg/mL)	Item	Material Name	Qty/L (g)
10.0	1	Selenium sulfide	10.0
2.0	2	Methyl paraben	2.0
10.0	3	Magnesium aluminum silicate type IIA	10.0
20.0	4	Titanium	20.0
0.170	5	Dye	0.170
230.0	6	Sodium alkyl ether sulfate/sulfonate	230.0
30.0	7	Surfactant cocamide DEA	30.0
40.0	8	Cocoamphocarboxyglycinate	40.0
10.0	9	Protein hydrolyzed	10.0
4.0	10	Perfume	4.0
QS	11	Acid citric	QS
QS	12	Sodium chloride	QS
QS	13	Water purified	QS to 1 L

Note: Item 11 used for pH adjustment, if necessary. Item 12 used for viscosity adjustment, if necessary.

Manufacturing Directions

1. Selenium sulfide is toxic. Handle carefully and use approved respiratory protection.

2. Add selenium sulfide. Seal the mill and agitate for approximately 10 minutes to wet down the powdered material.
3. Recycle for approximately 5 minutes. Stop agitation. If necessary, add purified water (25–30°C) to nearly cover the grinding media.
4. Seal the mill and recirculate the slurry for 1 to 2 hours to the required particle size specifications for the selenium sulfide.
5. Load 250 mL of purified water into a suitable jacketed mixing tank and heat to 60°C to 70°C. With good stirring, add and dissolve methyl paraben. Slowly add and disperse magnesium aluminum silicate. Continue mixing until fairly smooth. Stop mixing and allow hydrating for 1 hour.
6. Add and disperse titanium dioxide. Mix for 30 minutes.
7. With good stirring, add selenium sulfide slurry and rinse the mill with purified water. Mix for 30 minutes.
8. Stop mixing and add sodium lauryl ether sulfate/sulfonate. Mix slowly for 5 minutes. Add cocamide DEA. Mix slowly for approximately 3 minutes.
9. Add cocoamphocarboxyglycinate. Mix slowly for 30 minutes.
10. Separately dissolve hydrolyzed protein (Hydro gel) in 4 mL of purified water and mix until uniform. Add solution from above to the tank and mix until uniform.
11. Add perfume and mix for 1 minute. Dissolve dye in 2 mL warm purified water (50–60°C) and add to mixing tank. Mix until uniform. Check and record pH and adjust it to 4.5 to 5.0, if necessary, using citric acid.
12. Add purified water QS to 980 mL. Mix for 30 minutes. Check and record viscosity. If necessary, adjust by adding sodium chloride.
13. Deaerate by slow stirring under vacuum or use of a suitable deaerator. Mix for 1 hour.

SELENIUM SULFIDE LOTION

The active ingredient for selenium sulfide lotion is selenium sulfide, 2.5% w/v, in aqueous suspension; it also contains bentonite, lauric diethanolamide, ethylene glycol monostearate, titanium dioxide, amphoteric-2, sodium lauryl sulfate, sodium phosphate (monobasic), glyceryl monoricinoleate, citric acid, captan, and perfume.

SILICONE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Polawax NF	150.00
40.00	2	Oleyl alcohol	40.00
50.00	3	PEG-75 lanolin	50.00
150.00	4	Mineral oil 70 cS	150.00
50.00–100.00	5	Dimethicone	50.00–100.00
QS	6	Deionized water	QS to 1 kg

Manufacturing Directions

1. Heat water and oil phase separately to 60˚C to 65˚C.
2. Add water phase to oil phase while stirring. Stir to cool to 30˚C. Add perfume or color as desired.

SILVER SULFADIAZINE CREAM

Silver sulfadiazine cream, 1%, is a soft, white water-miscible cream containing the antimicrobial agent silver sulfadiazine in micronized form. Each gram of cream, 1%, contains 10 mg micronized silver sulfadiazine. The cream vehicle consists of white petrolatum, stearyl alcohol, isopropyl myristate, sorbitan monooleate, polyoxyl 40 stearate, propylene glycol, and water, with methyl paraben, 0.3%, as a preservative.

SILVER SULFADIAZINE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Silver sulfadiazine	10.00
5.00	2	Cetyl alcohol	50.00
8.00	3	Glyceryl monostearate A/S	80.00
8.00	4	Liquid paraffin	80.00
3.00	5	Tween 80	30.00
2.00	6	Tween 60	20.00
15.00	7	Propylene glycol	150.00
58.00	8	Water purified	580.00

Manufacturing Directions

1. Place items 2 to 6 in a fat-melting vessel, heat to 75°C, and then cool down to 60°C.
2. Add item 8 to Becomix and heat to 90°C. Cool down to 65°C.
3. Transfer step 1 into step 2, mix under vacuum, cool to 40°C.
4. In a separate vessel, add items 7 and 1 and homogenize.
5. Add to step 3 and mix. Cool to 25°C.
6. Transfer to storage vessel and fill.

SODIUM CHLORIDE OINTMENT

Sodium chloride ointment is a sterile ophthalmic ointment used to draw water out of the cornea of the eye. Each gram contains active ingredient sodium chloride, 5%, and inactives lanolin, mineral oil, white petrolatum, and purified water. Sodium chloride (approximately 0.9%) is used for treating cold sores and fever blisters and lesions associated with herpes virus.

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Liquid paraffin	50.00
10.00	2	White paraffin	100.00
30.00	3	Glycerin	300.00
8.00	4	Cetostearyl alcohol	80.00
0.30	5	Methyl paraben	3.00
3.60	6	Polyoxyethylene sorbitan monostearate	36.00
2.00	7	Glyceryl monostearate	20.00
QS	8	Water purified	QS to 1 kg
0.90	9	Sodium chloride	9.00

Manufacturing Directions

1. Preparation of water phase:
   a. Add purified water, polysorbate 60, and glycerin with agitation to a melting kettle.
   b. Heat the contents to 61°C to 65°C.
   c. Add methyl paraben and mix the composition to dissolve while maintaining temperature.
2. Preparation of oil phase:
   a. In a suitable vessel, place liquid paraffin, cetostearyl alcohol, white petrolatum, glycerol monostearate, and white beeswax and mix continuously while heating to 71°C to 75°C.
3. Mixing of phases:
   a. The mixture of step 2 is transferred to step 1's kettle, with the water phase maintained at less than 300 mbar vacuum.
   b. Add sodium chloride and dissolve.
   c. With mixing and keeping the temperature at 61°C to 65°C, draw the oil phase into the water phase.
   d. Mix for 15 minutes with agitation and vacuum at 300 mbar and 61°C to 65°C.
   e. While mixing and under vacuum, allow the mixture to cool gradually to room temperature.
4. Fill in appropriate container.

SODIUM SULFACETAMIDE LOTION

Each milliliter of sodium sulfacetamide lotion 10% contains 100 mg of sodium sulfacetamide in a vehicle consisting of purified water, propylene glycol, lauramide DEA and diethanolamine, polyethylene glycol 400 monolaurate, hydroxyethyl cellulose, sodium chloride, sodium metabisulfite, methyl paraben, xanthan gum, EDTA, and simethicone. Sodium sulfacetamide is a sulfonamide with antibacterial activity. Chemically, sodium sulfacetamide is N'-[(4-aminophenyl) sulfonyl]-acetamide, monosodium salt, monohydrate.

SPERMATOCIDAL EFFERVESCENT SUPPOSITORY

Manufacturing Directions

1. Melt together 80 g of polyethylene glycol (average molecular weight 950–1050), 23.5 g of polyethylene glycol (average molecular weight 1300–1600), 6 g of Menfegol, and 0.5 g of dioctyl sodium sulfosuccinate by heating to obtain a uniform mixture.
2. To this mixture add 5 g of anhydrous sodium sulfate and stir the mixture thoroughly to disperse. Then, successively add 10 g of sodium bicarbonate, 25 g of potassium hydrogen-tartrate, and 0.15 g of saponin, stir, and knead to uniformly disperse.
3. Inject the mixture, while hot, into a mold having a predetermined shape and cooled to below room temperature. Thereby, an effervescent vaginal suppository having a spermatocidal effect and weighing 1.5 g per unit is obtained.

SQUALENE CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Polyoxyethylene sorbitan monooleate	50.00
23.00	2	Cetyl alcohol	230.00
0.40	3	Cholesterol	4.00
0.20	4	Squalene	2.00
56.00	5	Water purified	560.00
10.00	6	Propylene glycol	100.00
5.00	7	L-cysteic acid	50.00
1.00 mL	8	Ethanolamine	10.00 mL

Manufacturing Directions

1. Heat items 1 to 4 in a jacketed kettle to 70°C.
2. In a separate kettle, heat items 5 to 8 to 70°C.
3. Add step 1 to step 2 at 72°C slowly with agitation.
4. Continue agitation until the mixture is congealed. The water-washable cream thus prepared consists of 5% active ingredient.

STARCH OINTMENT

The active ingredient in starch ointment is topical starch, 51%. It also contains benzyl alcohol, hydrogenated vegetable oil, and tocopheryl acetate.

SUCRALAFATE AND HYALURONIC ACID OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
30.00	1	Sucralafate (2–10 nm)	300.00
0.60	2	Hyaluronic acid	6.00
10.00	3	Pectin	100.00
10.00	4	Gelatin	100.00
4.00	5	Carboxymethylcellulose	40.00
60.00	6	Fractionated coconut oil	600.00

Manufacturing Directions

1. Mix finely divided sucralfate thoroughly with the other ingredients also in finely divided form.
2. Add fractionated coconut oil to the resulting powder and homogenize.

SUCRALAFATE OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
30.00	1	Sucralafate (2–10 urn)	300.00
10.00	2	Pectin	100.00
10.00	3	Gelatin	100.00
10.00	4	Carboxymethylcellulose	100.00
60.00	5	Fractionated coconut oil	600.00

Manufacturing Directions

1. Mix finely divided sucralfate thoroughly with the other ingredients also in finely divided form.
2. Add fractionated coconut oil to the resulting powder to a suitable consistency and homogenize.

SUCRALAFATE OPTHALMIC OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
2.00	1	Sucralafate (micronized less than 10 nm)	20.00
0.50	2	Carbopol 934	5.00
5.00	3	Mannitol	50.00
0.01	4	Benzalkonium chloride	0.10
0.05	5	Sodium EDTA	0.50
QS	6	Sodium hydroxide	QS
QS	7	Water purified	QS to 1 kg

SULFACETAMIDE OINTMENT

Sulfacetamide sodium ophthalmic solution and ointment USP, 10%, are sterile topical antibacterial agents for ophthalmic use. They contain sulfacetamide sodium, 10% (100 mg/g). The preservative is phenylmercuric acetate (0.0008%). Inactive ingredients are white petrolatum, mineral oil, and petrolatum and lanolin alcohol.

SULFACETAMIDE SODIUM AND PREDNISOLONE ACETATE OPTHALMIC OINTMENT

The sulfacetamide sodium and prednisolone acetate ophthalmic ointment USP is a sterile topical ophthalmic ointment combining an antibacterial and a corticosteroid. Active ingredients are sulfacetamide sodium, 10%, and prednisolone acetate, 0.2%. Inactives are phenylmercuric acetate (0.0008%), mineral oil, white petrolatum, and petrolatum and lanolin alcohol.

SULFANILAMIDE SUPPOSITORIES

The suppositories contain sulfanilamide, 15%, in a water-miscible, nonstaining base made from lactose, propylene glycol, stearic acid, diglycol stearate, methyl paraben, propyl paraben, trolamine, and water, buffered with lactic acid to an acid pH of approximately 4.3. Each suppository contains sulfanilamide 1.05 g with lactose in a base made from polyethylene glycol 400, polysorbate 80, polyethylene glycol 3350, and glycerin, buffered with lactic acid to an acid pH of approximately 4.5. The suppositories have an inert, white nonstaining covering that dissolves promptly in the vagina. The covering is composed of gelatin, glycerin, water, methyl paraben, propyl paraben, and coloring.

SULFATHIAZOLE CREAM

The cream contains sulfathiazole (benzenesulfonamide, 4-amino-N-2-thiazolyl-N1-2-thiazolylsulfanilamide), 3.42%, sulfacetamide (acetamide,N-[(4-aminophenyl)sulfonyl]-N-sulfanilylacetamide), 2.86%, and sulfabenzamide (benzamide,N-[(4-aminophenyl)sulfonyl]-N-sulfanilylbenzamide), 3.7%, compounded with cetyl alcohol, 2%, cholesterol, di-ethylaminoethyl stearamide, glyceryl monostearate, lanolin, lecithin, methyl paraben, peanut oil, phosphoric acid, propylene glycol, propyl paraben, purified water, stearic acid, and urea.

SULFUR OINTMENT

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
15.00	1	Sulfur precipitated	15.00
85.00	2	Kaolin	85.00
QS	3	White petroleum jelly	QS to 1 kg
60.00	4	Isopropyl palmitate	60.00
13.00	5	Camphor	13.00
13.00	6	Methyl salicylate	13.00
20.00	7	Lanolin	20.00
50.00	8	Tribehenin	50.00
50.00	9	Ozokerite wad	50.00
35.00	10	Sorbitan oleate	35.00
15.00	11	Deionized water	15.00
4.00	12	Salicylic acid	4.00
24.00	13	Glycerin	24.00
QS	14	Preservative	QS

Manufacturing Directions

1. Heat oils except sulfur and lanolin to 70°C. Disperse sulfur and kaolin in oil phase.
2. Heat water, glycerin, and salicylic acid gently. Add to oil phase while stirring. Stir to 55°C.
3. Mill to disperse sulfur.

TACROLIMUS OINTMENT

Tacrolimus ointment contains tacrolimus, a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. Each gram of ointment contains (w/w) either 0.03% or 0.1% of tacrolimus in a base of mineral oil, paraffin, propylene carbonate, white petrolatum, and white wax.

TERCONAZOLE VAGINAL CREAM

Terconazole vaginal cream, 0.4%, is a white to off-white water-washable cream for intravaginal administration containing 0.4% of the antifungal agent terconazole, compounded in a cream base consisting of butylated hydroxyanisole, cetyl alcohol, isopropyl myristate, polysorbate 60, polysorbate 80, propylene glycol, stearyl alcohol, and purified water. Terconazole vaginal cream, 0.8%, is a white to off-white water-washable cream for intravaginal administration containing 0.8% of the antifungal agent terconazole, cis-1-[p-([2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy)phenyl]-4-isopropylpiperazine, compounded in a cream base consisting of butylated hydroxyanisole, cetyl alcohol, isopropyl myristate, polysorbate 60, polysorbate 80, propylene glycol, stearyl alcohol, and purified water.

TERCONAZOLE VAGINAL SUPPOSITORIES

Terconazole vaginal suppositories are white to off-white suppositories for intravaginal administration containing 80 mg of the antifungal agent terconazole, cis-1-[p-([2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy)phenyl]-4-isopropylpiperazine in triglycerides derived from coconut or palm kernel oil (a base of hydrogenated vegetable oils) and butylated hydrox-yanisole.

TESTOSTERONE GEL

Testosterone gel is a clear, colorless hydroalcoholic gel containing 1% testosterone. It provides continuous transdermal delivery of testosterone, the primary circulating endogenous androgen, for 24 hours following a single application to intact, clean dry skin of the shoulders, upper arms, or abdomen. A daily application of 5, 7.5, or 10 g contains 50, 75, or 100 mg of testosterone respectively, to be applied daily to the skin surface. Approximately 10% of the applied testosterone dose is absorbed across skin of average permeability during a 24-hour period. The active pharmacologic ingredient is testosterone. Testosterone USP is a white to practically white crystalline powder chemically described as 17-beta hydroxyandrost-4-en-3-one. Inactive ingredients are ethanol 68.9%, purified water, sodium hydroxide, carbomer 940, and isopropyl myristate; these ingredients are not pharmacologically active.

TESTOSTERONE TRANSDERMAL SYSTEM

The testosterone transdermal system provides continuous delivery of testosterone (the primary endogenous androgen) for 24 hours following application to intact, nonscrotal skin (e.g., back, abdomen, thighs, and upper arms). Two strengths are available that deliver in vivo either 2.5 or 5 mg of testosterone per day across skin of average permeability. It has a central drug delivery reservoir surrounded by a peripheral adhesive area. The 2.5 mg system has a total contact surface area of 37 cm^2 with a 7.5-cm^2 central drug delivery reservoir

containing 12.2 mg testosterone USP dissolved in an alcohol-based gel. The 5 mg system has a total contact surface area of 44 cm^2 with a 15-cm^2 central drug delivery reservoir containing 24.3 mg testosterone USP dissolved in an alcohol-based gel. The delivery systems have six components. Proceeding from the top toward the surface attached to the skin, the system is composed of (1) metallized polyester/Surlyn (E.I. DuPont de Nemours Co; ethylene-methacrylic acid copolymer)/ethylene vinyl acetate backing film with alcohol-resistant ink; (2) a drug reservoir of testosterone USP, alcohol USP, glycerin USP, glycerol monooleate, methyl laurate, and purified water USP, gelled with an acrylic acid copolymer; (3) a permeable polyethylene microporous membrane; and (4) a peripheral layer of acrylic adhesive surrounding the central, active drug delivery area of the system. Before opening of the system and application to the skin, the central delivery surface of the system is sealed with a peelable laminate disc (5) composed of a five-layer laminate containing polyester/polyester urethane adhesive/aluminum foil/polyester urethane adhesive/polyethylene. The disc is attached to and removed with the release liner (6), a silicone-coated polyester film, which is removed before the system can be used.

TETRACAINE GEL AND CREAM

Tetracaine gel's active ingredient is tetracaine HCl, 2%, and it also contains ethoxydiglycol, eucalyptus oil, hydroxyethyl cellulose, maleated soybean oil, methyl paraben, propyl paraben, sodium lauryl sulfate, and water. The cream contains active ingredient tetracaine 2% as well as chloroxylenol, eucalyptus oil, hydrochloric acid, lauramide DEA, methyl paraben, sodium borate, sodium lauryl sulfate, steareth-2, steareth-21, stearic acid, water, and white wax.

TETRACYCLINE HYDROCHLORIDE OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
3.00	1	Tetracycline hydrochloride micronized (10% excess)	33.00
93.00	2	Petrolatum (white soft paraffin)	930.00
3.70	3	Mineral oil (liquid paraffin)	37.00
0.02	4	Vitamin E (oily)	0.20

Manufacturing Directions

1. Melt item 2 at 75°C in a fat-melting vessel.
2. In a suitable stainless-steel container, disperse item 1 in items 3 and 4 manually by using a spatula.
3. Transfer 89 g to 111 g of molten item 2 from step 1 to the mixer through stainless-steel mesh. Cool down to 50°C.
4. Load tetracycline dispersion from step 2 to the mixer. Start mixer at speed 10 rpm, homogenizer high speed for 20 minutes. Check evenness and smoothness of the dispersion.
5. Transfer the remaining quantity of molten item 2 from step 1 at 50°C to 55°C to the mixer through stainless-steel mesh while mixing and cooling at mixer speed 10 rpm, homogenizer high speed, under vacuum 0.4 to 0.6 bar for 30 minutes.
6. Stop homogenizer, continue mixing at 10 rpm, under vacuum 0.4 to 0.6 bar. Cool down to 28°C. Fill.

TGF ALPHA-OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
35.00	1	Polyethylene glycol 8000	350.00
36.70	2	Mineral oil	367.00
0.70	3	Tween 80	7.00
QS	4	Water purified	QS to 1 kg
29.30	5	Hydroxypropylmethylcellulose	293.00
2.50 mg	6	TGF-alpha	25.00 mg

Manufacturing Directions

1. Dissolve item 1 and add item 4 and heat to 80°C.
2. Add item 2 to step 1 and pass the mixture through a homogenizer until a fine emulsion is obtained.
3. Add item 5 to the emulsion in step 2 with vigorous mixing.
4. Homogenize again.
5. Sterilize the ointment at 121°C for 15 minutes in an autoclave.
6. Under sterile condition and at 4°C, transfer item 6 and mix thoroughly.
7. Sterile fill 5 g in capped ointment tube.

THERAPEUTIC SKIN LOTION

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
73.44	1	Water purified	734.40
2.50	2	Aloe vera gel	25.00
2.00	3	Walnut oil	20.00
2.00	4	Tocopherol acetate (vitamin E)	20.00
2.00	5	Glycerin	20.00
2.00	6	Stearic acid	20.00
2.00	7	1-Hexadecanol	20.00
2.00	8	Polysorbate 60	20.00
2.00	9	Apricot kernel oil	20.00
2.00	10	Jojoba oil	20.00
2.00	11	Glyceryl stearate	20.00
1.00	12	PEG-100 stearate	10.00
1.00	13	Dimethicone	10.00
1.00	14	PVP	10.00
0.50	15	Hyaluronic acid	5.00
0.50	16	Fibronectin	5.00
0.50	17	Allantoin	5.00
0.50	18	Triethanolamine	5.00
0.20	19	Carbopol 934	2.00
0.20	20	Potassium chloride	2.00
0.06	21	Urea	0.60
0.03	22	Calcium phosphate	0.30

TOLNAFTATE AND UNDECYLENATE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Glyceryl stearate and PEG-75 stearate	150.00
20.00	3	Hydrogenated palm/palm kernel oil PEG-6 esters	20.00
60.00	4	Mineral oil	60.00
0.50	5	Sorbic acid	0.50
0.50	6	Sodium methyl paraben	0.50
509.00	7	Deionized water	509.00
50.00	8	Undecylenic acid	50.00
200.00	9	Zinc undecylenate	200.00
10.00	10	Tolnafate	10.00

Manufacturing Directions

1. Mix and heat items 1 to 8 to 75°C.
2. Allow to cool and with gentle stirring. At 30°C add items 9 and 10.
3. Homogenize if necessary.

TRETINOIN AND ALPHA-BISABOLOL GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.05	1	Tretinoin	0.50
5.00	2	Lutrol E400	50.00
6.00	3	Cremophor RH400	60.00
0.04	4	Butylated hydroxytoluene	0.40
0.10	5	(-)Alpha-bisabolol natural (BASF)	1.00
70.30	6	Water purified	703.00
QS	7	Preservatives	QS
18.50	8	Lutrol F127	185.00

Manufacturing Directions

1. Add solution of items 7 and 6 slowly to the clear solution of items 1 to 5 at approximately 40°C.
2. Heat to approximately 50°C and dissolve approximately 14 g of item 8 in the combined solution of step 1.
3. Cool to approximately 6°C and dissolve the rest of the items. Maintain cool until the air bubbles have escaped.

TRETINOIN AND DEXPANTHENOL GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
50.00 mg	1	Tretinoin (BASF)	0.50
5.00	2	Lutrol E400	50.00
6.00	3	Cremophor RH40	60.00
40.00 mg	4	Butyl hydroxytoluene	0.40
68.40	5	Water purified	684.00
2.50	6	Dexpanthenol (BASF)	25.00
18.00	7	Lutrol F127	180.00

Manufacturing Directions

1. Add items 5 and 6 slowly to the clear solution of items 1 to 4 at approximately 40°C.
2. Heat to approximately 50°C and dissolve approximately 40 g of item 7 in step 1.
3. Cool to approximately 6°C and dissolve the rest of item 7.
4. Maintain cool until the air bubbles have escaped.

TRETINOIN CREAM

Tretonin cream, a topical retinoid, contains tretinoin 0.025% by weight in a hydrophilic cream vehicle of stearic acid, polyolprepolymer-2, isopropyl myristate, polyoxyl 40 stearate, propylene glycol, stearyl alcohol, xanthan gum, sorbic acid, butylated hydroxytoluene, and purified water. The tretinoin cream, 0.02%, contains the active ingredient tretinoin in a cream base. It is available at a concentration of 0.02% w/w in an oil-in-water emulsion formulation consisting of benzyl alcohol, butylated hydroxytoluene, caprylic/capric triglyceride, cetyl alcohol, edetate disodium, fragrance, methyl paraben, propyl paraben, purified water, stearic acid, stearyl alcohol, steareth 2, steareth 20, and xanthan gum.

TRETINOIN CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.05	1	Tretinoin (BASF)	0.50
8.00	2	Luvitol EHO	80.00
3.00	3	Cremophor A6	30.00
1.50	4	Cremophor A25	15.00
3.00	5	Glyceryl monostearate	30.00
3.00	6	Cetyl alcohol	30.00
0.50	7	Tegiloxan 100 (Goldschmidt)	5.00
0.04	8	Butyl hydroxytoluene	0.40
4.00	9	Propylene glycol	40.00
0.50	10	Preservatives	5.00
0.20	11	Perfumes	2.00
76.20	12	Water purified	762.00

Manufacturing Directions

1. Separately prepare solution of items 1 and 2 and a mixture of items 3 to 7 by heating to approximately 75°C.
2. Heat mixture of items 8 to 12 until a clear solution is formed.
3. To the warm mixture of step 2, mix step 1 and cool by stirring.

TRETINOIN GEL

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.05	1	Tretinoin (BASF)	0.50
15.00	2	Alcohol	150.00
1.00	3	Cremophor RH40	10.00
QS	4	Perfume	QS
0.04	5	Butyl hydroxytoluene	0.40
0.50	6	Carbopol 940	5.00
76.00	7	Water purified	760.00
0.70	8	Triethanolamine	7.00
6.60	9	Water purified	66.00

Manufacturing Directions

1. Prepare suspension of items 6 and 7 and add solution of items 8 and 9 to the well-stirred suspension.
2. When a clear mixture is formed, add solution of items 1 to 5.

TRETINOIN GEL MICROSPHERE

Tretinoin gel microsphere, 0.1%, is a formulation containing 0.1% by weight tretinoin for the topical treatment of acne vulgaris. This formulation uses patented methyl methacrylate/glycol dimethacrylate crosspolymer porous microspheres (Microsponge System®) to enable inclusion of the active ingredient tretinoin in an aqueous gel. Other components of this formulation are purified water, carbomer 934P, glycerin, disodium EDTA, propylene glycol, sorbic acid, PPG-20 methyl glucose ether distearate, cyclomethicone and dimethicone copolyol, benzyl alcohol, trolamine, and butylated hydroxytoluene.

TRIACONTANOL OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.0250	1	Methyl paraben	0.250
0.015	2	Propyl paraben	0.15
1.00	3	Sodium lauryl sulfate	10.00
12.00	4	Propylene glycol	120.00
25.00	5	Stearyl alcohol	250.00
25.00	6	White petrolatum	250.00
37.00	7	Water purified	370.00
0.01	8	Triacontanol	0.10

Manufacturing Directions

1. Melt the stearyl alcohol and the white petrolatum on a steam bath and warm to approximately 75°C.
2. Dissolve the other ingredients in the purified water and also warm to approximately 75°C.
3. Then mix all ingredients together and stir until the mixture congeals.

TRICLOSAN FOOT CARE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Glyceryl stearate (Gelol)	50.00
50.00	2	Propylene glycol stearate	50.00
100.00	3	Octyldodecyl myristate	100.00
50.00	4	Isostearyl isostearate	50.00
20.00	5	Dimethicone (100 cS)	20.00
651.00	6	Deionized water	651.00
50.00	7	Sucrose distearate	50.00
4.00	8	Phenoxyethanol, methyl paraben, ethyl paraben, and propyl paraben	4.00
20.00	9	Propylene glycol	20.00
3.00	10	Triclosan	3.00
2.00	11	Fragrance	2.00

Manufacturing Directions

1. Heat items 1 to 5 and items 6 to 7 separately to 75°C. Mix the two parts with turbine mixing for 1 minute.
2. Cool with gentle stirring.
3. Add items 9 and 10 and then item 11 with mixing at 30°C to 35°C.

TRICLOSAN FOOT CREAM

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Qty/L (g)
30.00	1	Alcohol and ceteareth-20 (Cosmowax EM5483)	30.00
30.00	2	Isopropyl myristate (Crodamol IPM)	30.00
5.00	3	Cetyl esters (Crodamol SS)	5.00
20.00	4	Oleyl alcohol	20.00
5.00	5	Propylene glycol	5.00
5.00	6	Carbopol 980	5.00
QS	7	Deionized water	QS to 1 L
300.00	8	Ethanol DEB100	300.00
2.00	9	Triclosan (Irgasan DP300)	2.00
0.50	10	Menthol	0.50
4.00	11	Triethanolamine 99% approximately to give pH 6–7	4.00

Manufacturing Directions

1. Preblend ethanol, Irgasan, and menthol and warm to 50°C.
2. Heat water and oil phases separately to 70°C.
3. Add water phase to oil phase while stirring. Stir to cool, adding the preblend at 60°C. Adjust pH.

TRIDAX PROCUMBENS OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	*Tridax procumbens* leaf extract	50.00
3.00	2	Carbopol 934	30.00
0.15	3	Methyl paraben	1.50
0.15	4	Propyl paraben	1.50
QS	5	Monoethanol amine	QS
QS	6	Propylene glycol:water purified (50:50)	QS to 1 kg

Manufacturing Directions

1. Shade dry the leaves of *T. procumbens* for 48 hours at room temperature.
2. Then soak the crushed leaves (500 g) with water (1 L) for 72 hours at room temperature.
3. Decant water and then concentrate to 100 mL by evaporating under vacuum at room temperature.
4. Then lyophilize this concentrated solution to obtain powder (item 1).
5. Disperse the *T. procumbens* leaf extract in pure propylene glycol along with propyl paraben (0.15%).
6. Thoroughly agitate the mixture to get a clear solution. Disperse Carbopol 934 in a propylene glycol and water (50:50) mixture along with methyl paraben in another vessel.
7. Stir the mixture continuously at 300 rpm for 2 to 3 hours.
8. Then add the *T. procumbens* solution and continue stirring for approximately 1 hour until a gel preparation is obtained.
9. Adjust the pH of this gel to 6 using monoethanolamine.

TROLAMINE SALICYLATE CREAM

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Qty/kg (g)
50.00	1	Glyceryl stearate	5.00
25.00	2	Cetyl alcohol	2.50
30.00	3	Cetyl phosphate and DEA cetyl phosphate	3.00
40.00	4	Stearyl stearoyl stearate	4.00
40.00	5	Cococaprylate/Caprate	4.00
40.00	6	Cetyl palmitate	4.00
5.00	7	Dimethicone	0.50
502.00	8	Deionized water	50.20
10.00	9	Propylene glycol, diazolidinyl urea, methyl paraben, and propyl paraben	1.00
5.50	10	Magnesium aluminum silicate	0.55
2.50	11	Xanthan gum	0.25
100.00	12	Deionized water	10.00
100.00	13	Trolamine salicylate (TEA salicylate)	10.00
50.00	14	Propylene glycol	5.00

Manufacturing Directions

1. Heat items 8 and 9 to 85°C, add items 10 and 11, and mix until well dispersed.
2. Add items 1 to 7 and mix well at 80°C to 85°C. Continue mixing.
3. While cooling to 65°C, add items 12 to 14 and continue mixing and cooling to 35°C. pH should be 5.5 to 5.6.

ULINASTATIN SUPPOSITORY

Manufacturing Directions

1. Weigh hard fat (Witepsol W 35, 167.4 g), pluronic F-127 (0.6 g), propyl paraoxybenzoate (0.2 g), and methyl paraoxybenzoate (0.2 g), melt at 50°C, and process to prepare a uniform oil-phase component which is held at 35°C to 45°C.
2. Prepare an aqueous solution of ulinastatin (ulinastatin: 4900 U/mL) to have a sodium chloride concentration of 9 mg/mL; to 24 mL of the solution, add gelatin (2.4 g), concentrated glycerin (4.8 g), and arginine hydrochloride (0.4 g) and heat the mixture to prepare a uniform aqueous-phase component which is held at 35°C to 45°C.
3. Mix steps 1 and 2 and emulsify with a homomixer; fill into suppository containers such that each contains a 1.7 g portion. Leave the contents to cool and solidify, yielding suppositories containing ulinastatin in a uniform amount.

ULTRASONIC ADHESIVE GEL

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Preservative (e.g., parabens)	5.00
754.00	2	Water	754.00
6.00	3	Carbopol 940 (Goodrich)	6.00
20.00	4	Sodium hydroxide solution 10%	20.00
15.00	5	Kollidon 30	15.00
200.00	6	Water	200.00

Manufacturing Directions

1. Prepare solution of item 1 in item 2 by heating to 70°C to 80°C and add item 3 slowly to obtain a homogeneous suspension.
2. Add items 4 to 6. A clear, colorless adhesive gel is obtained. Addition of sodium chloride changes consistency.

VITAMIN A OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
2.20	1	Vitamin A propionate	22.00
70.00	2	Alcohol SD40-A	700.00
5.00	3	Glycolic acid	50.00
20.00	4	Propylene glycol	200.00
4.00	5	Hydroxypropyl cellulose	40.00
5.00	6	Aloe vera extract	50.00
0.10	7	Lactil	1.00

Manufacturing Directions

1. Add 2.2 g vitamin A propionate to 70 g alcohol (SD40-A) and mix.
2. Add 5 g of glycolic acid to 20 g of propylene glycol and mix.
3. Add step 1 to step 2 at room temperature until the solution is homogeneous.
4. Sift in 4 g hydroxypropyl cellulose slowly, more than approximately 15 minutes while blending to avoid clumping.
5. While stirring, add 5 g extract of the aloe vera plant and 1 g Lactil.
6. Stir gently until cellulose is dissolved.

VITAMIN A SUPPOSITORIES

Bill of Materials

Scale (mg/ suppository)	Item	Material Name	Qty/1000 Suppositories (g)
150,000 IU	1	Vitamin A palmitate 1.7 M IU/g	88.23 g
1.00	2	Butyl hydroxytoluene	10
400.00	3	Cremophor RH 40	400
800.00	4	Lutrol E 1500	800
500.00	5	Lutrol E 4000	505

Manufacturing Directions

1. Dissolve butyl hydroxytoluene in the warm vitamin A, add Cremophor, and mix with the molten Lutrol E grades.
2. Fill into molds of suppositories to obtain the weight of 2 g.

VITAMIN C VAGINAL OINTMENT

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
12.50	1	Vitamin C	125.00
21.80	2	White Vaseline	218.00
23.00	3	Cetyl stearyl alcohol	230.00
39.50	4	Liquid paraffin	395.00

Manufacturing Directions

1. Charge items 2 to 4 in a melting tank and melt at 80°C.
2. Stir and homogenize for 20 minutes and cool.
3. At 30°C, add item 1 under vacuum and homogenize.

VITAMIN E GEL CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Vitamin E acetate	100.00
150.00	2	Propylene glycol pharma	150.00
200.00	3	Lutrol F 127	200.00
550.00	4	Water	550.00

Manufacturing Directions

1. Mix vitamin E acetate with propylene glycol and add the water. After cooling to approximately 6°C, dissolve Lutrol F 127 slowly in the well-stirred mixture.
2. Maintain cool until the air bubbles escape. A turbid white gel forms at temperatures between 20°C and 50°C. Viscosity at 25°C is approximately 120,000 mPa.

WOUND DEBRIDING OINTMENT

Manufacturing Directions

1. (% w/w) Castor oil, 90.0; hydrogenated castor oil, 10.0. Add the hydrogenated castor oil to the castor oil while mixing with a high shear mixer and mix until a semisolid is formed.
2. Wound debriding ointment (% w/w) Castor oil, 68.8; hydrogenated castor oil, 10.0; balsam Peru oil, 8.70; aluminum/magnesium hydroxide stearate, 2.00; trypsin, 0.018; safflower oil, QS add 100%.
3. In step 3, the wound debrider, disperse the aluminum/magnesium hydroxide stearate in the castor oil.
4. Thereafter add the hydrogenated castor oil while mixing with a high shear mixer, in particular, a turbo shear mixer.
5. Continue mixing until a semisolid forms. Then blend the remaining ingredients to the semisolid until homogeneous mixing appears.

ZINC OXIDE AND VITAMIN E CREAM

Bill of Materials

Scale (g/100 g)	Item	Material Name	Qty/kg (g)
7.50	1	Zinc oxide	75.00
5.00	2	White soft paraffin	50.00
6.50	3	Cetostearyl alcohol	65.00
11.00	4	Lanolin anhydrous	110.00
2.00	5	Castor oil	20.00
12.00	6	Liquid paraffin	120.00
0.50	7	Vitamin E oily	5.00
1.04	8	Sodium lauryl sulfate	10.40
10.00	9	Propylene glycol	100.00
1.00	10	Simethicone M30	10.00
0.04	11	Lavender oil	0.40
43.20	12	Water purified	432.00

Manufacturing Directions

1. Add item 12 (two-thirds) to Becomix, heat to 80°C to 85°C, and transfer to a stainless-steel covered container.
2. Place in a melting vessel items 2 to 7, one at a time, and heat to 70°C. Stir to meet and maintain temperature at 70°C to 75°C.
3. Transfer step 2 to Becomix after passing through a stainless-steel sieve while mixing.
4. Load item 12, set aside in a separate vessel, and stir to dissolve item 8 at 70°C to 75°C. Transfer this solution to Becomix through a stainless-steel sieve.
5. Homogenize for 10 minutes under vacuum 0.4 to 0.6 bar at 70°C to 75°C.
6. Cool down to 40°C to 45°C while mixing.
7. Place balance of item 12 at 70°C to 75°C and items 9 and 1 in a separate vessel. Mix using a stirrer, then cool down to 40°C to 45°C. Disperse zinc oxide in the solution while stirring and then pass dispersion twice through a homogenizer.
8. Transfer dispersion to Becomix and mix at slow speed.
9. Use item 12 to rinse vessel and add rinsings.
10. Homogenize at 35°C to 45°C under vacuum.
11. Add items 11 and 12 and mix again, homogenize again, and cool down to 25°C to 30°C.
12. Transfer to storage container and fill.

ZINC OXIDE LOTION

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
7.00	1	Magnesium aluminum silicate	7.00
641.00	2	Water	641.00
7.00	3	Unimulse C	7.00
30.00	4	Propylene glycol	30.00
30.00	5	Eucalyptus oil	30.00
30.00	6	Lanolin oil	30.00
50.00	7	Dimethicone 350 cs	50.00
50.00	8	C12-C15 alcohols benzoate	50.00
100.00	9	Polysorbate 80	100.00
50.00	10	Zinc oxide	50.00
10.00	11	Cornstarch	10.00
QS	12	Preservatives	QS

Manufacturing Directions

1. Add item 1 to the water slowly, agitating with maximum shear until smooth.
2. Add item 3 and 4, mixing each time, until uniform.
3. Mix items 5 to 10 until uniform and mix with other portions until uniform.
4. Add item 11 and 12 and mix until smooth.

ZINC OXIDE OINTMENT

(% w/w) Methyl benzethonium chloride, 0.1; sebacic acid, 10.0; acetylated lanolin, 2.0; zinc oxide, 20.0; perfume, 0.075; mineral oil gelled with 5% polyethylene (Plastibase 50 W), 67.825.

ZINC OXIDE OINTMENT

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
120.00	1	Ceteaiyl alcohol, PEG-40 castor oil, and sodium ceteaiyl sulfate	120.00
180.00	2	Petrolatum	180.00
60.00	3	Oleayl oleate	60.00
60.00	4	Mineral oil, light	60.00
100.00	5	Zinc oxide	100.00
QS	6	Water	QS to 1 kg
10.00	7	Propylene glycol, diazolidinyl urea, methyl paraben, and propyl paraben	10.00

Manufacturing Directions

1. Mix and heat item 1 to 5 to 70°C to 75°C.
2. Mix and heat items 6 and 7 to 70°C to 75°C. While stirring, add this to the mixture made earlier.
3. Begin cooling, continue stirring until batch reaches 30°C, and then homogenize.

ZINC OXIDE OINTMENT WITH VITAMIN E AND ALOE

Zinc oxide ointment with vitamin E and aloe's active ingredient is zinc oxide (11.3%). Its inactive ingredients are aloe vera gel, balsam (specially purified balsam Peru), beeswax, benzoic acid, dimethicone, methyl paraben, mineral oil, propyl paraben, purified water, sodium borate, and tocopheryl (vitamin E acetate).

ZINC PYRITHIONE DETERGENT LOTION

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg
547.50	1	Deionized water	547.50
7.50	2	Hydroxyethyl cellulose	7.50
347.00	3	TEA-lauryl sulfate	347.00
43.00	4	PEG-20 lanolin alcohol ether	43.00
20.00	5	Glycol stearate	20.00
15.00	6	Cocamide MEA	15.00
10.00	7	Zinc pyrithione 48%	20.00
QS	8	Fragrance, preservative	QS

Manufacturing Directions

1. Add item 2 to the water and mix. In a separate vessel, combine items 3 to 5, heat to 80°C, and mix.
2. Cool to 50°C. Add items 6 and 7 and mix. Add this mixture to mixture of item 2.
3. Cool to 40°C and add item 8.

ZINC UNDECYLENATE CREAM

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
7.50	1	Magnesium aluminum silicate	7.50
487.50	2	Deionized water	487.50
100.00	3	Sorbitol 70%	100.00
10.00	4	Polysorbate 80	10.00
200.00	5	Zinc undecylenate	200.00
50.00	6	Caprylic acid	50.00
30.00	7	C12-C15 alcohols benzoate	30.00
15.00	8	Polysorbate 80	15.00
20.00	9	C18-C36 acid	20.00
80.00	10	Glyceryl stearate and PEG-100 stearate	80.00
QS	11	Preservatives	QS

Manufacturing Directions

1. Slowly add item 1 in the water, mixing with maximum available shear until smooth.
2. Add items 2 to 5 in order, mixing each until uniform. Avoid incorporating air. Heat while stirring to 70°C to 75°C.
3. Heat items 6 to 10 separately to 70°C to 75°C and add to the above mixture, mixing while cooling. Fill at 45°C to 50°C.

ZIRCONIUM OXIDE LOTION

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
15.00	1	Magnesium aluminum silicate	15.00
3.00	2	Carboxymethylcellulose sodium medium viscosity	3.00
796.50	3	Water	796.50
40.00	4	Zirconium oxide	40.00
50.00	5	Propylene glycol	50.00
80.00	6	Isopropyl alcohol	80.00
15.00	7	Benzocaine	15.00
0.50	8	Menthol	0.50
QS	9	Preservative	QS

Manufacturing Directions

1. Dry blend items 1 and 2 and add them to water slowly while agitating with maximum shear until smooth.
2. Add items 4 and 5 and then items 6 to 9. Mix.

Part III

Commercial Pharmaceutical Formulations

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Commercial Pharmaceutical Formulations

- Accuzyme contains papain, USP (6.5 × 10.5 USP units of activity per gram of ointment) and urea, USP 10%, in a hydrophilic ointment base composed of emulsifying wax, fragrance, glycerin, isopropyl palmitate, lactose, methyl paraben, potassium phosphate monobasic, propyl paraben, and purified water.
- Acticin (permethrin) cream 5% is available in an off-white vanishing cream base. It is a yellow to light orange-brown, low-melting solid or viscous liquid. Each gram of Acticin cream, 5%, contains permethrin 50 mg (5%) and the inactive ingredients butylated hydroxytoluene, carbomer 934P, coconut oil, glycerin, glyceryl stearate, isopropyl myristate, lanolin alcohols, light mineral oil, polyoxyethylene cetyl ethers, purified water, and sodium hydroxide. Formaldehyde 1 mg (0.1%) is added as a preservative.
- Aldara: Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base consisting of isostearic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methyl paraben, and propyl paraben.
- Anbesol, active ingredients: Anbesol is an oral anesthetic which is available in a maximum strength gel and liquid. Anbesol Junior, available in a gel, is an oral anesthetic. Baby Anbesol, available in a grape-flavored gel, is an oral anesthetic and is alcohol free. Maximum strength Anbesol gel and liquid contain benzocaine, 20%. Anbesol junior gel contains benzocaine, 10%. Baby Anbesol gel contains benzocaine, 7.5%. Inactive ingredients: Maximum strength gel: Benzyl alcohol, carbomer 934P, D&C Yellow No. 10, FD&C Blue No. 1, FD&C Red No. 40, flavor, glycerin, methyl paraben, polyethylene glycol, propylene glycol, saccharin. Maximum strength liquid: Benzyl alcohol, D&C Yellow No. 10, FD&C Blue No. 1, FD&C Red No. 40, flavor, methyl paraben, polyethylene glycol, propylene glycol, saccharin. Junior gel: Artificial flavor, benzyl alcohol, carbomer 934P, D&C Red No. 33, glycerin, methyl paraben, polyethylene glycol, potassium acesulfame. Grape baby gel: Benzoic acid, carbomer 934P, D&C Red No. 33, edetate disodium, FD&C Blue No. 1, flavor, glycerin, methyl paraben, polyethylene glycol, propyl paraben, saccharin, water.
- AndroGel® (testosterone gel), 1%, is a clear, colorless hydroalcoholic gel containing 1% testosterone. AndroGel provides continuous transdermal delivery of testosterone, the primary circulating endogenous androgen, for 24 hours following a single application to intact, clean dry skin of the shoulders, upper arms, and/or abdomen. A daily application of AndroGel 5 g, 7.5 g, or 10 g contains 50 mg, 75 mg, or 100 mg of testosterone respectively, to be applied daily to the skin's surface. Approximately 10% of the applied testosterone dose is absorbed across skin of average permeability during a 24-hour period. The active pharmacologic ingredient in AndroGel is testosterone. Testosterone USP is a white to practically white crystalline powder. Inactive ingredients in AndroGel are ethanol, 67.0%, purified water, sodium hydroxide, carbomer 980, and isopropyl myristate; these ingredients are not pharmacologically active.
- Avar™-E emollient cream (sodium sulfacetamide, 10%, and sulfur, 5%) in each gram contains 100 mg of sodium sulfacetamide and 50 mg of colloidal sulfur in an emollient cream vehicle containing purified water, isostearyl palmitate, glyceryl stearate and PEG-100 stearate, sodium lactate USP, glycerin USP, self-emulsifying wax NF, zinc oxide USP, benzyl alcohol NF, nicotinamide, cetyl alcohol NF, dimethicone, sodium thiosulfate, phenoxyethanol, disodium EDTA, fragrance. Each gram of Avar-E green cream (sodium sulfacetamide 10% and sulfur 5%) color corrective emollient cream contains 100 mg of sodium sulfacetamide and 50 mg of colloidal sulfur in an emollient cream vehicle containing purified water, isostearyl palmitate, glyceryl stearate and PEG-100 stearate, sodium lactate USP, glycerin USP, self-emulsifying wax NF, zinc oxide USP, benzyl alcohol NF, chromium oxide green, nicotinamide, cetyl alcohol NF, dimethicone, sodium thiosulfate, phenoxyethanol, disodium EDTA, fragrance.
- Avar gel (sodium sulfacetamide 10% and sulfur 5%) in each gram contains 100 mg of sodium sulfacetamide and 50 mg of colloidal sulfur in an aqueous-based emollient gel vehicle containing purified water USP, sodium magnesium silicate, emulsifying lipids, nicotinamide, disodium EDTA, sodium thiosulfate, zinc oxide, benzyl alcohol, phenoxyethanol, glycerin, xanthan gum, sodium lactate, polyacrylamide, C13-C14 isoparaffin, laureth-7, fragrance. Each gram of Avar green (sodium sulfacetamide, 10%, and sulfur, 5%) color corrective gel contains 100 mg of sodium sulfacetamide and 50 mg of colloidal sulfur in an aqueous-based emollient gel vehicle containing purified water USP, sodium magnesium silicate, emulsifying lipids, nicotinamide, disodium EDTA, sodium thiosulfate, zinc oxide, benzyl alcohol, phenoxyethanol, glycerin, xanthan gum, sodium lactate, polyacrylamide, C13-C14 isoparaffin, laureth-7, fragrance, chromium oxide green.

- Avita® cream, a topical retinoid, contains tretinoin 0.025% by weight in a hydrophilic cream vehicle of stearic acid, polyolprepolymer-2, isopropyl myristate, polyoxyl 40 stearate, propylene glycol, stearyl alcohol, xanthan gum, sorbic acid, butylated hydroxytoluene, and purified water.
- Avita gel, a topical retinoid, contains tretinoin 0.025% by weight in a gel vehicle of butylated hydroxytoluene, hydroxypropyl cellulose, polyolprepolymer-2, and ethanol (denatured with tertiary butyl alcohol and brucine sulfate) 83% w/w.
- BenzaClin® topical gel contains clindamycin phosphate. BenzaClin topical gel also contains benzoyl peroxide for topical use. Each gram of BenzaClin topical gel contains, as dispensed, 10 mg (1%) clindamycin as phosphate and 50 mg (5%) benzoyl peroxide in a base of carbomer, sodium hydroxide, dioctyl sodium sulfosuccinate, and purified water.
- Brevoxyl-4 creamy wash and Brevoxyl-8 creamy wash are topical preparations containing benzoyl peroxide as the active ingredient. Brevoxyl-4 creamy wash and Brevoxyl-8 creamy wash contain 4% and 8% benzoyl peroxide respectively, in a lathering cream vehicle containing cetostearyl alcohol, cocamidopropyl betaine, cornstarch, dimethyl isosorbide, glycerin, glycolic acid, hydrogenated castor oil, imidurea, methyl paraben, mineral oil, peg-14 M, purified water, sodium hydroxide, sodium PCA, sodium potassium lauryl sulfate, titanium dioxide.
- Brevoxyl-4 gel and Brevoxyl-8 gel are topical preparations containing benzoyl peroxide 4% and 8% respectively, as the active ingredient in a gel vehicle containing purified water, cetyl alcohol, dimethyl isosorbide, fragrance, simethicone, stearyl alcohol, and ceteareth-20.
- Camptosar injection (irinotecan hydrochloride injection) is supplied as a sterile, pale yellow, clear, aqueous solution. It is available in two single-dose sizes: 2 mL fill vials contain 40 mg irinotecan hydrochloride, and 5 mL fill vials contain 100 mg irinotecan hydrochloride. Each milliliter of solution contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of sorbitol NF powder, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range: 3.0–3.8) with sodium hydroxide or hydrochloric acid. Camptosar is intended for dilution with 5% dextrose injection, USP (D5W), or 0.9% sodium chloride injection, USP, prior to intravenous infusion. The preferred diluent is 5% dextrose injection, USP.
- Carac® (fluorouracil cream) cream, 0.5%, contains fluorouracil for topical dermatologic use. Carac cream contains 0.5% fluorouracil, with 0.35% being incorporated into a patented porous microsphere (Microsponge) composed of methyl methacrylate/glycol dimethacrylate crosspolymer and dimethicone. The cream formulation contains the following other inactive ingredients: Carbomer 940, dimethicone, glycerin, methyl gluceth-20, methyl methacrylate/glycol dimethacrylate crosspolymer, methyl paraben, octyl hydroxy stearate, polyethylene glycol 400, polysorbate 80, propylene glycol, propyl paraben, purified water, sorbitan monooleate, stearic acid, and trolamine.
- Caverject contains alprostadil as the naturally occurring form of prostaglandin E 1. Caverject Impulse is available as a disposable, single-dose dual-chamber syringe system. The system includes a glass cartridge, which contains sterile, freeze-dried alprostadil in the front chamber and sterile bacteriostatic water for injection in the rear chamber. The alprostadil is reconstituted with the sterile bacteriostatic water just before injection. Caverject Impulse is available in two strengths for intracavernosal administration: (1) 10 μg—the reconstituted solution has a volume of 0.64 mL. The delivered volume, 0.5 mL, contains 10 μg of alprostadil, 324.7 μg of alpha-cyclodextrin, 45.4 mg of lactose, 23.5 μg of sodium citrate, and 4.45 mg of benzyl alcohol. (2) 20 μg—the reconstituted solution has a volume of 0.64 mL. The delivered volume, 0.5 mL, contains 20 μg of alprostadil, 649.3 μg of alpha-cyclodextrin, 45.4 mg of lactose, 23.5 μg of sodium citrate, and 4.45 mg of benzyl alcohol. When necessary, the pH of the alprostadil for injection was adjusted with hydrochloric acid and/or sodium hydroxide before lyophilization.
- Claripel cream, active ingredient: Hydroquinone USP 4%. Other ingredients: Avobenzone, ceteareth-20, cetostearyl alcohol, citric acid, diethylaminoethyl stearate, dimethicone, edetate disodium, glyceryl dilaurate, glyceryl monostearate, glyceryl stearate, PEG-100 stearate, hydroxyethyl cellulose, methyl paraben, octyldodecyl stearoyl stearate, octinoxate, oxybenzone, polysorbate 80, propylene glycol, propyl gallate, propyl paraben, purified water, quaternium-26, sodium metabisulfite, sodium PCA, squalane, ubiquinone, stearyl alcohol, water, glycerin, *Rumex occidentalis* extract.
- Cleocin vaginal ovules are semisolid, white to off-white suppositories for intravaginal administration. Each 2.5-g suppository contains clindamycin phosphate equivalent to 100 mg clindamycin in a base consisting of a mixture of glycerides of saturated fatty acids.
- Climara Pro™ (estradiol/levonorgestrel transdermal system) is an adhesive-based matrix transdermal patch designed to release both estradiol and levonorgestrel, a progestational agent, continuously upon application to intact skin. The 22 cm^2 Climara Pro system contains 4.40 mg estradiol and 1.39 mg levonorgestrel and provides a nominal delivery rate (mg/d) of 0.045 estradiol and 0.015 levonorgestrel. The Climara Pro system comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are

(1) a translucent polyethylene backing film, (2) an acrylate adhesive matrix containing estradiol and levonorgestrel, and (3) a protective liner of either siliconized or fluoropolymer-coated polyester film. The protective liner is attached to the adhesive surface and must be removed before the system can be used. The active components of the system are estradiol and levonorgestrel. The remaining components of the system (acrylate copolymer adhesive and polyvinylpyrrolidone/vinyl acetate copolymer) are pharmacologically inactive.

- Climara®, estradiol transdermal system, is designed to release 17(beta)-estradiol continuously upon application to intact skin. Six (6.5, 9.375, 12.5, 15.0, 18.75, and 25.0 cm^2) systems are available to provide nominal in vivo delivery of 0.025, 0.0375, 0.05, 0.060, 0.075, or 0.1 mg respectively of estradiol per day. The period of use is 7 days. Each system has a contact surface area of either 6.5, 9.375, 12.5, 15.0, 18.75, or 25.0 cm^2 and contains 2.0, 2.85, 3.8, 4.55, 5.7, or 7.6 mg of estradiol USP respectively. The composition of the systems per unit area is identical. The Climara system comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyethylene film and (2) an acrylate adhesive matrix containing estradiol USP. A protective liner (3) of siliconized or fluoropolymer-coated polyester film is attached to the adhesive surface and must be removed before the system can be used. The active component of the system is 17(beta)-estradiol. The remaining components of the system (acrylate copolymer adhesive, fatty acid esters, and polyethylene backing) are pharmacologically inactive.
- Clindagel® (clindamycin phosphate gel) topical gel, 1%, a topical antibiotic, contains clindamycin phosphate, USP, at a concentration equivalent to 10 mg clindamycin per gram in a gel vehicle consisting of carbomer 941, methyl paraben, polyethylene glycol 400, propylene glycol, sodium hydroxide, and purified water.
- Clindesse™ is a semisolid white cream, which contains clindamycin phosphate, USP, at a concentration equivalent to 20 mg clindamycin base per gram. The cream also contains edetate disodium, glycerol monoisostearate, lecithin, methyl paraben, microcrystalline wax, mineral oil, polyglyceryl-3-oleate, propyl paraben, purified water, silicon dioxide, and sorbitol solution.
- Clobevate® (clobetasol propionate gel) for topical administration contains clobetasol propionate 0.5 mg in a base of propylene glycol, carbomer 934P, sodium hydroxide, and purified water.
- Colace® (glycerin) suppositories, active ingredient (per suppository): Colace suppositories contain glycerin, USP 2.1 g. Inactive ingredients: Purified water, sodium hydroxide, stearic acid. Colace suppositories contains glycerin, USP 1.2 g.
- CombiPatch® (estradiol/norethindrone acetate transdermal system) is an adhesive-based matrix transdermal patch. The remaining components of the system are pharmacologically inactive. Two systems are available, providing the following delivery rates of estradiol and norethindrone acetate: 9 cm^2 round 0.62 mg estradiol and 2.7 mg NETA; release rates: 0.05/0.14 mg/d; 16 cm^2 round 0.51 estradiol and 4.8 mg NETA; release rates 0.05/0.25 mg/d respectively. Estradiol USP (estradiol) is a white to creamy-white, odorless crystalline powder. Norethindrone acetate USP is a white to creamy-white, odorless crystalline powder. CombiPatch transdermal systems are comprised of three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyolefin film backing; (2) an adhesive layer containing estradiol, norethindrone acetate, acrylic adhesive, silicone adhesive, oleyl alcohol, oleic acid NF, povidone USP, and dipropylene glycol; and (3) a polyester-release protective liner, which is attached to the adhesive surface and must be removed before the system can be used.
- Cutivate (fluticasone propionate ointment) ointment, 0.005%, contains fluticasone propionate, a synthetic fluorinated corticosteroid for topical dermatologic use. Each gram of Cutivate ointment contains fluticasone propionate 0.05 mg in a base of liquid paraffin, microcrystalline wax, propylene glycol, and sorbitan sesquioleate. Each gram of Cutivate lotion contains 0.5 mg fluticasone propionate in a base of cetostearyl alcohol, isopropyl myristate, propylene glycol, cetomacrogol 1000, dimethicone 360, citric acid, sodium citrate, and purified water, with imidurea, methyl paraben, and propyl paraben as preservatives. Each gram of Cutivate cream contains fluticasone propionate 0.5 mg in a base of propylene glycol, mineral oil, cetostearyl alcohol, ceteth-20, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water, and imidurea as preservative.
- Denavir containing penciclovir is available for topical administration as a 1% white cream. Each gram of Denavir contains 10 mg of penciclovir and the following inactive ingredients: Cetomacrogol 1000 BP, cetostearyl alcohol, mineral oil, propylene glycol, purified water, and white petrolatum.
- Diastat rectal delivery system is a nonsterile diazepam gel provided in a prefilled, unit-dose, rectal delivery system. Diastat contains 5 mg/mL diazepam, propylene glycol, ethyl alcohol (10%), hydroxypropylmethylcellulose, sodium benzoate, benzyl alcohol (1.5%), benzoic acid, and water. Diastat is clear to slightly yellow and has a pH between 6.5 and 7.2. Diazepam, the active ingredient of Diastat, is a benzodiazepine anticonvulsant with the chemical name 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1, 4-benzodiazepin-2-one.

- Differin® (adapalene) cream, 0.1%, contains adapalene 0.1% in an aqueous cream emulsion consisting of carbomer 934P, cyclomethicone, edetate disodium, glycerin, methyl glucose sesquistearate, methyl paraben, PEG-20 methyl glucose sesquistearate, phenoxyethanol, propyl paraben, purified water, squalane, and trolamine.
- Dilaudid suppositories (for rectal administration) contain 3 mg hydromorphone hydrochloride in a cocoa butter base with silicon dioxide.
- Dinoprostone vaginal insert is a thin, flat polymeric slab, which is rectangular in shape with rounded corners contained within the pouch of an off-white knitted polyester retrieval system. Each slab is buff-colored, semitransparent, and contains 10 mg of dinoprostone in a hydrogel insert. An integral part of the knitted polyester retrieval system is a long tape designed to aid retrieval at the end of the dosing interval or earlier if clinically indicated. The finished product is a controlled-release formulation, which has been found to release dinoprostone in vivo at a rate of approximately 0.3 mg/h. Each insert contains 10 mg of dinoprostone in 241 mg of a cross-linked polyethylene oxide/urethane polymer which is a semi-opaque, beige-colored, flat rectangular slab measuring 29 mm × 9.5 mm × 0.8 mm in thickness. The insert and its retrieval system, made of polyester yarn, are nontoxic and when placed in a moist environment absorb water, swell, and release dinoprostone.
- Diprolene® ointment contains betamethasone dipropionate. Each gram of Diprolene ointment 0.05% contains 0.643 mg betamethasone dipropionate. USP (equivalent to 0.5 mg betamethasone), in Actibase®, an optimized vehicle of propylene glycol, propylene glycol stearate (55% monoester), white wax, and white petrolatum.
- Diprolene AF cream, 0.05%, contains betamethasone dipropionate. Each gram of Diprolene AF cream 0.05% contains 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone), in an emollient cream base of purified water, USP; chlorocresol; propylene glycol, USP; white petrolatum, USP; white wax, NF; cyclomethicone; sorbitol solution, USP; glyceryl oleate/propylene glycol; ceteareth-30; carbomer 940, NF; and sodium hydroxide.
- Diprolene gel contains betamethasone dipropionate. Each gram of Diprolene gel contains 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone), in an augmented gel base of purified water, USP; propylene glycol, USP; carbomer 940, NF; and sodium hydroxide, NF or R. May also contain phosphoric acid, NF, to adjust the pH to approximately 4.5.
- Diprolene lotion contains betamethasone dipropionate. Each gram of Diprolene lotion 0.05% contains 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone), in a lotion base of purified water; isopropyl alcohol (30%); hydroxypropyl cellulose; propylene glycol; sodium phosphate monobasic monohydrate R; phosphoric acid used to adjust the pH to 4.5.
- Diprosone cream, 0.05%, contains betamethasone dipropionate. Each gram of Diprosone cream 0.05% contains 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone), in a hydrophilic emollient cream consisting of purified water, USP; mineral oil, USP; white petrolatum, USP; ceteareth-30; cetearyl alcohol 70/30 (7.2%); sodium phosphate monobasic monohydrate R; and phosphoric acid, NF; chlorocresol and propylene glycol, USP as preservatives. May also contain sodium hydroxide R to adjust pH to approximately 5.
- Dovonex® (calcipotriene ointment) ointment, 0.005%, contains calcipotriene 50 μg/g in an ointment base of dibasic sodium phosphate, edetate disodium, mineral oil, petrolatum, propylene glycol, tocopherol, steareth-2, and water. Dovonex (calcipotriene cream) cream, 0.005%, contains calcipotriene monohydrate, a synthetic vitamin D_3 derivative, for topical dermatological use. Calcipotriene monohydrate is a white or off-white crystalline substance. Dovonex cream contains calcipotriene monohydrate equivalent to 50 μg/g anhydrous calcipotriene in a cream base of cetearyl alcohol, ceteth-20, diazolidinyl urea, dichlorobenzyl alcohol, dibasic sodium phosphate, edetate disodium, glycerin, mineral oil, petrolatum, and water.
- Duac® topical gel contains clindamycin phosphate, equivalent to 1% clindamycin, and 5% benzoyl peroxide. Each gram of Duac topical gel contains 10 mg (1%) clindamycin, as phosphate and 50 mg (5%) benzoyl peroxide in a base consisting of carbomer 940, dimethicone, disodium lauryl sulfosuccinate, edetate disodium, glycerin, silicon dioxide, methyl paraben, poloxamer, purified water, and sodium hydroxide.
- Duac topical gel contains clindamycin phosphate, equivalent to 1% clindamycin, and 5% benzoyl peroxide. Each gram of Duac topical gel contains 10 mg (1%) clindamycin, as phosphate, and 50 mg (5%) benzoyl peroxide in a base consisting of carbomer 940, dimethicone, disodium lauryl sulfosuccinate, edetate disodium, glycerin, silicon dioxide, methyl paraben, poloxamer, purified water, and sodium hydroxide.
- Efudex cream is a topical preparation containing the fluorinated pyrimidine 5-fluorouracil. Efudex cream contains 5% fluorouracil in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60, and parabens (methyl and propyl).
- Elidel® (pimecrolimus) cream, 1%, contains the compound pimecrolimus. Each gram of Elidel cream, 1%, contains 10 mg of pimecrolimus in a whitish

cream base of benzyl alcohol, cetyl alcohol, citric acid, mono- and diglycerides, oleyl alcohol, propylene glycol, sodium cetostearyl sulphate, sodium hydroxide, stearyl alcohol, triglycerides, and water.

- Elocon® (mometasone furoate cream) cream, 0.1%, contains mometasone furoate, USP, for dermatologic use. Each gram of Elocon cream 0.1% contains 1 mg mometasone furoate, USP, in a cream base of hexylene glycol, phosphoric acid, propylene glycol stearate (55% monoester), stearyl alcohol and ceteareth-20, titanium dioxide, aluminum starch octenylsuccinate (gamma irradiated), white wax, white petrolatum, and purified water.
- Elocon (mometasone furoate ointment, USP) ointment, 0.1%, contains mometasone furoate, USP, for dermatologic use. Each gram contains 1 mg mometasone furoate, USP, in an ointment base of hexylene glycol, phosphoric acid, propylene glycol stearate (55% monoester), white wax, white petrolatum, and purified water.
- Elocon (mometasone furoate topical solution) lotion, 0.1%, contains mometasone furoate, USP, for dermatologic use. Each gram of Elocon lotion, 0.1%, contains 1 mg mometasone furoate, USP, in a lotion base of isopropyl alcohol (40%), propylene glycol, hydroxypropyl cellulose, sodium phosphate monobasic monohydrate R, and water. May also contain phosphoric acid used to adjust the pH to approximately 4.5.
- Elspar (asparaginase): The specific activity of Elspar is at least 225 IU/mg of protein, and each vial contains 10,000 IU of asparaginase and 80 mg of mannitol, an inactive ingredient, as a sterile, white lyophilized plug or powder for intravenous or intramuscular injection after reconstitution.
- Erygel® topical gel contains erythromycin. Each gram of Erygel topical gel contains 20 mg of erythromycin, USP, in a base of alcohol 92% and hydroxypropyl cellulose.
- EstroGel® (estradiol gel) contains 0.06% estradiol in an absorptive hydroalcoholic gel base formulated to provide a controlled release of the active ingredient. An EstroGel unit dose of 1.25 g contains 0.75 mg of estradiol. The active component of the transdermal gel is estradiol. The remaining components of the gel (purified water, alcohol, triethanolamine, and carbomer 934P) are pharmacologically inactive.
- Evoclin (clindamycin phosphate) foam, 1%, a topical antibiotic in a foam vehicle, contains clindamycin phosphate, USP, at a concentration equivalent to 10 mg clindamycin per gram in a vehicle consisting of cetyl alcohol, dehydrated alcohol (ethanol 58%), polysorbate 60, potassium hydroxide, propylene glycol, purified water, and stearyl alcohol, pressurized with a hydrocarbon (propane/butane) propellant.
- Finacea® (azelaic acid) gel, 15%: Each gram of Finacea gel, 15%, contains 0.15 g azelaic acid (15% w/w) as the active ingredient in an aqueous gel base containing benzoic acid (as a preservative), disodium-EDTA, lecithin, medium-chain triglycerides, polyacrylic acid, polysorbate 80, propylene glycol, purified water, and sodium hydroxide to adjust pH.
- Gynazole 1® (butoconazole nitrate) vaginal cream, 2%, contains butoconazole nitrate 2%, an imidazole derivative with antifungal activity. Gynazole 1 contains 2% butoconazole nitrate in a cream of edetate disodium, glyceryl monoisostearate, methyl paraben, mineral oil, polyglyceryl-3 oleate, propylene glycol, propyl paraben, colloidal silicon dioxide, sorbitol solution, purified water, and microcrystalline wax.
- Hydrocortisone, 1%, inactive ingredients: BHA, car-boxymethylcellulose sodium, cetyl alcohol, citric acid, edetate disodium, glycerin, glyceryl oleate, glyceryl stearate, lanolin, methyl paraben, petrolatum, propyl gallate, propylene glycol, propyl paraben, simethicone, sodium benzoate, sodium lauryl sulfate, stearyl alcohol, water, xanthan gum.
- Indocin suppositories for rectal use contain 50 mg of indomethacin and the following inactive ingredients: Butylated hydroxyanisole, butylated hydroxytoluene, edetic acid, glycerin, polyethylene glycol 3350, polyethylene glycol 8000, and sodium chloride.
- Klaron® (sodium sulfacetamide lotion) lotion, 10%, contains 100 mg of sodium sulfacetamide in a vehicle consisting of purified water; propylene glycol; lauramide DEA (and) diethanolamine; polyethylene glycol 400, monolaurate; hydroxyethyl cellulose; sodium chloride; sodium metabisulfite; methyl paraben; xanthan gum; EDTA; and simethicone.
- Loprox® gel (ciclopirox), 0.77%: Each gram of Loprox gel contains 7.70 mg of ciclopirox in a gel consisting of purified water USP, isopropyl alcohol USP, octyldodecanol NF, dimethicone copolyol 190, carbomer 980, sodium hydroxide NF, and docusate sodium USP. Loprox gel is a white slightly fluid gel.
- Lotrimin cream contains 10 mg clotrimazole, USP, in a vanishing cream base of benzyl alcohol NF (1%), cetearyl alcohol 70/30 (10%), cetyl esters wax NF, octyldodecanol NF, polysorbate 60 NF, sorbitan monostearate NF, and purified water USP.
- Lotrisone cream and lotion contain combinations of clotrimazole and betamethasone dipropionate. Each gram of Lotrisone cream contains 10 mg clotrimazole and 0.643 mg betamethasone dipropionate (equivalent to 0.5 mg betamethasone) in a hydrophilic cream consisting of purified water, mineral oil, white petrolatum, cetyl alcohol plus stearyl alcohol, ceteareth-30, propylene glycol, sodium phosphate monobasic monohydrate, and phosphoric acid; benzyl alcohol as preservative.
- Lotrisone lotion contains 10 mg clotrimazole and 0.643 mg betamethasone dipropionate (equivalent to 0.5 mg betamethasone) in a hydrophilic base of purified water, mineral oil, white petrolatum, cetyl

alcohol plus stearyl alcohol, ceteareth-30, propylene glycol, sodium phosphate monobasic monohydrate, and phosphoric acid; benzyl alcohol as a preservative. Lotrisone lotion may contain sodium hydroxide.

- Lustra-Ultra™, USP 4%, other ingredients (Lustra®): Purified water USP, phenyl trimethicone, glycerin 99% USP, glyceryl stearate (and) PEG-100 stearate, alcohol, cetyl alcohol NF, cyclopentasiloxane (and) polysilicone-11, linoleic acid, glycolic acid, polyacrylamide (and) c13-14 isoparaffin (and) laureth-7, cetearyl alcohol (and) ceteareth-20, triethanolamine 99% USP, tocopheryl acetate USP, hydrogenated lecithin, phenoxyethanol, magnesium 1-ascorbyl phosphate NF, benzyl alcohol NF, dimethiconol, sodium metabisulfite NF, sodium citrate USP, disodium EDTA USP, butylated hydroxytoluene, vitamin E USP, carbomer NF, fragrance. Other ingredients (Lustra-AF®): Purified water USP, octyl methoxycinnamate, glycerin 99% USP, phenyl trimethicone, glyceryl stearate (and) PEG-100 stearate, cetyl alcohol NF, alcohol, avobenzone, cyclopentasiloxane (and) polysilicone-11, linoleic acid, glycolic acid, polyacrylamide (and) C 13-14 isoparaffin (and) laureth-7, cetearyl alcohol (and) ceteareth-20, triethanolamine 99% USP, hydrogenated lecithin, tocopheryl acetate USP, phenoxyethanol, benzyl alcohol NF, magnesium 1-ascorbyl phosphate NF, dimethiconol, sodium metabisulfite NF, sodium citrate USP, disodium EDTA USP, butylated hydroxytoluene, vitamin E USP, carbomer NF, fragrance. Other ingredients (Lustra-Ultra): Purified water USP, octinoxate USP, propylene glycol USP, cetyl alcohol NF, glyceryl stearate (and) PEG-100 stearate, avobenzone USP, cyclomethicone NF, cetearyl glucoside, capric caprylic triglyceride, microcrystalline wax NF, dimethicone NF, magnesium ascorbyl phosphate, polysorbate 20 NF, xanthan gum NF, retinol, sodium metabisulfite NF, methyl paraben NF, disodium EDTA USP, propyl paraben NF, vitamin E USP
- Luxiq contains betamethasone valerate, USP. Each gram of Luxiq contains 1.2 mg betamethasone valerate, USP, in a hydroalcoholic, thermolabile foam. The foam also contains cetyl alcohol, citric acid, ethanol (60.4%), polysorbate 60, potassium citrate, propylene glycol, purified water, and stearyl alcohol and is dispensed from an aluminum can pressurized with a hydrocarbon propellant (propane/butane).
- Mederma® is a topical gel for scar treatment. Ingredients: Water (purified), PEG-4, *Allium cepa* (onion) bulb extract, xanthan gum, allantoin, fragrance, methyl paraben, sorbic acid.
- Menostar, estradiol transdermal system, is designed to provide nominal in vivo delivery of 14 μg 17(beta)-estradiol per day continuously upon application to intact skin. The period of use is 7 days. The transdermal system has a contact surface area of 3.25 cm^2 and contains 1 mg of estradiol USP. The Menostar transdermal system comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyethylene film and (2) an acrylate adhesive matrix containing estradiol USP. A protective liner (3) of siliconized or fluoropolymer-coated polyester film is attached to the adhesive surface and must be removed before the transdermal system can be used. The active component of the transdermal system is 17(beta)-estradiol. The remaining components of the transdermal system (acrylate copolymer adhesive, fatty acid esters, and polyethylene backing) are pharmacologically inactive.
- Mentax® cream, 1%, contains the synthetic antifungal agent, butenafine hydrochloride. Each gram of Mentax cream, 1%, contains 10 mg of butenafine HCl in a white cream base of purified water USP, propylene glycol dicaprylate, glycerin USP, cetyl alcohol NF, glyceryl monostearate SE, white petrolatum USP, stearic acid NF, polyoxyethylene (23) cetyl ether, benzyl alcohol NF, diethanolamine NF, and sodium benzoate NF.
- Metrogel-Vaginal is the intravaginal dosage form of the synthetic antibacterial agent, metronidazole, USP, at a concentration of 0.75%. Metrogel-Vaginal is a gelled, purified water solution containing metronidazole at a concentration of 7.5 mg/g (0.75%). The gel is formulated at pH 4. The gel also contains carbomer 934P, edetate disodium, methyl paraben, propyl paraben, propylene glycol, and sodium hydroxide. Each applicator full of 5 g of vaginal gel contains approximately 37.5 mg of metronidazole.
- Naftin® cream, 1%, contains naftifine hydrochloride 1%. Inactive ingredients: Benzyl alcohol, cetyl alcohol, cetyl esters wax, isopropyl myristate, polysorbate 60, purified water, sodium hydroxide, sorbitan monostearate, and stearyl alcohol. Hydrochloric acid may be added to adjust pH.
- Naftin gel, 1%, contains naftifine hydrochloride. Naftin gel, 1%, is for topical use only. Active ingredient: Naftifine hydrochloride, 1%. Inactive ingredients: Polysorbate 80, carbomer 934P, diisopropanolamine, edetate disodium, alcohol (52% v/v), and purified water.
- Nitro-Dur (nitroglycerin) transdermal infusion system is a flat unit designed to provide continuous controlled release of nitroglycerin through intact skin. The rate of release of nitroglycerin is linearly dependent upon the area of the applied system; each square centimeter of applied system delivers approximately 0.02 mg of nitroglycerin per hour. Thus, the 5, 10, 15, 20, 30, and 40 cm^2 systems deliver approximately 0.1, 0.2, 0.3, 0.4, 0.6, and 0.8 mg of nitroglycerin per hour respectively. The remainder of the nitroglycerin in each system serves as a reservoir and is not delivered in normal use. After 12 hours, for example, each system has delivered approximately 6%

of its original content of nitroglycerin. The Nitro-Dur transdermal system contains nitroglycerin in acrylic-based polymer adhesives with a resinous cross-linking agent to provide a continuous source of active ingredient. Each unit is sealed in a paper polyethylene-foil pouch.

- Noritate® (metronidazole cream) cream, 1%, is an emollient cream; each gram contains 10 mg micronized metronidazole USP, in a base of purified water USP, stearic acid NF, glyceryl monostearate NF, glycerin USP, methyl paraben NF, trolamine NF, and propyl paraben NF.
- Olux foam contains clobetasol propionate, USP. Each gram of Olux Foam contains 0.5 mg clobetasol propionate, USP, in thermolabile foam, which consists of cetyl alcohol, citric acid, ethanol (60%), polysorbate 60, potassium citrate, propylene glycol, purified water, and stearyl alcohol. Olux foam is dispensed from an aluminum can pressurized with a hydrocarbon propellant (propane/butane).
- Ovide lotion contains 0.005 g of malathion per milliliter in a vehicle of isopropyl alcohol (78%), terpineol, dipentene, and pine needle oil.
- Oxistat cream and lotion, Oxistat cream contains 10 mg of oxiconazole per gram of cream in a white to off-white opaque cream base of purified water USP, white petrolatum USP, stearyl alcohol NF, propylene glycol USP, polysorbate 60 NF, cetyl alcohol NF, and benzoic acid USP 0.2% as a preservative. Oxistat lotion contains 10 mg of oxiconazole per gram of lotion in a white to off-white opaque lotion base of purified water USP, white petrolatum USP, stearyl alcohol NF, propylene glycol USP, polysorbate 60 NF, cetyl alcohol NF, and benzoic acid USP 0.2% as a preservative.
- Oxytrol (oxybutynin) transdermal system is designed to deliver oxybutynin continuously and consistently over a 3 to 4 day interval after application to intact skin. Oxytrol is available as a 39 cm^2 system containing 36 mg of oxybutynin. Oxytrol has a nominal in vivo delivery rate of 3.9 mg oxybutynin per day through skin of average permeability (interindividual variation in skin permeability is approximately 20%).
- Panafil ointment contains papain, USP (not less than 405,900 USP units of activity based on Lot I0C389 per gram of ointment), urea, USP 10%, and chlorophyllin copper complex sodium USP 0.5% in a hydrophilic base composed of boric acid, chlorobutanol (anhydrous) as a preservative, polyoxyl 40 stearate, propylene glycol, purified water, sodium borate, sorbitan monostearate, stearyl alcohol, and white petrolatum.
- Pandel cream contains hydrocortisone probutate. Each gram of Pandel (hydrocortisone probutate cream) cream, 0.1%, contains 1 mg of hydrocortisone probutate in a cream base of propylene glycol, white petrolatum, light mineral oil, stearyl alcohol, polysorbate 60, sorbitan monostearate, glyceryl monostearate, PEG-20 stearate, glyceryl stearate SE, methyl paraben, butylparaben, citric acid, sodium citrate anhydrous, and purified water.
- Permethrin lotion, each fluid ounce contains active ingredient: Permethrin 280 mg (1%). Inactive ingredients: Balsam fir Canada, cetyl alcohol, citric acid, FD&C Yellow No. 6, fragrance, hydrolyzed animal protein, hydroxyethyl cellulose, polyoxyethylene 10 cetyl ether, propylene glycol, stearalkonium chloride, water, isopropyl alcohol 5.6 g (20%), methyl paraben 56 mg (0.2%), and propyl paraben 22 mg (0.08%).
- Premarin®, each gram of Premarin (conjugated estrogens) vaginal cream contains 0.625 mg conjugated estrogens, USP, in a non-liquefying base containing cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, benzyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil. Premarin vaginal cream is applied intravaginally. Premarin (conjugated estrogens) vaginal cream contains a mixture of conjugated estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains as concomitant components, as sodium sulfate conjugates, 17-alpha-dihydroequilin, 17-alpha-estradiol, and 17-beta-dihydroequilin.
- Preparation H is available in ointment, cream, gel, and suppository product forms. The ointment contains petrolatum, 71.9%, mineral oil, 14%, shark liver oil, 3%, and phenylephrine HCl, 0.25%. The maximum strength cream contains white petrolatum, 15%, glycerin, 14.4%, pramoxine HCl, 1%, and phenylephrine HCl, 0.25%. The suppositories contain cocoa butter, 85.5%, shark liver oil, 3%, and phenylephrine HCl, 0.25%. The cooling gel contains phenylephrine HCl, 0.25%, and witch hazel, 50%. Inactive ingredients: Ointment: Benzoic acid, BHA, BHT, corn oil, glycerin, lanolin, lanolin alcohol, methyl paraben, paraffin, propyl paraben, thyme oil, tocopherol, water, wax. Maximum strength cream: Aloe barbadensis leaf extract, BHA, carboxymethylcellulose sodium, cetyl alcohol, citric acid, edetate disodium, glyceryl stearate, laureth-23, methyl paraben, mineral oil, panthenol, propyl gallate, propylene glycol, propyl paraben, purified water, sodium benzoate, steareth-2, steareth-20, stearyl alcohol, tocopherol, vitamin E, xanthan gum. Suppositories: Methyl paraben, propyl paraben, starch. Cooling gel: Aloe barbadensis gel, benzophenone-4, edetate disodium, hydroxyethyl cellulose, methyl paraben, polysorbate 80, propylene glycol, propyl paraben, sodium citrate, vitamin E, water.

- Prochieve® (progesterone gel) is a bioadhesive vaginal gel containing micronized progesterone in an emulsion system, which is contained in single-use, one-piece polyethylene vaginal applicators. The carrier vehicle is an oil-in-water emulsion containing the water-swellable, but insoluble, polymer, polycarbophil. The progesterone is partially soluble in both the oil and water phases of the vehicle, with the majority of the progesterone existing as a suspension. Physically, Prochieve has the appearance of a soft, white to off-white gel. The active ingredient, progesterone, is present in either a 4% or an 8% concentration (w/w). Progesterone exists in two polymorphic forms. Form 1, which is the form used in Prochieve, exists as white orthorhombic prisms with a melting point of 127°C to 131°C. Each applicator delivers 1.125 g of Prochieve gel containing either 45 mg (4% gel) or 90 mg (8% gel) of progesterone in a base containing glycerin, mineral oil, polycarbophil, carbomer 934P, hydrogenated palm oil glyceride, sorbic acid, purified water, and may contain sodium hydroxide. Form 2, which is not used in pharmaceutical dosage forms, is thermodynamically unstable.
- Proctofoam®-HC (hydrocortisone acetate, 1%, and pramoxine hydrochloride, 1%) is a topical aerosol foam for anal use containing hydrocortisone acetate, 1%, and pramoxine hydrochloride, 1%, in a hydrophilic base containing cetyl alcohol, emulsifying wax, methyl paraben, polyoxyethylene-10-stearyl ether, propylene glycol, propyl paraben, purified water, trolamine, and inert propellants: Isobutane and propane.
- Protopic (tacrolimus) ointment contains (w/w) either 0.03% or 0.1% of tacrolimus in a base of mineral oil, paraffin, propylene carbonate, white petrolatum, and white wax.
- Psoriatec (anthralin cream, 1%, USP) is a smooth yellow cream containing 1% anthralin USP in an aqueous cream base of glyceryl monolaurate, glyceryl monomyristate, citric acid, sodium hydroxide, and purified water.
- Rosac cream, each gram of Rosac® cream with sunscreens contains 100 mg of sodium sulfacetamide and 50 mg of sulfur in a cream containing avobenzone, benzyl alcohol, C12-15 alkyl benzoate, cetostearyl alcohol, dimethicone, edetate disodium, emulsifying wax, monobasic sodium phosphate, octinoxate, propylene glycol, purified water, sodium thiosulfate, steareth-2, steareth-21.
- Sulfamylon cream is a soft, white, non-staining, water-miscible, anti-infective cream for topical administration to burn wounds. Each gram of Sulfamylon cream contains mafenide acetate equivalent to 85 mg of the base. The cream vehicle consists of cetyl alcohol, stearyl alcohol, cetyl esters wax, polyoxyl 40 stearate, polyoxyl 8 stearate, glycerin, and water, with methyl paraben, propyl paraben, sodium metabisulfite, and edetate disodium as preservatives.
- Temovate (clobetasol propionate cream and ointment) cream contains clobetasol propionate 0.5 mg/g in a cream base of propylene glycol, glyceryl monostearate, cetostearyl alcohol, glyceryl stearate, PEG-100 stearate, white wax, chlorocresol, sodium citrate, citric acid monohydrate, and purified water. Temovate ointment contains clobetasol propionate 0.5 mg/g in a base of propylene glycol, sorbitan sesquioleate, and white petrolatum.
- Temovate (clobetasol propionate gel) contains clobetasol propionate 0.5 mg/g in a base of propylene glycol, carbomer 934P, sodium hydroxide, and purified water.
- Temovate (clobetasol propionate scalp application) contains clobetasol propionate 0.5 mg/g in a base of purified water, isopropyl alcohol (39.3%), carbomer 934P, and sodium hydroxide.
- Testim® (testosterone gel) is a clear to translucent hydroalcoholic topical gel containing 1% testosterone. Testim provides continuous transdermal delivery of testosterone for 24 hours, following a single application to intact, clean, dry skin of the shoulders and upper arms. The active pharmacological ingredient in Testim is testosterone.
- Vivelle® (estradiol transdermal system) contains estradiol in a multi-polymeric adhesive. The system is designed to release estradiol continuously upon application to intact skin. Five systems are available to provide nominal in vivo delivery of 0.025, 0.0375, 0.05, 0.075, or 0.1 mg of estradiol per day via skin of average permeability. Each corresponding system having an active surface area of 7.25, 11.0, 14.5, 22.0, or 29.0 cm^2 contains 2.17, 3.28, 4.33, 6.57, or 8.66 mg of estradiol USP respectively. The composition of the systems per unit area is identical. The Vivelle system comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent flexible film consisting of an ethylene vinyl alcohol copolymer film, a polyurethane film, urethane polymer, and epoxy resin; (2) an adhesive formulation containing estradiol USP, acrylic adhesive, polyisobutylene, ethylene vinyl acetate copolymer, 1,3-butylene glycol, styrene-butadiene rubber, oleic acid NF, lecithin, propylene glycol, bentonite NF, mineral oil USP, and dipropylene glycol; and (3) a polyester release liner that is attached to the adhesive surface and must be removed before the system can be used. The active component of the system is estradiol. The remaining components of the system are pharmacologically inactive.
- Thera-Gesic, active ingredients: Methyl salicylate 25%, menthol 4%. Inactive ingredients: Aloe vera, carbomer 980, dimethicone, glycerin, methyl paraben, propyl paraben, sodium lauryl sulfate, trolamine, water.

- Topicort® LP (desoximetasone) cream, 0.05%, Topicort (desoximetasone) cream, 0.25%, Topicort (desoximetasone) gel, 0.05%, and Topicort (desoximetasone) ointment, 0.25%, contain the active synthetic corticosteroid desoximetasone. Each gram of Topicort LP cream, 0.05%, contains 0.5 mg of desoximetasone in an emollient cream base consisting of white petrolatum, purified water, isopropyl myristate, lanolin alcohols, mineral oil, cetostearyl alcohol, and edetate disodium. Each gram of Topicort cream, 0.25%, contains 2.5 mg of desoximetasone in an emollient cream base consisting of white petrolatum, purified water, isopropyl myristate, lanolin alcohols, mineral oil, and cetostearyl alcohol. Each gram of Topicort gel, 0.05%, contains 0.5 mg of desoximetasone in a gel base consisting of purified water, docusate sodium, edetate disodium, isopropyl myristate, carbomer 940, trolamine, and SDAG-3, 95% alcohol. Each gram of Topicort ointment, 0.25%, contains 2.5 mg of desoximetasone in an ointment base consisting of white petrolatum and fractionated coconut oil.
- Tri-Luma® cream (fluocinolone acetonide, 0.01%, hydroquinone, 4%, tretinoin, 0.05%) contains fluocinolone acetonide, USP, hydroquinone, USP, and tretinoin, USP, in a hydrophilic cream base for topical application. Each gram of Tri-Luma cream contains active ingredients: Fluocinolone acetonide, 0.01% (0.1 mg), hydroquinone, 4% (40 mg), and tretinoin, 0.05% (0.5 mg). Inactive ingredients: Butylated hydroxytoluene, cetyl alcohol, citric acid, glycerin, glyceryl stearate, magnesium aluminum silicate, methyl gluceth-10, methyl paraben, PEG-100 stearate, propyl paraben, purified water, sodium metabisulfite, stearic acid, and stearyl alcohol.
- U-Kera™ is a keratolytic emollient, which is a gentle, yet potent, tissue softener for nails and/or skin. Each gram of U-Kera contains urea USP (40%), purified water USP, light mineral oil NF, white petrolatum USP, glycolic acid, propylene glycol USP, trolamine NF, glyceryl stearate SE, cetyl alcohol NF, L-arginine USP, and xanthan gum NF.
- Vanos™ (fluocinonide) cream, 0.1%, 1 mg micronized fluocinonide in a cream base of propylene glycol USP, dimethyl isosorbide, glyceryl stearate (and) PEG-100 stearate, glyceryl monostearate NF, purified water USP, Carbopol 980 NF, diisopropanolamine, and citric acid USP.
- Vicks® VapoRub® active ingredients: Camphor, 4.8%, eucalyptus oil, 1.2%, menthol, 2.6%.
- Vivelle-Dot® (estradiol transdermal system) contains estradiol in a multi-polymeric adhesive. The system is designed to release estradiol continuously upon application to intact skin. Five dosage strengths of Vivelle-Dot are available to provide nominal in vivo delivery rates of 0.025, 0.0375, 0.05, 0.075, or 0.1 mg of estradiol per day via the skin. Each corresponding system has an active surface area of 2.5, 3.75, 5.0, 7.5, or 10.0 cm^2 and contains 0.39, 0.585, 0.78, 1.17, or 1.56 mg of estradiol USP respectively. The composition of the systems per unit area is identical. Vivelle-Dot is comprised of three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyolefin film; (2) an adhesive formulation containing estradiol, acrylic adhesive, silicone adhesive, oleyl alcohol, NF, povidone, USP, and dipropylene glycol; and (3) a polyester release liner which is attached to the adhesive surface and must be removed before the system can be used. The active component of the system is estradiol. The remaining components of the system are pharmacologically inactive.
- Zovirax ointment, 5%, contains 50 mg of acyclovir in a polyethylene glycol (PEG) base. Zovirax cream, 5%, is a formulation for topical administration. Each gram of Zovirax cream, 5%, contains 50 mg of acyclovir and the following inactive ingredients: Cetostearyl alcohol, mineral oil, poloxamer 407, propylene glycol, sodium lauryl sulfate, water, and white petrolatum.

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Index